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Theoretical Calculations on the Conformational/Tautomeric Equilibria for Small Molecules in Solution

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Abstract

The prevailing conformation and/or tautomeric form of a species may affect the product in chemical reactions. Determination of the predominant ligand structure is also important in theoretical drug design, where the goal is finding the best fit between the structurally flexible ligand and the receptor. The present review surveys the computational problems encountered in structure determination of small organic molecules in solution. The discussed issues include the method of the geometry optimization, the needed level of theory and basis set, choice of the modeling parameters, and the determination of the relative standard chemical potentials for estimating the equilibrium constant in relation to the molar concentration of the participants through the chemical transformation.

Keywords: Ab initio; DFT; Continuum solvent; Monte Carlo; FEP

Introduction

This review intends to survey theoretical calculations for conformational and/or tautomeric equilibria of small organic molecules in solution. The phase "solution" should be emphasized, since many theoretical studies have considered gas-phase processes, whereas much less investigations have been performed for exploring equilibria in solution. Experimental studies available on this field are of paramount importance because they provide a basis for comparison with theoretical results, providing credit to the applied method(s) or calling attention for a need to develop improved methodology.

First, it has to be identified what will be considered herein as a conformational or tautomeric change. By conformation, the author means a specific geometric arrangement of the atoms in the molecule with well-defined composition and atom-atom bonding pattern. Some restrictions are, however, to be mentioned. No conformation issue emerges for a two-atomic molecule, because the difference in the bond length upon vibration or excitation is not to be considered here as a change in the conformation. Also, the planar and symmetric benzene molecule or its mono-halogen derivative should not be studied from a conformational point of view. Although the C-C distances and the CCC angles may change upon a halogen substitution compared with them in the parent benzene, neither the benzene nor the mono-halogen derivative exhibits conformational variety.

However, if the hydroxy-benzene (phenol) molecule is studied, the conformational issue emerges. The composition and the atom-atom connections are still set for this molecule, but the position of the hydroxy hydrogen with reference to the plane of the benzene ring may vary. The gas-phase stable structure of phenol has been identified as of planar arrangement [1]. If the hydroxy-hydrogen rotates about the C-O bond, its every position corresponds to a different, new conformation with reference to the energy-minimum planar structure. None of these intermediate conformations is stable, but one may want to calculate the energy/free energy need for an OH out-of-plane rotation by a predefined torsion angle. Upon the symmetry, the largest energy increase is needed for a rotation halfway between two, equal-energy and undistinguishable in-plane positions of the rotating hydrogen. Theoretical studies consider this conformation as a transition state (TS), and many papers deal with the calculation of the required activation energy.

Thus, as a partial definition in this review, the conformation corresponds to the result of a rotation about a covalent bond. Sometimes the conformers cannot turn into each other without absorbing large activation energy. An important example is the cis-trans isomerism with reference to a double bond. Satisfactorily large activation energy could disrupt the π bond and the connecting groups could rotate about the remaining σ bond into the more favorable steric position. At the end of the process, the π bond is formed again. Such conformational changes will not be the subject of the present review.

One of the subjects here is the torsional change about a single covalent bond. In the case of phenol, different torsional positions are possible about a formally single covalent bond, but these structural changes do not lead to the formation of a stable conformer. 120° rotations of the OH hydrogen atom of methanol lead to three, indistinguishable and stable positions of the hydroxy-hydrogen with reference to the methyl hydrogens, whereas all intermediate states correspond to an unstable conformation, including TS at 60° rotation defined by the symmetry. However, through the rotation of the hydroxyl-hydrogen of ethanol (2OH-ethane) about the single, covalent C-O bond, different, distinguishable, and stable conformers may come into existence. This is the consequence of the difference in the symmetry: C_s for the transformation in the gas phase (HOCC=180°) compared to C_1 for the gauche conformation [2]. Most of the papers to be reviewed here follow rotations about a single bond into structures with different symmetries.

For many of the studied systems below, there are two polar groups in 1,2 positions in a molecule. If both are capable to be involved in an intramolecular hydrogen bond, conformational equilibrium may enter. Whether the indicated bond should be considered as a hydrogen bond on the basis of a topological definition, the atom-in-molecules (AIM)

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theory of Bader can be applied to find the bond critical points (BCP) and to analyze them in terms of electron densities and their Laplacians [3,4]. According to this theory, qualification of a hydrogen bond is related to the existence of a bond critical point (BCP) of (3,-1) type. Although a hydrogen bond may be expected on the basis of the H…X distance (X a hydrogen bond acceptor atom), the (3,-1) BCP topology was not found for 1,2-dihydroxy ethane [5], catechol [6], and morphine [7] with geometries optimized in the gas phase. Mandado et al. [6] pointed out, however, that after a slight distortion of the optimized catechol geometry, the (3,-1) BCP appears. In the forthcoming survey, hydrogen bonds will be accepted on the basis of the H…X distance.

Another important field of the conformational changes is the possibly back-and-forth flip from the chair structure to the twist-boat (skew) form for six-member saturated rings. Even the unsubstituted cyclohexane molecule presents this sort of structural changes, with further complication in cases of one or more substituent(s). As well known from elements, the substituents may take so-called equatorial and axial positions depending on the ring conformation. The absolute configuration of the carbon atom(s) connecting to the substituent(s) will not change upon a chair-twist transformation, but the positions of two or more substituents relative to each other will alter. This maintenance of the absolute configuration of the atoms is an important feature of any conformational change.

Definition of the tautomeric transformations to be considered in this review is much simpler than that of the conformational changes. A structural transformation will be characterized as tautomeric, if a proton relocates in the system. The simple definition allows for classifying many simple reactions as a tautomeric one. Indeed, tautomerism may be considered as a chemical reaction, since the process proceeds through bond breaking and making, resulting in a new atom-atom binding pattern with isomeric composition. Nonetheless, the tautomeric "reaction" is relatively simple in comparison with formation of isomers (*e.g.*, the ethanol–dimethyl ether pair). Famous tautomeric changes include the keto-enol, lactam-lactim transformations, or those when the proton relocates on a heterocyclic ring. The specific tautomerism of the zwitterion formation and the hydrogen-bonded ion-pair formation will be also reviewed here.

It is always a problem when writing a review: what to be included and where to close the survey. For example; the effect of the tautomeric equilibria of the DNA bases on spontaneous mutation is a central biochemical problem. Detailed consideration of the vast amount of the published papers exceeds, however, the limits of this review. Just as a few examples, the water-assisted tautomerization of adenine and purine [8,9], the double proton transfer for adeninine-thymine and guaninine-cytosine pairs [10], the combined effect of stacking and solvation on the spontaneous mutation in DNA [11] and the double proton transfer mechanism of the adenine-uracil pairs and the spontaneous mutation of the RNAduplex [12] are typical studies on this field.

According to the best knowledge of the author, no comprehensive review has been published so far on the field specified in the title of this paper. Although this title allows for a survey of the wide research activity of the scientific community, only a more modest goal has been set forth as an aim in this review: consideration of the theoretical studies on the in-solution conformational and tautomeric equilibria for small, biological important molecules including mainly 1,2-disubstituted ethanes, ortho phenols, and five- and six-member ring systems. For systems as amino acids, oximes, different phenols, for which a very large number of papers have been published, only strongly shortened overviews became possible.

The lists of the corresponding references are far from being complete. Generally the more recent publications are mentioned in company with a few former, landmark papers. Before surveying the actual calculations for estimating equilibrium structures and compositions, the applied methodologies will be briefly discussed. The recent publications include references to papers reporting earlier stages of the methods.

Methodology

Geometry optimization and the level of theory

For a successful theoretical calculation it may be a basic requirement that the structure (geometry) of the involved species be correctly determined. Since, however, equilibrium studies always consider relative energy terms, the question emerges: could reasonable relative energies/free energies be obtained on the basis of not very precisely determined molecular geometries? Implicit in this question is that cancellation of errors in molecular energies due to imprecision in geometries is possible. On the other hand, error cancellation is also possible due to an inappropriate energy calculation by the applied theoretical method, irrespective of the correct individual geometries. Thus one can never know how reliable the obtained results are in the absence of some control based on experiment. Unfortunately, experimental results regarding the structures of molecules involved in-solution equilibria are generally missing, or are available only for one of the involved species. On this basis, one may assess how well the structure of one component has been determined, but possibly nothing is known about the other (further) participant(s). Comparison of theoretical and experimental compositions (if available) is perhaps more helpful, although the relevance of the underlying geometries remain undiscovered. Thus a possible approach is to optimize the individual geometries and calculating the related energies at a level as high as possible. This seems to be a normal expectation, which could be seriously hindered by technical problems.

Geometries are mostly optimized at the MP2 level or by means of some DFT method. MP2 calculations with satisfactorily large basis set, e. g., 6-311++G** are very time consuming. Recent DFT-D methods, where the dispersion interactions are already considered correctly, serve a good solution for the balance of precision and affordable computer time. Using a DFT-D method, even application of the aug-cc-pvtz basis set for in-solution geometry optimization has become feasible for small molecules with 8-10 C, N, O atoms and related hydrogens.

Even if one can afford large-basis-set geometry optimizations, energy calculations generally require the consideration of even larger basis sets. In principle, only a complete basis set (CBS) calculation is exact, but this limit technically unreachable. Hobza proposed a formula [13], which could be favorably applied for calculating relative energies at the CCSD(T) level (coupled cluster for singles and doubles with non-iterative triples [14,15]).

$$\Delta E^{CCSD(T)}{}_{CBS} = \Delta E^{MP2}{}_{CBS} + (\Delta E^{CCSD(T)} - \Delta E^{MP2})_{small\ basis\ set} \quad (1)$$

where $\Delta E^{MP2}{}_{CBS}$, the complete basis set limit MP2 energy difference could be calculated by means of different extrapolation formulae [16-18].

$$E^{MP2}{}_{CBS} = E(X) - A/X^n \quad (2)$$

For obtaining A and then E (CBS) in eq. 2, single-point calculations are to be performed with double-zeta (X=2) and triple-zeta (X=3) basis sets at the optimized geometry. The proposed values for the "n" exponent are 3 and 2.2 [17,18] respectively. Using the aug-cc-pvqz basis set, X=4 [19].

Continuum solvent models

If the geometry of a molecule is optimized in the gas phase, then the minimum of the $E=\langle\Psi|\ H\ |\Psi\rangle$ expression is sought in the energy-variation method. Here H is the gas-phase Hamiltonian and Ψ is a normalized trial function. If E is minimized, the corresponding Ψ_g is the converged wave function and the underlying geometry is the ground state optimized molecular geometry.

The common practice nowadays for optimizing a molecule in solution is the application of some continuum dielectric method [20-32] where the solute is placed in a cavity carved into the solvent. The solvent is modeled generally as a polarizable dielectric continuum characterized by its bulk dielectric constant, and some other parameters accounting for non-electrostatic solute–solvent interaction terms. The advantage of this approach is that it accounts for the very important long-range electrostatic interactions in a fairly simple way.

If the molecule is immersed into the cavity in the solvent, the solute polarizes the homogenous dielectric, generates a so-called V reaction field in it, which exerts forces on the solute atoms. Then, the positions of the atomic centers will be modified, a new wave function is calculated, which generates a new reaction field. The procedure is conducted in a self-consistent field (SCF) way until the net forces acting on the atoms and the atomic displacements, as well as the changes in the wave function and in the generated reaction field become smaller than the predefined corresponding threshold values.

The energy of the solute with optimized geometry in the given solvent, E_{sol} is provided as:

$$E_{sol} = \langle\Psi_s|\ H + \tfrac{1}{2}\ V|\Psi_s\rangle \quad (3)$$

Here H, V and Ψ_s are the gas-phase Hamiltonian, the converged reaction-field operator and solute's wave function, respectively. The internal energy, E^s_{int}, and the solute-solvent electrostatic interaction energy, E_{elst}, are calculated as follows:

$$E^s_{int} = \langle\Psi_s|\ H\ |\Psi_s\rangle \quad (4a)$$

$$E_{elst} = \langle\Psi_s|\ \tfrac{1}{2}V\ |\Psi_s\rangle \quad (4b)$$

It is always true that $\langle\Psi_s|\ H\ |\Psi_s\rangle$ is less negative than $\langle\Psi_g|H\ |\Psi_g\rangle$ because the latter stands for the minimum of $\langle\Psi|H|\Psi\rangle$ value calculated at the gas-phase optimized geometry. Any deviation from this geometry results in an increase in the $\langle\Psi|H|\Psi\rangle$. Thus the mentioned relationship is a natural consequence of the solvation, and the increase of the E_{int} energy upon polarization and geometry distortion is entailed with the formation of a more negative $E_{elst}=\langle\Psi_s\ |\tfrac{1}{2}V|\Psi_s\rangle$ term. Their balance will assure the minimum $E_{sol}=E^s_{int} + E_{elst}$ value.

There has been remarkable progress since the first proposition of a continuum solvent model by the Tomasi group [20]. From electrostatic point of view, the solvent is characterized by its bulk dielectric constant, ε, in the PCM (polarizable continuum method) [20-24] and in the SMx and SMD approaches [25,26]. In a series of papers by Orozco et al. [27], the MST method was developed as a variant of the integral-equation formalism of PCM with a dual-cavity strategy [27]. Klamt and Schüürmann [28] proposed, however, another approach: the solvent is considered as behaving with a conductor-like screening character (COSMO). This approximation was further developed by Klamt et al. [29,30] and by Barone and Cossi [31,32]. The conductor-like and dielectric behaviors become identical with $\varepsilon \to \infty$, but the approach is less justified for solvents with small dielectric constants. An advantage of the method is, however, that first and second derivatives of the molecular free energy with respect to the motion of nuclei can be efficiently calculated. The Gaussian 09 [33] codes for the COSMO-type solvation procedure is SCRF=CPCM based on the formulae of Barone and Cossi [31,32], whereas SCRF=IEFPCM (Gaussian 09 default, in contrast to Gaussian 03) and SCRF=SMD commands are to be used for the integral-equation formalism of the PCM and SMD methods, respectively.

The other important difference among the methods stems from the estimation of the solute cavity. In the simplest approach the cavity is a sphere, whereas the reaction field and the ab initio solute wave function are calculated in an SCF procedure. Thus the approach is an ab initio/SCRF extension of the simple Onsager reaction field method, where the solute is characterized only by a point dipole in a cavity of the solvent. The accepted cavity radius is crucial and clearly has an effect on the calculated energy results. Wong et al. [34] calculated the cavity radius for the sulfanic acid from the molar volume of the crystal and added 0.5 Å to account for the nearest approach of solvent molecules.

In more specific studies, the cavity is formed by overlapping spheres centered on the solute atoms, with different sets for these atomic radii, as compared by Marenich et al. [26]. The values may differ by tenths of an Å for some atoms in different parameterization sets, indicating remarkable method dependency. The standard set in PCM is the UA0 united atom set of radii, but the input allows user-defined radii. Nagy et al. [35] proposed the use of Bondi radii [36], scaled by a factor of 1.2 for polar atoms, whereas scaled radii were accepted for the united-atom CH, CH_2 and CH_3 groups. A recent study [37] pointed out the negligible effect of the use of the united alkyl-group model as compared with its all-atom model on the optimized molecular geometry in aqueous solution.

By applying electronic isodensity contours for the solute, the cavity could be defined in a more solute-shape matching way [38]. Zhan and Chipman [39] considered the isodensity contours in the 0.0005 – 0.002 a.u. range in conformational analyses, and found that the optimal value could be about 0.0010 a.u. for most systems. It is worth mentioning, however, that by acceptance of the 0.001 a.u. value in SCI-PCM calculations, the geometry optimization became very slow even at the HF/6-31G* level for the aspartic acid zwitterionic species in aqueous solution [40].

Provided the cavity, the non-electrostatic solute-solvent interaction terms can be calculated as G_{drc}=G(dispersion) + G(repulsion) + G(cavity). Different methods apply different formulae and parameter sets for calculating these terms, too. In the MST method [27], separate sets of cavity radii are used for calculating the electrostatic and non-electrostatic contributions to the solvation free energy.

In summary, all methods follow some complicated, method-specific procedure for obtaining the parameter set to be used in geometry optimization and energy calculation. Parameterization is based frequently on training sets with known free energy of hydration for the elements. Accurate theoretical prediction of the free energy of hydration for a molecule is, however, challenging. The gas-phase term could be reliably predicted; the protonation energy and gas-phase basicity were successfully calculated recently for a few molecules [41,42] applying satisfactorily high-level of energy calculations and by assuming ideal gas behavior. By combination of the classical limit expression for the translational, rotational energy and entropy and using the rigid-rotor/harmonic oscillator approach, [43] good agreement with experimental values was reached. The results suggest that the commonly used thermodynamic expressions for gas-phase

molecules provide reasonable enthalpy and entropy values. Estimation of the free energy of a molecule in a solvent is more difficult. Proper calculation of the cavity shape and size, and the free energy of the cavitation is the first problem. If the cavity is formed, the solvent molecules in a real (not continuum solvent) solution reorganize, which may entail with remarkable enthalpy and entropy changes. This effect could be taken into consideration through the parameterization process using the training set, but the general applicability of derived solvent parameters remains a question. Not surprisingly, calculated free energy of hydration for some molecules may deviate by 10-20% from the experimental value [44-46].

Much less problem is met when in-solution conformational/tautomeric equilibria are calculated. The bonding matrix is preserved in different conformations, and only small structural changes take place through proton relocation. For small molecules, the cavity size remains nearly unaltered, and although the individual contributions to G_{drc} could amount to tens of a kcal/mol using PCM, ΔG_{drc} is generally only a few tenths of a kcal/mol [47-49].

Explicit solvent methods

The major weakness of the continuum solvent approach is that a structureless medium does not take into consideration the quantum-mechanical consequences of hydrogen-bond interactions between polar solutes and hydrogen-bond donor/acceptor solvents. The surface charges generated in the polarized solvent may be expected to take the opposite sign as a derivable atomic charge for the close solute atom, nonetheless referred papers in the following sections suggest that the difference between the ΔG (solv) values estimated by the continuum solvent and explicit solvent methods stems from the different appreciation of the solute-solvent hydrogen bonds.

In principle, the problems could be overcome by a high-theoretical-level investigation of a quantum-mechanical system with a large number of solvent molecules, where geometry change for each participant is allowed and thermodynamic averages are obtained after long simulations. This goal would be achieved by ab initio molecular dynamics (AIMD) simulations. However, consideration of the electron correlation at a high level and application of a satisfactorily large basis set probably prohibits calculations nowadays if hundreds of solvent and a few solute molecules are to be considered for modeling real, dilute solutions. The AIMD-type calculations could be much speeded up; if a properly selected DFT method [50] accounting for the dispersion interactions has been chosen. Nonetheless, the basis-set problem still remains.

As a simplification compared with AIMD, the effective fragment potential method (EFP) as a quantum-mechanics-based theoretical approach for modeling environmental effects on the structure of some central (solute) species has been worked out [51]. From the point of view of the conformational analysis, the original theoretical development is relevant, which aims to study weak interactions between solute-solvent and solvent-solvent molecules. Its extension to consider covalent bonds may be important when tautomeric equilibria are investigated through bond breaking and making. The method was successfully applied in estimating the proton affinity of lysine and the Gly-Lys-Gly tripeptide, calculating binding energies for water clusters, reaction free energies for the Menshutkin reaction, and the tautomeric equilibrium for glycine [51].

EFP uses an ab initio Hamiltonian that calculates coulombic induction and repulsive interaction terms by considering one-electron energies. To facilitate its application to any solvent and accelerate the calculations, a perturbation expansion utilizing first-principle terms was introduced to account for exchange repulsion/charge penetration energy contributions. The EFP method is a basis-set dependent approach.

Both the AIMD (and its DFT/MD variant) and EFP methods are time consuming approaches due to the SCF problem and the calculation of specific integrals. A break-through was provided by Car and Parrinello [52] in their proposed molecular dynamics method, CPMD. As Tse [50] writes "the CPMD method, initially intended to alleviate the problem in the diagonalization of large matrices in condensed-matter physics calculations, has developed into a very useful tool in quantum chemistry. The extended variable Lagrangian (Hamiltonian) formalism lends itself to efficient implementation of other dynamical variables. The pseudo-potential planewave approach with periodic boundary conditions is computationally highly efficient for the calculation of large systems, although in principle these conditions need not be imposed". The CPMD procedure has not been, however, frequently used in conformational/tautomeric equilibrium study, thus future investigations are needed for assessing the potential of the method in this field.

A less ambitious goal would be the application of the widely used QM/MM methods [53-55]. Geometric changes allowed for the elements of the solution, and performing large-basis-set QM calculations for ultimately obtaining average thermodynamic parameters would probably be still prohibitive, even considering only 20-25 solvent molecules in the QM region. Thus application of effective pair-potentials in Monte Carlo (MC) and molecular dynamics (MD) simulations is the general practice, primarily for large biomolecular solutes. The present review considers these latter solution-modeling procedures applied for small organic molecules.

If the solute geometry is allowed to change then the structure depends on the performance of the applied pair potential. Relative solvation free energies depend mainly on the conformation of a species in a preserved tautomeric state. The empirical force fields are generally not parameterized specifically for solutes with polar, hydrogen-bonding substituents in 1,2 or 1,3 positions. As a consequence, their optimized torsion angles may considerably differ from those determined by ab intio studies. For example, an early paper by Nagy et al. [56] comparing geometries optimized upon the AMBER parameterization [57] and at the HF/6-31G* level found remarkable deviations in some optimized torsion angle values for histamine, and some conformations were not found as stably existing for the gas-phase 1,2-dihydroxy ethane by AMBER. Thus the question emerges, what is the better methodology: allowing the torsional change by the applied force-field or using rigid geometries optimized in high-level quantum-mechanical calculations utilizing some continuum dielectric model. The dilemma exists only for small molecules, because calculation of the geometry for a protein or a DNA model at high quantum-mechanical level is impossible today. The review below deals with studies where the accepted geometry was optimized quantum mechanically in the gas phase or by applying a continuum dielectric solvent method for solutions.

Tautomerism along an intramolecular proton relocation path requires generally relatively large activation energy. In protic solution, however, a solvent-catalyzed mechanism is also possible, thus the solvent does not simply exert a through-space effect, but becomes active participant of the process. A conformational change may take place also along a tautomeric pathway: the hydrogen-bonded proton of the solute is picked up by a protic solvent molecule and is returned

into a new conformational position of the solute by another solvent molecule. This mechanism hypothesizes the existence of an extended solvent network around the solute, which is certainly true in aqueous solution. If one wants to explore the most favorable arrangements of the water molecules around the solute, preliminary model calculations are useful for optimizing the positions of a limited number of the water molecules. Calculations in the gas-phase provide with the optimized structure of gas-phase hydrates, and will be called microsolvation below [58-61]. Since gas-phase mono-, di-, etc. hydrate structures could be experimentally observed, comparison of the theoretical end experimental results could serve as a check for the capacity of the theoretical method.

If the hydrate/solvate structure is reoptimized by means of a continuum dielectric solvent method when the hydrate/solvate is placed into a cavity carved within the polar solvent, the approach is called the supermolecule+continuum method. The optimization proceeds just like as it was outlined in the previous section, but the solute is now the supermolecule. This approach allows for charge transfer between the central solute and the explicit solvent molecules, which affect the derived atomic charges for the solute (see next section).

The usefulness of the supermolecule approach is not unequivocal. Perhaps its largest benefit is that it helps devise tautomerization pathways [62]. On the other hand, it reflects energy minimized structure in contrast to the general solute arrangement in the first solvation shell, as can be derived from Monte Carlo or molecular dynamics simulations accounting for the thermal motion. Furthermore, the solvent molecules may form artificial aggregates in the absence of periodic boundary conditions, typical when the supermolecule+continuum approach is utilized. Thus it is a question, whether the cavity can be correctly determined by the pure solute or upon the supermolecule. Also one has to make a choice if the optimized solute geometry is being used as a rigid one in explicit solvent simulations. An attempt for resolving the problem was made by Nagy [19] who compared the IEF-PCM optimized geometries of the internally hydrogen-bonded 2-F-ethanol and its monohydrate in aqueous solution. In that lucky case, the characteristic HOCC and OCCF torsion angles did not change too much, thus the geometry of the optimized bare solute was accepted in further studies. Serious problems were met, however, by Crittenden et al. [63] through the optimization γ-amino butyric acid surrounded by five water molecules. An opposite example was found in the literature by Lu et al. [64], who successfully reoptimized the gas-phase $Al(H_2O)_6^{3+}.12H_2O$ and $Al(OH)_4^-.12H_2O$ clusters in continuum water. Artificial coagulation of the water molecules was avoided presumably because of the strong ion-water interactions, the extended water-water hydrogen-bond pattern, and due to the nearly spherical symmetry of the supermolecules.

If water/solvent molecules act only as a catalyst for a process, they will not affect the equilibrium composition governed by relative free energies. Nevertheless, explicit consideration of water molecules in processes where they act as participating partners or help stabilize some structure is inevitable for understanding the mechanism of the process and exploring possible reaction routes [8-12,65]. The kinetics of the reaction, specifically the reaction rate constant is related to the free energy of the transition state with reference to local energy minimum structures. Although the reaction could proceed along all reaction routes, their rate could be enormously different. Also it is worth mentioning that the tunneling effect, a pure quantum mechanical effect, could also be an important factor, mainly at a lower temperature. By the tunneling effect the reaction need not proceed along the so-called adiabatic reactants – transition state – products path, and in this case the reaction rate could remarkably increase. Hammes Schiffer and Tully [66] compared the calculated adiabatic and nonadiabatic proton transfer reaction rates for a phenol-amine complex in solution (liquid methyl chloride). They found that inclusion of nonadiabatic transitions reduced the calculated rate constant by a factor of 2.3. Still consideration of the nonadiabatic corrections is important and becomes even more important at lower temperature, where the rate becomes increasingly controlled by tunneling. Both the tunneling and the overall rate constants were calculated by Gorb et al. [10] for the double proton transfer in the guaninine-cytosine pairs.

For conformational equilibria with relatively low barriers the tunneling effect may not be important at room temperature. In contrast, its effect in proton transfer reactions should be taken into consideration. For the theoretical background of the generalized transition state theory and further examples, the reader is referred to an important recent review [67].

Relative total free energy

The equilibrium condition for a chemical process is the equality of the chemical potentials for the reactants and the products. Based on a thermodynamic derivation, the chemical potential of the "i"-th component is defined in solution [68] as

$$\mu_i(a_i) = \mu_i^o + RT \ln a_i \quad (5a)$$

in terms of the solute "a_i" activity and μ_i^o hypothetical standard potential. By application of the equilibrium condition, the equilibrium constant, K, can be derived as $-RT \ln K = \Delta\Sigma_i \nu_i\mu_i^o$, where ν_i is the corresponding stoichiometric coefficient for the reactants. The hypothetical standard state is not feasible, however, for theoretical calculations, and an alternative formulation was proposed recently [41] considering the 1 molar solution as the standard state:

$$\mu_i(c_i) = \mu_i^o + RT \ln \gamma_i(c_i)\,(c_i/c_o) \quad (5b)$$

Here c_i is the solute concentration, $\gamma_i(c_i)$ is the related activity coefficient, and $c^o = 1$ mol/dm^3 is the unit chemical concentration making the argument of the logarithmic term dimensionless. From the definition equations in [41], $\gamma_i=1$ when $c_i=c_o=1$, letting $\mu_i\,(c_i=1)=\mu_i^o$. The consequence of setting the 1 molar solution to the standard state is that the γ_i coefficients do not converge to unity for an infinitely dilute solution in contrast to the formulation when the composition is characterized by the molar fraction [68].

The standard potential can be divided into internal and solvation-related parts as $\mu_i^o=\mu_i^o(\text{int})+\mu_i^o(\text{solv})$. The internal part can be calculated in a continuum dielectric solvation approach (eq. 4a) by assuming that $\mu_i^o(\text{int})$ is concentration independent, thus its calculated value from infinitely dilute model is still applicable for the standard state in 1 M solution. This assumption may be less valid for the solvation part due to possible solute association even in case of solvent separated solutes. Thus, relevant estimation of $\mu_i^o(\text{solv})$ is problematic.

In determining $\Delta\Sigma_i\,\mu_i^o(\text{int})$, the accepted geometries may stem either from gas-phase optimizations followed by single-point calculations in the solvent or directly from in-solution calculations. In the former case, the geometry distortion upon solvation has not been taken into consideration. A typical case is when the system presents an intramolecular hydrogen bond in a gauche conformation, which is geometrically more sensitive to the solvation than a trans moiety with obviously disrupted H-bond.

Common geometry optimizations take place at HF, MP2 ab intio and DFT levels utilizing different basis sets. If one chooses the DFT optimization, a number of functionals are available, which could be freely combined with the basis set. Special attention will be paid in this review to the most widely used B3LYP method [69,70], the B97D method of Grimme [71] and the recently developed and successful M05 and M06 series by Zhao and Truhlar [72].

If ab initio geometry optimization was chosen, upto very recently it generally has not exceeded the MP2 level with the 6-311++G** Pople basis [73] or the Dunning basis set aug-cc-pvtz [74-76]. Use of the latter basis set, however, requires long calculations and slow convergence for the in-solution geometry [19,49].

Relative E^s_{int} energies, ΔE^s_{int} could be obtained directly from DFT calculations for a pair of solutes by means of eq. 4a applied for each species. The ab initio internal energy from a PCM calculation could be ameliorated by extrapolation to the complete basis set (CBS) limit.

Irrespective of the theoretical level where it was obtained, ΔE^s_{int} is still energy, not free energy. Generally not included explicitly in published papers, but thermal contributions including solute translation, rotation, and vibration should also be considered. For calculating thermal corrections, the following expression has been applied by the author and coworkers in many applications:

$$\Delta G_{th} = \Delta ZPE + \Delta(H(T) - ZPE) - T\Delta S(T) \quad (6)$$

where ZPE is the zero-point vibrational energy, H(T) and S(T) are the enthalpy (not including the internal energy) and the entropy, respectively, at T=298 K and p=1 atm, calculated in the rigid-rotor, harmonic oscillator approximation. Overall, the accepted expression in these publications for ΔG_{tot} is:

$$\Delta G_{tot} = \Delta E^s_{int} + \Delta G_{th} + \Delta G(solv) \quad (7a)$$

where ΔG(solv) in PCM calculations, by applying eq. 4b, has two contributions:

$$\Delta G(solv, PCM) = \Delta E_{elst} + \Delta G_{drc} \quad (7b)$$

From eq. 7a, $\Delta E^s_{int} + \Delta G_{th} = \Delta \mu_i^o(int)$, providing the required component to $\Delta \mu_i^o$.

Since we do not know the proper in-solution translational and rotational partition functions, contributions due to these degrees of freedom to the total free energy might also be considered through the parameterization of a continuum dielectric solvent method. Ho et al. [77] commented the explicit consideration of the translational and rotational terms as a sort of double counting and were somewhat surprised that reasonable ΔG_{tot} values were obtained this way by different research groups. Gaussian calculates contributions to ΔG_{th} on the basis of the gas-phase partition functions. Although they are probably poorly applicable for in-solution equilibria, if one assumes that translational energy and entropy depend only on the molecular mass (with nearly equal solution volume for the explicit solvent model of dilute solutions of the conformers), they cancel out anyhow for different conformers or through the tautomeric transformations. If the moments of inertia change only a little, as frequently happens in these processes, near cancellation of the rotation terms is a reasonable approach, irrespective of the correct, but unknown mathematical form for the rotational enthalpy and entropy as a function of the moments of inertia in solution. Thus only the vibrational term will have a meaningful contribution to ΔG_{th} in eq. 6. This contribution, however, cannot be parameterized in general because vibrational frequencies are related to the structure of the solute. The solvent effect is indirect in this case, and is represented primarily through the modified geometry and polarized electron distribution of the solute.

ΔG (solv), as a separate term in eq. 7a, may be calculated in some theoretical way different from that given in eq. 7b. The equation 7b is obtained from a PCM calculation by taking the difference of the individual E_{elst} and G_{drc} terms. The very popular free energy perturbation, FEP method [78,79] calculates directly the ΔG (solv) value for two species. Its wide applicability is reflected by calculating the relative solvation free energy for methanol and ethane [79], as well as estimating the effect of a site-specific mutation on the stability of trypsin [80] in good agreement with available experimental data in both cases.

As reveals from the name, the FEP method is a perturbation-based calculation of the relative free energy for two systems. The truncated series for the perturbation expression [78-83] is fulfilled the better, the structural deviation the smaller. The interaction energy of the point-like elements of the system (assigned to different molecules) can be calculated by a number of effective pair-potentials [84-95]. The Van der Waals and electrostatic interactions are calculated by means of mathematically different functions. It is common, however, in the pair-potentials that the atom is characterized generally by two Van der Waals parameters, which are included in the programs library (although the user can modify it) and at least by a set of atomic net charges considered in Coulomb-type electrostatic interactions. For determination of the net atomic charges, different procedures are proposed. AMBER uses electrostatic potential fitted charges [96,97] or RESP charges [98], Jorgensen et al. [99] suggested the use of the CHELPG charges, fitted also to the molecular electrostatic potential [100].

The total ΔG (solv) is a sum of the incremental ΔG_i(solv) relative free energies calculated in the "i"th perturbation step:

$$\Delta G(solv) = \Sigma_i \Delta G_i(solv) = -RT \Sigma_i \ln \langle \exp(-\Delta E_i/RT) \rangle_i \quad (8)$$

Here $\langle \exp(-\Delta E_i/RT) \rangle_i$ is the average of the $\exp(-\Delta E_i/RT)$ function obtained by considering a large number of configurations, and ΔE_i is the energy difference of the system with the perturbed and the "i"th reference solute structure in a configuration. A configuration means a given geometric arrangement of the elements of the system. Generation of a new configuration is method dependent: in Monte Carlo programs different sampling methods are accepted, in molecular dynamics programs the displacements of the atoms are calculated on the basis of the net forces acting on each of them. For details of the FEP method, the reader is referred to reviews [81-83] and also for alternatives methods as thermodynamic integration [101] and slow growth calculations of the relative free energy [81,82].

The FEP method has been implemented in the major molecular mechanics/molecular dynamics softwares as AMBER, CHARMM, and Gromacs, as well as in the Monte Carlo-based BOSS software [102] and the present version of the MCCCS Towhee package [103] based on the MCCCS program (Monte Carlo for complex chemical systems) [104].

Calculation of the equilibrium constant

Whenever ΔG(solv) has been calculated in one way or another, eq. 7a is applicable to the determination of ΔG_{tot}. A serious problem has, however, remained: how is ΔG_{tot} related to an equilibrium ratio? It reveals from the experimental results of Moriyasu et al. [105] and De Oliveira et al. [106] that the equilibrium ratio of the conformers varies at different total solute concentrations. It reaches a limit value in dilute

solution, and the question is: does this limit ratio give the equilibrium constant, and how does the theoretically calculated ΔG_{tot} relate to the equilibrium constant, K?

By means of eq. 5a, two formulations are derivable for K:

$$K_x = \exp(-(\Sigma_i \nu_i \mu_i^o)/RT) = \Pi(a_i)^{\nu i} \quad (9a)$$

The first equation clearly indicates that K is a dimensionless constant, irrespective of the interpretation of the standard μ_i^o values expressed in energy unit. ν_i is the stoichiometric coefficient for the "i"th compound, negative for the reactants. The individual solute activities are, however, different in solutions with different total solute concentrations. A convenient way to relate the activity to the fraction of the species (dimensionless molar fraction, x_i) is the introduction of the activity coefficient, γ_{xi} as $a_i=\gamma_{xi} x_i$ [68]. In this formulation,

$$K_x = \Pi(\gamma_{xi})^{\nu i} \Pi(x_i)^{\nu i} \quad (9b)$$

Now K_x can still remain constant if the $\Pi(x_i)^{\nu i}$ product changes in parallel with a reciprocal change of the $\Pi(\gamma_{xi})^{\nu i}$ factor. Thus experimentally found different equilibrium ratios at different total solute concentrations would not violate the need for the constancy of K_x. The molar-fraction related activity coefficients converge to 1 for any solute in satisfactorily dilute solution, thus the true K_x can be experimentally determined upon analysis of the composition in a dilute solution as $\lim_{(c\to 0)} \Pi(x_i)^{\nu i} = K_x = K$ [105].

By applying a continuum dielectric solvent approximation, the theoretically calculated in-solution ΔG_{tot} could be related to the experimental K only by accepting that ΔG_{tot} (in solution)$=\Delta\Sigma_i \nu_i \mu_i^o$. No thermodynamic derivation proves, however, this relationship, mainly by considering that μ_i^o is a hypothetical standard chemical potential and the corresponding state physically does not exist. Although considering the derivation of μ_i^o as a function of the chemical potential of the pure liquid solute (which, however, may not even be a liquid in its pure form), its vapor pressure and Henry constant, a *numerical value* could be assigned to the hypothetical standard chemical potential without a possibility for the representation of the state [68]. The assumptions made when ΔG_{tot} was theoretically obtained cannot model this hypothetical state and, consequently, ΔG_{tot} cannot be correctly applied for estimating K_x=K. Thus a definition of the standard state of the solute with a reproducible molecular model is desirable.

If the standard state is the 1 M solution, as considered in a number of pK_a calculations [107-109], the equilibrium constant, K_c can be derived by utilizing eq. 5b providing

$$K_c = \Pi(\gamma_i(c_i)\ (c_i/c_o))^{\nu i} \quad (9c)$$

The problem with the eq. 9c formulation is that the γi(ci) coefficients need not converge theoretically to 1 even in dilute solution, thus in a conformational/tautomeric equilibrium for species "m" and "n", the relation holds even for very dilute solutions:

$$K_c = (\gamma_n(c_n)/\gamma_m(c_m))_{lim}\ (c_n/c_m)_{lim} \quad (9d)$$

Accordingly, $K_c \neq (c_n/c_m)_{lim}$, and K_c cannot be precisely obtained experimentally by concentration determination unless $(\gamma_n(c_n)/\gamma_m(c_m))_{lim}$ could be measured or estimated. A theoretical method was recently proposed to overcome the problem caused by the unknown γi(ci) coefficients (except [110]). If the standard state is the 1 M solution (eq. 5b) where $\gamma_i(c_i=1)$ is equal to 1, the FEP method could be applied to determine ΔG(solv) for the 1 M solutions of the conformers. This ΔG(solv) then could be used as the solvation related contribution to $\Delta\mu^o$ as:

$$\Delta\mu^o = \Delta\mu^o(int) + \Delta\mu^o(solv) = \Delta\mu^o(int) + \Delta G(solv) \quad (10)$$

It is to be noted, however, that 1 molar solutions could be modeled by 9 small organic solutes in a box of about 470 TIP4P water molecules [111] at T=298 K and p=1 atm through the FEP calculations, thus ΔG(solv)=ΔG(solv, FEP)/9. (In order to assure the cutoff < edge/2 relationship, the requirement when the periodic boundary condition is applied, a cubic water box with edge size of at least 24-25 Å has to be considered if the cutoff has been set to 12 Å. Then the starting box corresponds to a pre-equilibrated water box with 512 TIP4P water molecules in BOSS, and 4-5 water molecules per solute should be removed in order to prevent poor contacts in the starting configuration. For a molar solution model with nine solutes, the average solution volume should be around 14950 $Å^3$). Studies for molar solution models [37,110,112] indicate non-negligible solute association, although mostly without contact solute pairs. This finding suggests that the continuum solvent determination of the ΔE^s_{int} term is probably still a good approximation for 1 mole of individual solutes, and eqs. 1, 4a, 6 and 10 could be applied in calculating equilibrium constants. Nonetheless, the calculated equilibrium compositions were always calculated [110] by using the approximation $K=\exp(-\Delta G_{tot}/RT)$ in the reviewed papers below, thus they are probably meaningful only for equilibria in very dilute solutions. In fact, the study in ref. 110 showed that ΔG(solv, FEP)/9 for a 1 molar solution is nearly equal to ΔG(solv) for a 0.1 molar solution considered to represent the dilute solution limit for the tautomeric equilibrium ratio in water solvent [105].

Conformational Equilibria

1,2-disubstituted systems

2-substituted ethanol: If a 1,2-disubstituted molecule has two polar substituents capable of forming an intramolecular hydrogen bond, then these structures are subject to an equilibrium of the conformers with and without such a bond. Conformational equilibria were studied for a number of the family members both in the gas phase and in solution.

The classical example is 1,2-ethanediol (ethylene glycol, 1,2-dihydroxy ethane). Upon MP2/cc-pvdz optimization of Cramer and Truhlar [113], the molecule has ten stable conformers in the gas-phase, with an all trans HO-CH_2-CH_2-OH conformer of C_{2i} symmetry and nine conformers with no symmetry and of individual degeneracy of 2 or 4. Six and four conformers take the OCCO gauche and trans arrangements (G, T), respectively, with different conformations for the HOCC moiety for each (g^+, g^-, t). The relative energies were calculated at the [MP2/cc-pvtz + CCSD(T)/cc-pvdz – MP2/cc-pvdz)] level. The most stable conformer is the tG^+g^- structure followed by the $g^+G^+g^-$ conformation higher in ΔG by 0.42 kcal/mol at T=298 K. Both structures exhibit an intramolecular hydrogen bond. Gas-phase experimental studies (the papers listed in refs. [113,114]) support the theoretical results.

Nagy et al. [114,115] studied the solvent effect on the conformations in aqueous solution. These authors considered only five G and one T conformers and predicted 99.5:0.5 for their ratio. The relative fractions may not correspond, however, to the real G:T ratio in aqueous solution. Indeed, Pachler and Wessels [116] found about 12% T structure upon the proton magnetic spectra of ethylene glycol in D_2O, where all conformations can appear. The most abundant conformation predicted theoretically by Nagy et al. [114] was the tG^+g^+ structure (using the code by Cramer and Truhlar [113] without an intramolecular hydrogen

bond. This result indicates large solvent effect in aqueous solution, since theoretical calculations and experimental results unanimously found an internally hydrogen-bonded conformer, tG^+g^- prevalent in the gas-phase.

Comparing the conclusions from the above aqueous-solution calculations with those by Cramer and Truhlar [113,117] the difference is very remarkable. These latter authors considered all ten conformers and found the OCCO trans fraction as of 4-16%, in good agreement with the ~12% experimental value, as a consequence of an about 40-50% relative increase of the T fraction upon solvation. Nonetheless, Cramer and Truhlar [117] still found 36-54% tG^+g^-, as the predominant conformer with an intramolecular hydrogen bond in solution as compared with the 56% fraction in the gas phase. Thus the two aqueous-solution calculations show the typical difference noticed in a number of studies below: explicit solvent calculations applying the free energy perturbation method frequently prefer the disrupted intramolecular hydrogen bond opposite to a solute structure with an intramolecular hydrogen bond. Cramer and Truhlar [113] emphasize that determination of the correct value for the relative internal free energy is a decisive factor, because they provide a large contribution to ΔG_{tot} in eq. 7a. Part of the problem is the obtainment of the relevant in-solution geometry.

In the molecular dynamics study by Hooft et al. [118] the geometry of each appearing conformer could change governed by the GROMOS force field. Their calculated G:T ratio is of about 67:33, with altogether 46% fraction for the conformers with a possible intramolecular hydrogen bond within the G conformers. The tG^+g^+ fraction of the G conformers is 20%. These values indicate about 31% internally hydrogen-bonded conformer for ethylene glycol considering the total distribution of the conformer population in aqueous solution, whereas the population of the tG^+g^+ structure without the internal hydrogen bond is about 13% as calculated on the same basis. Nagy et al. [119] found tG^+g^+ as the far most populated conformer out of the six considered structures. In contrast, Cramer and Truhlar [113] found 73-84% conformers with an intramolecular hydrogen bond. Thus the three simulations, performed in the early nineties, lead to remarkably different conclusions and call attention to revisit the problem by applying higher-level theoretical methods possible today.

2-F-ethanol and 2-NO_2-ethanol were studied by Nagy using the IEF-PCM method and calculating relative solvation free energies at the FEP/MC level [19]. Relative internal free energies were obtained at the ab initio IEF-PCM/CCSD(T)/CBS//IEF-PCM/B3LYP/6-311++G** and the IEF-PCM/B97D/aug-cc-pvtz levels, using geometries from optimizations in water and chloroform. The internally hydrogen-bonded OCCX (X=F, NO_2) gauche conformers were preferred over the gauche structure with a disrupted intramolecular hydrogen bond (HOCC ~ 180°). FEP/MC calculations using electrostatic-potential fitted CHELPG charges led to similar conclusion, however, the ΔG_{tot} free energy from eq. 7a differed up to about one kcal/mol by the two approaches. For 2-F ethanol, the OCCF gauche structure must be the predominant conformation in solution, since Pachler and Wessels [116] found only about 5% trans conformer experimentally.

2-substituted ethylamine: An aliphatic amine with protonation constant, pK_a of about 10-11 is protonated in pure water only a few percent with concentration 0.1 molar or larger. If biological conditions are considered, where the pH=7.4 is maintained in blood, these amines are protonated generally 93% or more [119]. Accordingly, in studying these molecules neutral and protonated forms deserve separate considerations.

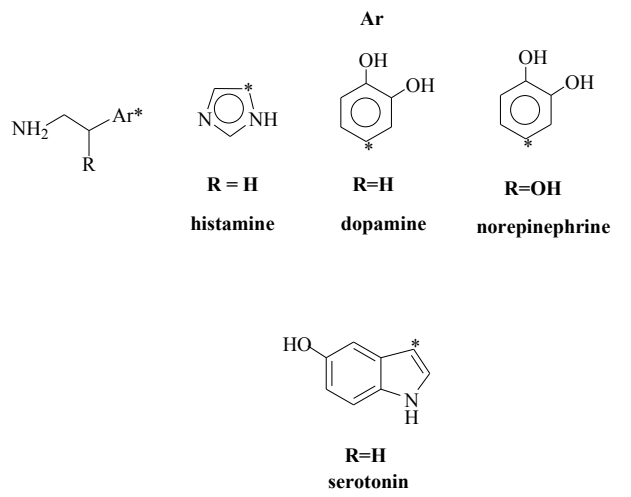
2-NH_2-ethylamine is the simplest saturated diamine with pK_a values of 10.71 and 7.56 [120] thus both amine groups are supposed to be largely protonated under biological conditions. Boudon and Wipff [121] calculated the torsional NCCN potential of the diprotonated species as a sum of the gas-phase HF/6-31G* energy and the relative solvation free energy from FEP calculations. Pair potential parameters, including atomic charges were taken from Jorgensen and Gao [122] who derived them for the methylammonium cation-water interactions using ab initio calculations. The gas-phase potential found a maximum at NCCN=0°, whereas the in-solution minimum free energy structure corresponds to the trans conformation, NCCN=180°. On the basis of the total energy curve, the gauche structure is higher in energy than the trans by 2-3 kcal/mol.

The gauche and trans monoprotonated structures were optimized at the IEF-PCM/B97D/aug-cc-pvtz level in aqueous and chloroform solutions [123] The gauche structure forms an intramolecular N-H^+…N hydrogen bond with H^+…N distance of 2.15-2.32 Å, and is more stable internally by 11–12 kcal/mol than the trans conformer in solution. Relative solvation free energies are 9.3 and 6.3 kcal/mol, however, in favor of the trans structure from IEF-PCM calculations in the two solvents, respectively. The FEP/MC relative free energy in aqueous solutions is 8.7 ± 0.2 kcal/mol, close to the PCM value, whereas the in-chloroform FEP/MC ΔG(solv) is less by 4 kcal/mol than the PCM value. In total, the gauche form is more stable than the trans by at least 3.3 kcal/mol in either solvent, leading to an almost exclusive presence of the internally hydrogen-bonded conformer in solution at T=298 K.

Conformational analysis for the neutral 2-OH-ethylamine (also can be considered as 2-aminoethanol) was recently performed at the IEF-PCM/CCSD(T)/CBS and IEF-PCM/B97D/CBS levels, in combination with FEP/MC simulations for the relative solvation free energy [19]. Two OCCN gauche structures with and without an intramolecular O-H…N hydrogen bond were considered for the neutral form in aqueous solution. Nonetheless, the OCCN trans conformer is the prevalent form with trans:gauche ratio of 93:7. The trans form shows some association even in an 0.22 molar aqueous solution, although no doubly hydrogen-bonded dimer was found upon potential of mean force calculations, in contrast to experiments for solutions upto 0.4 molar fraction for water [124]. The protonated gauche species is more stable internally ($\Delta E^s_{int}+\Delta G_{th}$) by 7.3-8.6 kcal/mol than the trans form as calculated at the IEF-PCM/B97D/aug-cc-pvtz level in chloroform and water [123]. The optimized gauche structure exhibits a N-H^+…O hydrogen bond with H^+…O distance of 2.38 and 2.41Å in water and chloroform, respectively. The NOOC torsion angle is about 60° in both solvents. The total relative free energy is at least 2.3 kcal/mol in favor of the gauche form, with a calculated fraction of 98% at least.

2-COOH-ethylamine is commonly known as the simplest β-amino acid. Details of a recent theoretical study [123] will be provided in relation to its neutral form/zwitterion equilibrium.

For the forthcoming discussion of neurotransmitters, structures are indicated in Scheme 1. Šolmajer et al. [125] studied the conformational equilibria experimentally for some neurotransmitters as dopamine (4-(2-aminoethyl)benzene-1,2-diol), norepinephrine (4-[(1*R*)-2-amino-1-hydroxyethyl]benzene-1,2-diol) and ephedrine ((R*,S*)-2-(methylamino)-1-phenylpropan-1-ol) in the pH range of 2.0-11.5. The molecules are protonated upto about pH=8 and gradually lose the proton in the range of pH=8-10. Above pH=11.5, less than 5% of the base is protonated. In the zero net charge form, alkylaminophenols exhibit a tautomeric equilibrium for the neutral and the zwitterionic species. This equilibrium always exists and makes the prediction of



Scheme1: The neurotransmitter derivatives of 2-ethylamine. The Ar group is shown, with an asterisk for the connection site of the aromatic ring. The R group is H except for norepinenephrine, where R = OH.

the conformer equilibria even more complicated in the non-acidic aqueous solutions. For example, the non-protonated species amounts to 3-7% for dopamine and norepinephrine at pH=7.4. The ratio of the zwitterion/neutral form is pH independent and is about 0.1 and 0.9 for dopamine and norepinephrine, respectively [126]. Population of the CCCN transformation is system dependent: it increases and decreases for dopamine and norepinephrine, respectively, with increasing pH.

Urban et al. [127] studied the conformational equilibrium for dopamine at the AM1 + AMSOL level, considering different protonation states in aqueous solution. For the protonated dopamine they calculated 63% population in comparison with the experimental value of 42% at pH=7.0. The trend was not predicted, however, correctly: the calculated trans fraction decreases with increasing pH in contrast to the experiment.

Alagona and Ghio [128] applied the PCM approach and used the HF/6-31G* ab initio level for predicting the conformer populations. On the basis of the relative G_{SCR} values and accepting two major gauche and one trans-conformer in aqueous solution, the predicted G:T ratio is 73:27 compared with the experimental of 58:42. Similar results, G:T at least 75:25 were obtained by Nagy et al. [129] when the gas-phase QCISD(T)/6-31G*//HF/6-31G* energies and FEP/MC relative solvation free energies were combined. For considering the counterion effect on the conformational equilibrium, a chloride cation was kept at a fix distance of 6 Å from the nitrogen atom.

Using the PCM method by Alagona and Ghio [130] at the HF/6-31G* and MP2/6-31G*//HF/6-31G* levels for studying the neutral and protonated norepinephrine in aqueous solution, different conformational preferences were estimated for the protonated species. HF and MP2 predicted ratios are T:G=89:11 and 44:56, respectively, in comparison with the experimental composition of 65:35 at pH =7.0 For the neutral species, the trans form is populated experimentally by about 59% (pH=11.5), whereas the calculated value is 61-72%. Theoretical calculations, however, did not take into consideration the zwitterion / neutral form tautomerism, which rises up to a ratio of 48:52 [126]. In their study, Alagona and Ghio investigated the effect of a strongly bound water molecule on the equilibrium geometry. Such studies are important for 1,2-disubstituted ethane molecules in a gauche conformation, because water can compete with the intramolecular hydrogen bond [5]. The published results do not compare the key intramolecular hydrogen-bond parameters and the change of the CCCN torsion angles for the pure norepinephrine and its monohydrate. In a recent study for 2F-ethanol [19], isomeric monohydrates have larger energy separations than the corresponding pure solute molecules in aqueous solution, whereas the OCCF torsion angle increased by about 3-4°.

The protonated form was studied by Nagy et al. [110] by the combination of the gas-phase MP2/6-31G*//HF/6-31G* relative internal free energies and the FEP/MC relative solvation free energies. Calculations were sensitive to the accepted solute geometry, which was determined through gas-phase monohydrate geometry optimization. Both the HF/6-31G* CCCN and OCCN torsion angles could change by upto 6°. The experimental composition at T=293 K° and pH=7.0 was T:G1:G2=65:24:11 in comparison with the theoretically obtained corresponding conformer population of 39: 29: 32 from a calculation modeling the aqueous solution at T=310 K° at pH=7.

Histamine (2-(1*H*-imidazol-4-yl)ethanamine) is the theoretically most thoroughly studied neurotransmitter to date. The nomenclature is not uniform in the literature. The code used in this review calls the imidazole nitrogen as N1 next to the carbon atom substituted by the ethylamino group (proximal), whereas N3 (distal) is separated by another carbon in the ring form the aliphatic chain. Recent and former determinations of the pK_a values for the amino group and the imidazole ring N as of 9.75-9.80 and 6.04-6.08, respectively, agree within the experimental error at T=25°C [119,131]. After earlier gas-phase computational studies, in-solution conformational and tautomeric equilibria have been calculated both for the neutral and protonated forms by different groups. Worth and Richards [132] investigated the imidazole 3H-1H tautomerism for the N-amino protonated species. A HF/6-31G*//HF/3-21G ab initio calculation referring to the intramolecular relative free energy in combination with FEP/molecular dynamics in explicit water (TIP3P model) resulted in an equilibrium constant of 6.7 within the experimental range of 2.3-9. Calculations needed careful charge parameterization and correction for the long-range electrostatic effects. Conformational/tautomeric equilibria in aqueous solution were predicted by Nagy et al. [133] by combination of gas-phase ab initio QCISD/6-31G*//HF/6-31G* and MP2/6-311++G**//HF/6-31G* calculations with FEP/MC estimation of the relative solvation free energies for the neutral and protonated histamine. The trans side-chain was predicted for the neutral form, whereas the gauche CCCN arrangement is the predominant for the protonated amine. In both states, the N3H imidazole was found as the favorable tautomer.

Karpińska et al. [134] applied a continuum solvent SCRF method at the MP2/6-31G level for assigning the most stable neutral and protonated structure in aqueous solution. They found that the N3H tautomer is dominant in water and the side chain takes a strong intramolecular hydrogen bond when histamine is protonated at the amino group. Ramirez et al. [135] studied the conformational/tautomeric equilibrium for the neutral form at the PCM/B3LYP/6-311G** level in aqueous solution. The study predicted almost exclusive presence of the N3H-gauche species. In the most comprehensive study, Raczyńska et al. [136] investigated all structural problems of histamine and compared with available experimental data. Theoretical calculations were performed in several solvents utilizing the PCM approach at the HF, MP2, and B3LYP levels with basis sets up to 6-311++G**. Their results indicate gauche-trans equilibrium for the

neutral N1H tautomer in aqueous solution, whereas the trans N3H form was found predominant for histamine protonated at the amino site. The comparison of the different experimental methods did not provide clear-cut preference for the dominant structures.

Forti et al. [137] published recently a paper describing a multilevel strategy for the exploration of the conformational flexibility of small molecules. As an application of the method, the neutral histamine was studied in the continuum solvent MST approach, using the B3LYP/6-31G*, MP2/aug-cc-pvdz and MP2/aug-cc-pvtz theoretical levels. Very remarkable is the basis-set and/or DFT/MP2 dependence of the calculated total trans/gauche ratio, changing from 64/36 to 48/52 from the B3LYP/6-31G* to the MP2/aug-cc-pvtz level. The N1/N3 ratio was predicted constantly as 48:52. Thus, in summary, structure predictions for histamine in aqueous solution have resulted in largely diverging predictions, mainly for the neutral form. Whereas the N3H structure is considered as predominant for histamine protonated on the $–NH_2$ group in aqueous solution, both experimental and computational results scatter in a wide range.

Structure analysis for serotonin (5-Hydroxytryptamine) was performed by Alagona et al. [138]. In contrast to norepinephrine and histamine, the $–NH_3$ group cannot form a strong, intramolecular $–NH_3$…O or $–NH_3$…N bond in any conformation of the molecule, thus the competition with a water solvent must have a smaller effect on the prevailing solute geometry in this case. By exploring the B3LYP/6-31G* potential map as a function of two key torsion angles, three main local minima (two CCCN gauche and one trans) were identified. Re-optimization of the structures in aqueous solution at the PCM/B3LYP/6-31G* level led to only small departures from the gas-phase torsion angles. Total relative free energies were estimated by considering FEP/MC solvation terms. Calculation results indicate sensitivity to the modeling parameters, whether CHELPG or RESP charges were applied and if a chloride counterion was also considered. The relative total free energies were within about 1 kcal/mol for a CCCN trans and gauche conformations, thus equilibrium with the presence of both conformers has been predicted for the protonated serotonin in aqueous solution. In a separate study [139], application of the IEF-PCM method for the aqueous solution resulted in conformer populations largely depending on the theoretical level. Whereas the HF method, using either the 6-31G* or the 6-311++G** basis sets predicts only up to 0.25 kcal/mol preference for a G conformation over the T, relative free energies are more negative by 1.6 kcal/mol comparing the more stable G and T conformers at the IEF-PCM/MP2/6-31G* level. As in most calculations for strongly polar/ionic solutes, consideration of an explicit water model in comparison with the polarizable continuum dielectric solvent approach could lead to predicted conformer populations largely deviating in cases when relative total free energies differ by no more than about 1 kcal/mol.

Ortho phenols: Ortho phenols (the substituent is next to the OH group on the benzene ring) show conformational variety if the neighboring group can be involved in an intramolecular hydrogen bond. Such groups are typically OH, OCH_3, COOH, NH_2, NO_2 and halogens. Stretching and torsional IR frequencies for the hydroxy group in $CDCl_3$, CCl_4, DMSO solvents for a number of 2-substituted phenols are provided [140-143].

Reynolds [144] estimated the relative free energies of several ortho substituted phenols and naphthols with OH and Cl substituents (and also sometimes with a third substitutent on the benzene ring) by means of combined MP2/gas-phase and FEP/MC calculations in aqueous solution. The relative free energies were utilized in predicting delete it electrode potentials for benzoquinones and naphthoquinones. Possible intramolecular hydrogen bonds were considered in aqueous solution for O-H…O-H, O-H…Cl and O-H…O= moieties. The internally hydrogen bonded form was found as more stable, with the exception for the O-H…Cl moiety.

Theoretical and experimental considerations of the conformation problem for ortho halogen phenols, prior to 2002, were summarized by Simperler et al. [140] and Silvi et al. [141]. The latter authors performed AM1 semiempirical gas-phase calculations and applied the SM4.5 approach for accounting for the solvent effects. The O-H…X (X=F, Cl, Br) cis conformer with the intramolecular hydrogen bond was found always of lower enthalpy than the trans-conformer with the disrupted hydrogen bond in the gas phase. CCl_4 solvates the transformation preferably; still the cis form remains the predominant conformer in a low-dielectric-constant solvent with relative enthalpy of –0.5 to –0.8 kcal/mol. Theoretically calculated OH stretching frequencies in the gas phase showed red shifts in the cis form compared with the trans structure. The experimental OH torsional frequencies showed a blue shift for the cis compared with the trans structure.

Microsolvation of o-methoxy and o-nitro-phenol by DMSO was theoretically studied by Litwinienko et al. [58]. Preference of the intramolecular O-H…O was predicted on the basis of B971/CBS relative enthalpies at T=298, accepting no entropy change upon conformational transformation for the o-phenol molecules. The o-phenol:DMSO adduct is still most stable with the O-H…O intramolecular hydrogen bond, whereas a bifurcated H-bond to the DMSO oxygen was formed. Nonetheless, disruption of the intramolecular hydrogen bond and the formation of an o-phenol… DMSO intermolecular bond are still feasible. This structure is only 1 kcal/mol higher in enthalpy than the most stable adduct. Without the stabilization by DMSO, the O-H…O bond disruption was predicted to need 5.4 kcal/mol. Interpretation of the experimental IR spectra in CCl_4 with increasing DMSO fraction is in accord with the theoretical results: DMSO does not disrupt the intramolecular hydrogen bond for o-methoxy phenol. Although the intramolecular hydrogen bond is still maintained in the most stable 1:1 o-nitrophenol : DMSO complexes according to the theoretical calculations and only bifurcated intermolecular bonds were predicted, interpretation of the IR spectra regarding the role of DMSO in interaction with o-nitrophenol is not straightforward. Role of one molecule DMSO in interaction with the 2,4-diformyl and 7-hydroxyindanone solute is different. It disrupts the intramolecular hydrogen bond for the former but not for the latter.

Relative acidities for ortho-substituted phenols were calculated by Himo et al. [145] in dielectrics with ε=4 and 80. The gas-phase geometries and energies were obtained at the B3LYP/6-311+G(2d,2p)// B3LYP/6-31G(d,p) level. Solvent effects were estimated on the basis of single-point SCI-PCM/B3LYP/6-311+G(2d,2p) calculations. The obtained trend for ΔpK_a relative to the parent phenol follows that from experimental values for $2CH_3$, $2SCH_3$, 2Cl, and $2NO_2$ derivatives, but is overestimated by 2–4 pK_a units for the o-chloro and o-nitro derivatives. The considered geometries corresponded to that for the lowest energy conformer, thus the possible conformational equilibria were not taken into account.

Conformational equilibria for 2F-, $2NH_2$-, $2NO_2$- phenols in chloroform and aqueous solutions were recently studied by Nagy [19]. The geometries were optimized at the IEF-PCM/B3LYP/6-311++G** and IEF-PCM/B97D/aug-cc-pvtz levels in the two solvents, obtaining nearly coplanar OCCX moieties. The relative free energies were calculated at the CCSD(T)/CBS and B97D/aug-cc-pvtz levels, applying

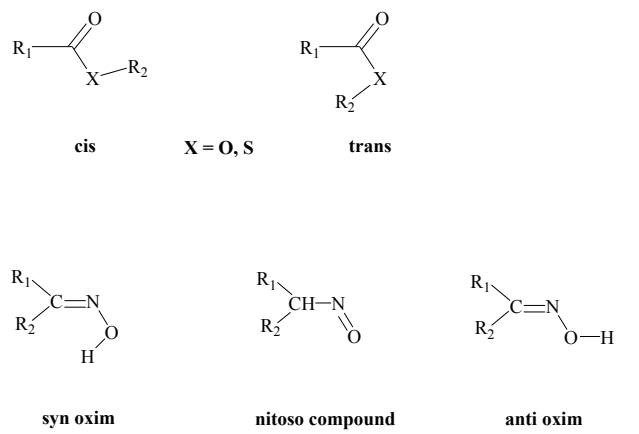
ΔG(solv) both from IEF-PCM and FEP/MC studies. The predominant conformers maintain the intramolecular O-H…X (X=F, O) hydrogen bond for the fluoro and nitro derivatives in both solvents. For the 2-NH_2 derivative, the hydroxy hydrogen is mostly free in chloroform, whereas a subtle equilibrium has been predicted for the O-H…N and N-H…O bonded systems in aqueous solution. The conformer without the intramolecular hydrogen bond in 2NO_2- phenol was predicted as providing an experimentally undetectable fraction in both solvents. The calculated O-H vibration frequency, taking the IEF-PCM/B97D/aug-cc-pvtz geometry, was in excellent agreement with the available data measured in chloroform solvent [143].

Conformational equilibrium for 2-COOH-phenol (salicylic acid, o-hydroxy benzoic acid) in aqueous solution was studied by Nagy et al. [146]. Geometries were optimized in the gas phase at the HF/6-31G* level, and relative internal free energies were calculated upon single-point calculations at the MP2/6-31G* level. Relative solvation free energies were estimated by means of the FEP/MC method. The conformer with the internal HOC=O…HO bond is the most stable in the gas phase. It still remains the prevailing structure even in aqueous solution with ΔG_{tot}=-1. 4 kcal/mol despite the relative solvent effect, ΔG(solv) of about 1.5 kcal/mol favoring the disruption the intramolecular hydrogen bond.

Other equilibria

Esters: Gas-phase studies predict that the O=C-O-C conformation of the (simple) esters is predominantly cis (Z) compared to the trans (E) structure. The relative energy, depending on the applied theoretical level is 7-10 kcal/mol. The question is, whether the dominating cis/Z preference is maintained in solution. For ester and oxim conformations (see next type of equilibria) general structures are shown in Scheme 2.

Alagona et al. [147], using the PCM method found that the gas-phase relative free energy for methyl formate decreases by about four kcal/mol on the basis of 4-31G calculations for systems with dielectric constants changing from ε=1 to 78.5. Wiberg and Wong [148] applied the SCRF solvation model and the MP2/6-31+G** level of theory when spherical cavities were applied for the methyl formate and methyl acetate solutes. Considering the relative free energies in the gas-phase and acetonitrile solution, the cis/Z conformer was found more stable in both phases for methyl formate, but the relative ΔG_{tot} decreased from 5.2 to 1.7 kcal/mol upon solvation. The corresponding ΔG_{tot} values for methyl acetate are 8.5 and 5.2 kcal/mol, respectively. The predicted gas-phase activation energy for the conformational change of about 13 kcal/mol at the barrier top with O=C-O-C torsion angle of 90-100°, decreases by about 2 kcal/mol in acetontirile.



Scheme 2: Oxo- and thio-esters, and oxime conformations. The nitroso compound is a stable isomer/tautomer of an oxim, which could facilitate the R_2C=NO(H) cis to trans transformation (not indicated).

Evanseck et al. [149] calculated the Z/E conformational free energy difference for methyl acetate in acetonitrile and aqueous solution. Using the OPLS 12-6-1 pair potential for calculating the atom-atom interaction energies in different molecules, the united methyl atom model for the ester, and the TIP4P water model, FEP/MC calculations were carried at 25°C and at p=1 atm in the isothermal-isobaric ensemble. The relative solvation free energy is –2.7 ± 0.1 and –3.0 ± 0.2 kcal/mol in favor of the E form in acetonitrile and aqueous solution, respectively. These computed values still leave the cis(Z) form almost exclusively existing in solution.

Byun et al. [150] studied the cis-trans equilibrium for methyl acetate applying a QM/MM method in aqueous solution. Adopting a dual-level molecular dynamics technique (B3LYP/aug-cc-pvdz level in the gas-phase in combination with HF/3-21G:TIP3P simulations for estimating the change in the solvation term) they found that the gas-phase relative free energy of 7.6 kcal/mol for the trans (E) form decreases by 4.4 ± 0.5 kcal/mol in aqueous solution. In solution, induced dipole moments of about 0.6 and 1.4 D for the Z and E conformers, respectively, indicate larger polarization of the E compared with the Z conformer. The torsional barrier decreases from its gas-phase value by about 3 kcal/mol to 10.5 kcal/mol in aqueous solution.

In both of the above two studies, the increased acidity of the E conformer in aqueous solution was studied by considering the methyl acetate anion. Evanseck et al. [149] found the solvent effects of 1.5 ± 0.2 and 2.3 ± 0.2 kcal/mol in favor of the E anion in acetonitrile and water, respectively. Byun et al. [150] found the E anion stabilization by 3.5 ± 0.5 kcal/mol in aqueous solution. This latter average value allows the slight dominance of the E anion over the Z form in solution, considering the Z preference by only 3.2 kcal/mol in the gas phase.

The CH_3COXCH_3 cis-trans conformational equilibria for the oxo- and thioester (X=O, S) were studied by Nagy et al. [47] in the gas-phase and in solution at the B3LYP/6-311++G** level. The trans form is higher in free energy than the cis by 8.1 and 6.1 kcal/mol in the gas phase for the oxo and thioester, respectively. Relative free energies in chloroform, acetone, acetonitrile and water were calculated upon single-point PCM calculations. Solvents always interact with the trans rather than the cis form more preferably. The solute polarization energy is larger by up to 1 kcal/mol for the trans compared with the cis conformer, providing the basis for the more negative G(solv) for the former. Nonetheless, the overall total relative free energy favors the planar cis conformation in the studied solvents by at least 5 and 4 kcal/mol for methyl acetate and methyl thioacetate, respectively. The gas–phase B3LYP/6-311++G** energy barrier for the cis-trans interconversion decreases from 13.1 to 12.1 kcal/mol for methyl acetate in water, whereas the corresponding values for methyl thioacetate are 13.1 and 12.9 kcal/mol.

In contrast to those regarding the above simple esters, more complicated conformational equilibria were found by Coriani et al. [151] for the stereoisomers of the ROOC substituted γ-butyrolactone (R = CH_3, C_2H_5) in the gas phase and methanol. Having also a neighboring methyl ring substituent, 5 and 15 conformers were identified in the gas-phase with R = CH_3 and C_2H_5, respectively. Unfortunately, the conformations do not reveal from the paper (but are available from the authors upon request). The large number of the conformers for

the ethyl ester must account for differences not only in the structure of the ester group, but also due to the rotation of the CH_3 end-group in the ethyl group, as well as from different puckered structures for the γ-butyrolactone ring. However, comparison of the conformer populations in the gas phase and in methanol (obtained upon PCM/B3LYP/6-31G** optimizations and finding 5 and 14 conformers for the esters above) reveals the large solvent effect on the equilibrium systems. Consideration of the solvent effect and weighted individual conformer contributions were necessary in order to obtain total optical rotatory power in accord with the experimental values.

Rincon et al. [152] studied the conformations of two ester groups for cocaine both in the gas phase and in aqueous solution with optimization at the PCM/B3LYP/6-31G** level in the latter case. Two and one low-energy conformations were identified in the gas-phase and in solution, respectively. The ester groups adopted almost coplanar cis conformations and the solvent effect was negligible on the torsion angles. Low-energy conformers for the ecgonine methyl ester, a metabolized derivative of cocaine, when the benzoyl ester is hydrolyzed showed similar structural features. Nonetheless, the authors argue that the "benzoyloxy group restricts the accessible conformational space" in the cis-ester conformation region. As a consequence, an intermolecular N-H…O= bond becomes stronger and affects the distribution of the conformer populations.

Oximes/nitroso compounds: Oximes and nitroso compounds form tautomeric systems. Oximes have a general structure of $R_1C(R_2)$=N-OH, whereas if the proton jumps to the indicated carbon atom, the $R_1CH(R_2)$-N=O nitroso tautomer comes into existence. A few paper deals with this tautomeric change theoretically, whereas most results have been published for the conformational equilibria of oximes, regarding the C=N-O-H torsion angle. This angle is primarily near to 0 or 180° corresponding to the syn and the anti conformer, respectively.

Depending on the R groups connecting to the C atom, oximes are categorized as aldoximes (R_1=H) or ketoximes, where both R's are alklyl/aryl groups. The R-C=N-O torsion angles are close to 0 or 180° (Z/E isomers). According to the definition assumed in the Introduction, rotation about the N-O bond for the oximes is a conformational issue, whereas the Z and E structures form cis-trans isomers. Since Z and E free energies differ, however, only slightly for many systems, their interconversion could be thermodynamically allowed. Speculations about the possible route can be found in the literature, and could be summarized so that although the direct thermal rotation about the C=N double bond would require large activation energy, a tautomeric change to the nitroso compound or nitrone (the O-H proton moves to the nitrogen and results in a formally single C-N bond) would facilitate the rotation about the formally single C-N bond. This way the more stable R-C-N-O conformer can be formed or a Z/E equilibrium can develop. Finally the proton gets back to the O atom and the C=N double bond is formed again.

Experimental studies were reported in a series of papers by Karabatsos et al. [153] back into the sixties. Considering simple oximes in neat liquids, acetonitrile, and CCl_4, the authors found an increasing R_1-C=N-O fraction of about 0° torsion angle (R_1=H, methyl, ethyl, isopropyl) with more bulkier R_2 groups. For aldoximes (R_1=H) the isomer ratio varies between about 1:2 and 2:1 depending on R_2, for ketoximes the $(H_3)CC(R_2)NO$ ~ 0° isomer is predominant. The C=N-O-H conformation was predicted between 90° and 180°.

High-theoretical-level gas-phase studies for the simplest aldoxime, H_2C=N-O-H [154] found the HONC ~ 0° form preferable over the nitrosomethane, CH_3-N=O tautomer by more than 10 kcal/mol. The system was studied by Long et al. both in the gas phase and in aqueous solution [155]. The gas-phase nitroso compound was calculated higher in energy by 12-13 kcal/mol than the anti(s-trans) oxime, and if two explicit water molecules are considered in SCIPCM/MP2/6-311++G** and /B3LYP/6-311++G** calculations, the relative nitrosomethane energy further increases by 3-5 kcal/mol. The syn(s-cis) C=N-O-H conformer is higher in energy than the trans species by 5-6 kcal/mol in the gas phase.

Utilizing the results above, Nagy studied the C=N-O-H anti (trans) formaldoxime - nitrosomethane relative free energies in dichloromethane, methanol, and water [110]. IEF-PCM/QCISD(T)/CBS and /B3LYP/aug-cc-pvtz relative free energies varied in the 12.5-13.3 kcal/mol range. Considering the relative solvation free energy calculated upon explicit solvent FEP/MC calculations with B3LYP/aug-cc-pvtz charge parameterization, ΔG_{tot} increased by about 2 kcal/mol in aqueous solution, indicating that consideration of explicit water molecules in the vicinity of solutes increases the relative free energy of nitrosomethane, a conclusion in qualitative agreement with those by Long et al. [155].

Enchev et al. [156,157] studied the conformational/tautomeric issue quantum mechanically for acenaphthenequinonemonooxime and ortho-nitrosonaphthols. For the former, 6-31G**+Onsager (SCRF) calculations predict the oxime form much more stable than the nitroso tautomer in CCl_4 and DMSO, although NMR spectroscopy found both tautomers existing in solution. The oxime was theoretically predicted to adopt both syn and anti C=N-O-H conformations separated by about 1.4 kcal/mol in the gas phase, and the energy separation decreases in solution. Ivanova and Enchev [157] found, however, only the oxime form existing for 1-nitroso-2-naphtol and 2-nitroso-1-naphtol on the basis of PCM/6-31G* calculations for solutions in $CHCl_3$ and DMSO. The oximes can adopt both C=N-O-H syn and anti conformations in equilibrium.

The C=N-O-H syn/anti conformational equilibrium was considered for codeine-6-one oxime and its 7,8-dihydro derivative at the PCM/B3LYP/6-31G* level in chloroform and in the water/acetonitrile 85:15 mixture [158]. The predicted equilibrium ratio was slightly underestimated on the basis of ΔG_{tot} for codeine-6-one oxime as compared with that from experiments by NMR spectroscopy, but was in good agreement with the HPLC determined composition in water/acetonitrile mixture. Calculations predicted more than 90% anti C=N-O-H conformer in both solvents, whereas experiments showed that practically only the anti conformer exists in solution. The shift of the conformer ratio was attributed to the remarkable geometric change in the connecting ring upon hydrogenation.

The theoretical conformational and configurational analysis of an *N,N* carbonyl dipyrrinone-derived oximate and nitrone was performed by Walton et al. [159]. The analysis was based on the comparison of the experimental and calculated proton NMR shifts, obtained theoretically by means of the B3LYP/6-311++G(2d,2p), and the gauge-independent atomic orbitals methods (GIAO). A self-consistent reaction field model was applied for simulating the solvent effect of DMSO. The authors determined the position of the –CH=N-O-H oxime chain and the –$CH=NH^+$-O^- nitrone chain relative to the three-ring system. Relative energies between C=N-O-H syn and anti conformers were found small, about 0.3 kcal/mol for the lowest two conformers in DMSO. The theoretically calculated NMR shifts agreed well with the experimental values.

γ-substituted aliphatic acids: Four rotatable sigma bonds in γ-substituted aliphatic acids allow for 4^3=81 main conformations with individual torsional angles of about +/-60° and 180°. Although a full exploration of the potential energy hypersurface is possible already nowadays, computer resources confined the theoretical calculations to the consideration of some "reasonable" geometries in the past decades. A principle could be considering structures with intramolecular hydrogen bonds, although in aqueous solutions the non-hydrogen-bonded structures could be also populated. Recent gas-phase studies for 1,5-pentadiol and 1,6-hexadiol [160] found prevailing conformations without an intramolecular hydrogen bond. An X-CH_2-CH_2-CH_2-COOH structure (X=OH, NH_2) with an aliphatic C_3 spacer could represent a borderline case. X=NH_2 allows for a zwitterion/neutral form equilibrium in protic solvents, making the theoretical predictions far more complicated.

For γ-hydroxybutyric acid, GHB, no zwitterion can come into existence, and the study of the neutral form in aqueous solution is reasonable [161]. Considering the pK_a of 4.46 ± 0.01 at T = 25°C [162], about 98% of the solute takes the non-dissociated form in a 0.1 molar aqueous solution. Optimizing eight structures at the HF/6-311++G** and MP2/6-311++G** levels in the gas phase [161], the torsional angles generally differ only by a few degrees, but the deviations for the H…O distances in intramolecular hydrogen bonds could amount to more than 0.2 Å. Whereas the intramolecular OH…O=COH bond stabilizes a seven-member ring in the gas phase, the two prevailing in-water conformers correspond to extended-chain structures upon consideration of the FEP/MC relative solvation free energies. The extended rather than the internally bound conformation was found also in a mixed organic solvent with molar composition of MeOH:$CHCl_3$ = 2:1.

The structure of γ-aminobutyric acid (GABA) in water was studied by Ramek and Nagy [163]. Relative gas-phase free energies were calculated at the MP2/6-311++G**//HF/6-311++G** level. The in-solution relative free energies were obtained as a sum of the gas-phase ΔG and ΔG (solv) from FEP/MC calculations. GABA exists in the neutral form in the gas phase, thus structure determination for the optimized free zwitterionic tautomer is not possible directly. Accordingly, the zwitterionic dihydrate conformers were determined and the solute geometry itself was applied in FEP/MC. Ultimately five neutral and three zwitterionic structures were studied in aqueous solution, and a fairly extended zwitterionic form was found as far the most stable GABA species.

Crittenden et al. [63] determined the relative free energies of nine neutral and nine zwitterionic tautomers/conformers at the MP2/6-31+G*//B3LYP/6-31+G* level, optimizing the structures by means of the COSMO reaction field method in continuum water. All zwitterionic forms turned out to be more stable by at least 16 kcal/mol than the neutral structures, and the two most stable zwitterionic conformers are stabilized by intramolecular NH^+…$^-$OCO hydrogen bonds. If, however, the gas-phase dihydrates were solvated, fairly extended conformers are exclusively populated, in line with the results of Ramek and Nagy above.

Relative partition coefficients of GHB and GABA were theoretically calculated for the chloroform/water and dichloromethane/water partitions [162]. The geometry for the neutral GABA was reoptimized in the gas phase at the HF/6-311++G** level, as such geometry must be closer to the real one in a slightly polar solvent than the dihydrate obtained [163]. Calculating relative solvation free energies through FEP/MC simulations for the different conformers, the predicted relative log P for the neutral GABA does not differ significantly from the GHB value for the chloroform/water partitioning. The calculated log P for the neutral GABA increases when the solvent is the more polar dichloromethane rather than chloroform. Large, 17-23 kcal/mol activation free energy was predicted for the direct partitioning of the zwitterionic GABA into the studied organic solvents.

Aryl/alkyl disubstituted guanidines: Conformational equilibria for the neutral and protonated diphenyl-guanidine were studied by Alagona et al. [164]. Relative internal free energies were calculated at the MP2/4-31G//HF/4-31G level in the gas phase, whereas single point PCM/HF/4-31G calculations were performed for calculating total in-water free energies. Relative values were compared with AMBER//GB/SA results. Both sets of calculations predict the predominance of the anti-syn arrangement of the phenyl rings for the neutral form, whereas the syn-syn phenyl arrangement is the most preferred for the cation.

The prevailing protonation state is, however, the monocation. Using the HF/4-31G gas-phase geometries above, Nagy and Durant [165] estimated the relative rotamer free energies for the diphenyl-guanidinium cation in aqueous solution as a sum of the relative MP2/6-31G* internal free energies and ΔG(solv) from FEP/MC calculations. Small free energy difference was predicted for the symmetrical, $H_2NC^+(NHPh)_2$ anti-anti phenyl (most preferred) and syn-syn rotamers. Definitely larger, at least 1.3 kcal/mol relative free energy was predicted for the anti-anti and anti-syn conformers. The predicted ΔG(solv) sensitively depends on the accepted atomic charge sets. Furthermore, a close acetate or chloride counterion (R = 4.6 Å) stably held in this relative position largely stabilizes the NC^+NC(Ph) anti-anti rotamer. The counterion effect becomes nearly negligible only at about R = 12 Å. Recent studies suggest, however, that a free chloride counterion would wander in the solution and takes sometimes a hydrogen bond with the cation, whereas the cation – anion distance may increase temporarily even to about 14 Å in a dilute solution [37,41,42,112].

Although it is not a conformational issue, the potential of mean force (pmf) calculations by Soetens et al. [166] for a pair of two guanidium ions should be mentioned here in relation to the discussion above. Such a pmf helps understand the arginine-arginine interaction in proteins. The study focused on the role of the important effect of polarizability on the determined pmf in aqueous solution. The results indicated the stability both of the contact and solvent separated cation pair, with stabilization free energy strongly depending on the applied water models.

Alagona et al. [167] investigated the conformational equilibria for the neutral and protonated **N,N'**-dimethyl- and N-methyl,N'-acetyl guanidine in aqueous and chloroform solutions by means of PCM/MP2/6-311++G**//MP2/6-31G*(gas) calculations. Considering a number of structural isomers and combinations of the syn and anti positions of the substituents with respect to the H_2N-C bond, two conformers have been found for each studied neutral species separated by 0.6-1.2 kcal/mol both in chloroform and water, forming thus equilibrium of two comparable fractions. The syn-syn and syn-anti substituent positions with respect to the H_2N-C^+ bond are almost equally populated for the cations in chloroform, whereas the syn-syn structure is prevailing in water. Partitionig between chloroform and water must be largely shifted toward the in-water dissolution even for the neutral species. An acetyl instead of a methyl substituent of guanidine would increase the log P value by about a unit.

Peroxynitrate: Peroxynitrite, O=N-O-O$^-$ is a stable anion in a biological medium, whereas the parent acid, HOONO has only a short lifetime at neutral pH and isomerizes to nitric acid. Due to the limited interest at present, the first high-level theoretical study on the conformation of HOONO in aqueous solution was performed only in 2000 by Doclo and Rothlisberger [168]. These authors carried out first-principles molecular dynamics study at the BLYP level, considering Kohn-Sham orbitals expanded in plane waves. One solute and 52 water molecules were considered, and the relative Helmholtz free energy was determined along the ONOO torsion potential curve. The relative energy difference is 15 ± 5 kJ/mol in favor of the ONOO cis conformer compared with the trans, whereas the barrier for the isomerization is 89 ± 10 kJ/mol at T = 300 K°. The NOOH torsion angle was calculated as varying between 79-108° through the conformational change. No intramolecular O…HO bond was predicted at any ONOO arrangement.

The structure of the stable ONOO$^-$ species in aqueous solution was investigated by Tsai et al. [169] at the SCI-PCM/B3LYP/6-311+G* level. The cis form was found more stable than the trans by 4.4 kcal/mol. Nagy [170] compared relative free energies in aqueous solution at the SCI-PCM/B3LYP/6-311+G* optimized geometries, whereas relative solvation free energies were calculated both in the polarizable continuum solvent approach and from FEP/MC. Whereas the SCI-PCM calculations predict a relative free energy of 4.3 kcal/mol for the trans form, FEP/MC solvation-based free energies scatter in the range of ΔG_{tot}=1.8–8.3 kcal/mol, strongly depending on the accepted atomic charge sets. Nonetheless, any calculation predicts the overwhelming cis preference.

Ring inversion: Cyclohexane is known to adopt the chair conformation as its most stable structure. The much less stable twist-boat (skew) conformation is calculated generally higher in energy by about 6 kcal/mol in the gas phase depending on the applied method. Having a ring substituent, it takes the equatorial position according to the consensus, and can reach it through chair/twist-boat/chair series of ring inversions if needed. The chair/twist-boat equilibrium is much more important for disubstituted derivatives. For some isomers, it is impossible to take the equatorial position for each substituent at a time. In this case, the system should undergo a series of conformational changes along the chair/twist-boat/chair path in order to provide the equatorial position to the substituent, which assures the lower total free energy for the system. If the saturated ring includes one or more heteroatoms, the problem is more complicated because the heteroatom interacting with a substituent may stabilize some twist-boat structure. The role of the solvent is important and may remarkably affect the activation free energy. Furthermore, as revealed from the paper of de Oliveira et al. [106], the solute concentration also affects the equilibrium composition.

Nagy and coworkers studied the problem through the alternative protonation for saturated heterocycles with two nitrogens and for the neutral 1,4-dioxane. The relative internal energy for N-methyl-piperazine protonated at the secondary (Ns) rather than the tertiary nitrogen (Nt) is 4.6 kcal/mol, as calculated at B3LYP/6-311++G**//B3LYP/6-31G* level in aqueous solution, considering the chair (ch) ring conformation [41]. The respective Ns and Nt relative internal energies are 8.1 and 3.5 kcal/mol with the twist-boat (tb) ring conformation. Formation of an intramolecular (N)H…N hydrogen bond with length of about 2.4 Å is feasible for the twisted ring species. Although the protonation site causes energy differences also of 4.6 kcal/mol for the tb species, the difference is fully compensated by the solvation energies of -2.0 and +2.6 kcal/mol, respectively. Overall, each tb form is higher in free energy than the most stable Nt protonated chair structure by about 6 kcal/mol in aqueous solution (ΔG_{drc} is small). In dichloromethane, similar calculations predicted 5.6-6.2 kcal/mol total relative energy for twist-boat rings.

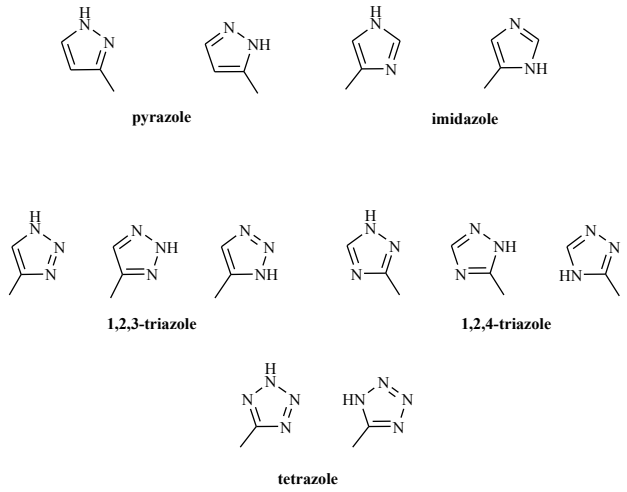
The tb structure is higher in relative total free energy by 6.5-6.8 kcal/mol than the chair form, as calculated for 1,4-dioxane at the IEF-PCM/B3LYP/6-31G* level in water [171]. The internal energy relative to the chair form is 7.0-7.3 kcal/mol. The increased ΔE_{int} compared with that for N-methyl-piperazine is due to the structural peculiarity that there are two oxygen lone pairs facing each other for dioxane in contrast to the intramolecular hydrogen bond in the twist-boat protonated N-methyl-piperazine.

Tautomeric Equilibria

Intramolecular proton relocation

Aromatic heterocycles: Perhaps the best-known examples for the proton-relocation tautomeric processes are those for five- and six-member heterocycles and their condensed derivatives. The subject of the present review is the in-solution equilibrium, thus many theoretical calculations having been performed for gas-phase systems [172,173] are not considered. Intramolecular proton relocation requires generally relatively large activation energy. In protic solution, however, a solvent-catalyzed mechanism is possible, and as a first step for exploring the relevant relocation path, gas-phase microsolvation studies are useful [58-61]. Structures of some heterocycles to be discussed below are shown in Scheme 3.

The N-H…N tautomerism for 3-OH pyrazole was studied by Parchment et al. [174] and Cao et al. [175] both by means of the continuum solvent approximation and considering the FEP method. The relative free energies for 1,2,3- and 1,2,4-triazoles were studied by Cox et al. [176] and Murdock et al. [177] utilizing the free energy perturbation and thermodynamic integration methods. Wong et al. [178] investigated the in-solution behavior of tetrazole by means of a continuum solvent approach.



Scheme 3: Methyl substituted azoles. The indicated structures are of different internal energies and distinguishable. For triazoles, the two possible sites for methyl substitution are equivalent. Each of 3-methyl pyrazole and 4-methyl imidazole has two tautomers of different energies. The tautomeric trasformation for the 4-methyl pyrazole and the 2-methyl imidazole leads to an indistinguishable new molecule.

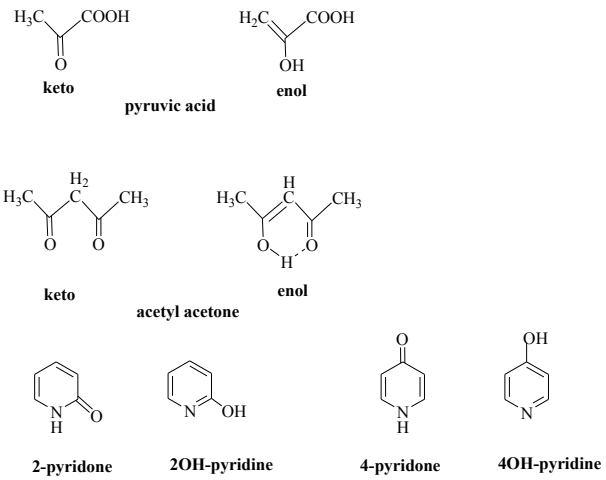
Nagy et al. [179] studied in-solution equilibria for a full family of the asymmetrically methyl-substituted five-member heterocycles with 2-4 nitrogen atoms. Calculated IEF-PCM/B3LYP/6-311++G**// IEF-PCM/B3LYP/6-31G* relative free energies differ generally only by a few tenths of a kcal/mol for the two most stable tautomers of heterocycles with two and three nitrogen atoms in $CHCl_3$, CH_3COCH_3, CH_3OH and water. Larger differences emerge for tetrazole derivatives. The derived ΔG_{tot}, however, depends on the accepted ΔG(solv) term. Relative solvation free energies from continuum solvent and FEP/MC calculations could deviate by up to about 3 kcal/mol resulting in even the change of the preference for the prevailing tautomeric form.

Using the PCM/B3LYP/6-31+G** level of theory, Abdalla and Springborg [180] studied different isomers and tautomers for methylphosphino- and phenylphosphino-substituted cyclic imidazoline, oxazoline, and thiazoline. Inclusion of three explicit water molecules changed the preference of the tautomers and/or modified their relative energies in aqueous solution. Consideration of bound water molecules, which allows for accounting for solute-solvent hydrogen bonds, apparently largely affects relative tautomer stabilities. Thus, like above, explicit consideration of the water solvent may be decisive in studying tautomeric equilibria for systems capable of forming intermolecular hydrogen bonds.

Tautomeric paths may be easily devised for molecules with favorable geometric arrangements for a solute dimer. Even in the absence of a favorable geometric fit, a network of protic solvent molecules or, *e.g.*, solvents with a hydrogen-bond acceptor O= group like acetone and DMSO, could catalyze the pick-up of the proton at the less favorable site. After a series of proton jumps along a solvent network, the more favorable site would be protonated [62]. Such mechanism is, however, hardly imaginable in slightly polar solvents as $CHCl_3$. Nagy et al. [179] proposed a possible mechanism for a number of associated solutes in chloroform solvent, where the proton jumps from one neighbor to the other as the current flows in a ring. This idea was originally raised by Kikalishvili and Kereselidze [181], who performed semiemepirical AM1 calculatiosn for an imidazole trimer in the gas phase. The model predicted N…H distances and N-H…N bond angles of 2.94 Å and 154.3°, respectively.

Oxo/hydroxy tautomerism: Such tautomerism is well known both for heterocycles and aliphatic systems. The 2-OH-pyridine/2-pyridone equilibrium is a classical example (Scheme 4). In the first successful combination of the ab initio relative internal free energy with the relative solvation free energy calculated by means of the FEP method (in a molecular dynamics application), Cieplak et al. [182] pointed out the shift of the hydroxy preference in the gas phase toward the 2-pyridone structure in aqueous solution. Despite the uncertainties in the calculations, the trend was well demonstrated in accord with the experimental results. The same study produced qualitative agreement with the experimental values, predicted correctly the prevalent tautomer of 2OH-pyrimidine and cytosine in solution. The solvent effect is decisive in both cases: stabilizes the keto form for 2OH-pyrimidine opposite to the gas-phase preference, and makes the amino tautomer exclusive in solution for cytosine.

Wong et al. [183] calculated the relative free energies in the gas phase, and in cyclohexane and acetonitrile solvents. Very good agreement with the experimental values was obtained if the gas-phase relative energy was calculated at the QCISD/6-31+G** level. Ab initio SCRF solvation energy calculations pointed out the gradual stabilization of the keto form with larger dipole moment in dielectrics characterized by ε=2 and 36.



Scheme 4: Keto-enol and oxo-hydroxy tautomers.

The effect of the polarization of the solute by the solvent was emphasized by Gao and Shao [184] on the basis of QM/MM Monte Carlo simulations in water and chloroform. The calculated relative free energies were close to the experimental values. The trends of the solvation free energies (also calculated for the 4-pyridone system, see below) were found to be consistent with the in-solution dipole moments. The polarization effect is particularly large for systems with conjugated π delocalization.

Wang and Boyd [185] studied the 2-, 3-, 4-OH pyridine/pyridone equilibrium at the ab inito SCRF level. Using the gas-phase HF/6-31G** optimized geometries, the calculations predicted the stability of the pyridone form for each of the 2-OH and 4-OH isomers both in chloroform and acetonitrile, in accord with the experimental findings. In the low polarity cyclohexane, however, the calculated 2-hydroxypyridine preference is in contrast to the experimental data. The authors only emphasize that the tautomer preference is opposite in cyclohexane compared with chloroform and water. Furthermore, quite disappointing is that the MP2/6-31+G**-based relative energies were in contrast to the experiment in all cases. For the 3-OH isomer, the calculations unanimously predicted the stability of the hydroxy form in all three solvents, but no experimental data were published for comparison.

The 4-OH-pyridine/4-pyridone equilibrium was studied by Nagy et al. [35] in tetrahydrofuran (THF), methanol and water up to the IEF-PCM/B3LYP/6-311++G** level. Both the gas phase and the in-solution relative free energies are close to the experimental values. The hydroxy form is prevailing in the gas phase, whereas a large solvent effect makes the keto form exclusive in aqueous solution. The FEP/MC relative solvation free energies are less and more negative by 2-4 kcal/mol in THF and water, respectively. Provided a non-negligible basis set effect for the internal energy, as well, only the stabilization of the 4-pyridone form in aqueous solution is obvious from the calculations.

Analogue to the above problems is the tautomerism of 3-OH- and 5-OH-isoxazole with a five-member aromatic ring. Proper handling of the electron correlation effect for the ring moiety O-N must be, however, challenging. Woodcock et al. [186] studied the problem by considering FEP/MD, PCM and ab initio/SCRF continuum solvent methods with relative gas-phase internal energies at the MP4/6-31G**//HF/3-21G level. Each method predicted the preference of the

hydroxy form of 3-OH-isoxazole both in the gas-phase and in solution, in agreement with the experiment. The ab initio method predicted a conformational change for the 3-OH-isoxazole upon considerable increase of the dipole moment through solvation of the N=C-O-H anti conformer. Only the ab initio/SCRF continuum solvent method could predict the preference of the 2H-oxo form of 5-OH-isoxazole in solution, in agreement with the experimental results. This latter problem was revisited by Gould and Hillier [187], where both the ab initio/SCRF and the PCM approaches produced the largest stability for the 2H-oxo tautomer by about 1.2 kcal/mol compared with the second stable 4H-oxo form. The agreement seems to stem from a beyond-dipole approximation in the SCRF method and new cavity parameters in PCM calculations. The level of theory for estimating the relative gas-phase energy is crucial in the above problem, as revealed from the tautomerization study by Cramer and Truhlar [188] for 5-OH-isoxazole and its methyl- and dimethyl derivatives. Gas-phase calculations were performed up to the CCSD(T)/cc-pvdz//MP2/cc-pvdz and CCSD/aug-cc-pvdz//MP2/cc-pvdz levels. Results obtained with AM1-SM1a and AM1-SM2 solvation models were compared with those from the SCRF/Onsager and PCM solvation free energies for the 5-OH-isoxazole tautomers/conformers. After a thorough analysis of the possible uncertainties in the calculations, these authors predicted the 4H-oxo form of 5-OH-isoxazole prevailing in aqueous solution. The preference is gradually shifted toward the 2H-oxo tautomer upon ring substitution by one and two methyl groups, based on, however, corrected AM1 gas-phase relative energies.

Quinone/enol equilibria in parallel with amine-imine tautomerization emerge for ortho-hydroxy-naphthaldehyde anils [189]. Relative internal energies were calculated at the IEF-PCM/QCISD(T)/6-31G*//IEF-PCM/B3LYP/6-31G** level. Single-point IEF-PCM/B3LYP/6-311++G** and IEF-PCM/MP2/6-311++G** relative energies provided too negative and positive values, respectively, in comparison with the experimental data. A combination of the QCISD(T) relative internal energy with the relative solvation free energy from FEM/MC calculations predicted fair and good agreement for the equilibrium constants in methanol, acetonitrile, and carbon tetrachloride.

The enolimine – ketoenamine equilibrium was studied by Sahoo et al. [190] for a Schiff base derived from pyridoxal and o-phenylenediamine. The quantum chemical calculations were performed at the DFT/B3LYP level with basis sets up to 6-311++G**, and the solvent effect was considered at the SCRF=CPCM level both for the neutral and the protonated forms of the solute. Molecular geometries were optimized at the B3LYP/6-31G** level in water, ethanol and chloroform. Protonation has a dramatic effect on the equilibrium composition. Whearas the neutral ketoenamine form is higher in energy by 2.37-2.80 kcal/mol in solution (increasing dielectric constant decreases the relative energy), the protonated ketoenamine is higher energy than the enolimine form only by 0.13, 0.24, and 0.26 kcal/mol in chloroform, ethanol, and water, respectively. The calculated values predict that the neutral Schiff base exists almost exclusively in the enolimine form in solution, whereas the protonated solute exhibits an observable equilibrium with the ketoenamine fraction of 39-45% in the different solvents, as calculated by the approximation $\Delta E \approx \Delta G^{o}$.

For aliphatic systems, the corresponding equilibria are generally called as keto-enol tautomerism (Scheme 4). It can emerge for any system with a carbonyl group next to a CH_2 group. The keto form is the more stable species (see, e. g. the acetaldehyde – vinylalcohol equilibrium) most of the time but a subtle equilibrium can come into existence for the classical β-diketone system, acetylacetone. The keto-enol form with an intramolecular O-H…O= hydrogen bond is the stable tautomer in the gas phase and in several organic solvents [105]. In aqueous solution, however, the diketo form is the prevailing tautomer.

In-solution relative free energies have been calculated by several groups using different methods. Eventually, Schlund et al. [191] concluded that even high-level theoretical calculations within the PCM framework cannot predict the preference of the diketo form of acetylacetone in water. By using the RISM-SCF theorem, a quite different approach, Ishida et al. [192] succeeded in calculating the diketo preference in water, but in contrast, the method failed for correctly predicting the predominant gas-phase structure and strongly overestimated the prevailing tautomer in CCl_4.

The problem of the acetylacetone tautomerism in THF, methanol, and water was studied by Nagy et al. at the IEF-PCM level [35]. Good agreement with the experimental ΔG_{tot} values was obtained for the solvation in the organic solvents at the IEF-PCM/B3LYP/6-31G* level, but not for the aqueous solution. A study of the relative internal free energy indicated strong basis-set dependence at the QCISD(T) level. The in-water tautomerism was revisited by Alagona et al. [65]. Applying the IEF-PCM approach for optimizing the geometries in aqueous solution, the relative internal free energy was obtained at the extrapolated CCSD(T)/CBS level. Still the enol form was predicted more stable if the PCM relative solvation free energies were taken into consideration. Only the acceptance of the relative solvation free energy estimation from FEM/MC simulations (and consideration of a remarkable change in the thermal corrections for the two tautomers) helped predicting the diketo tautomer. Even at this level, and considering possible solute association in a 0.1 molar solution, the theoretical keto/enol ratio was predicted as 60/40 compared with 75/25 to 88/12 found experimentally (see references in the paper). The calculations revealed, however, that both the accepted optimized geometry and the charge parameterization in FEP/MC have sensitive effects on the final result.

The tautomerism of cyclohexane-1,3-dione in tetrahydrofuran (THF) and water was studied by Alagona and Ghio [193] up to the IEF-PCM/B3LYP/6-311++G** level. Calculations stably predicted the 1,3-diketo form for cyclohexanedione at any theoretical level in both solvents. The good result was attributed to the lack of a possible intramolecular hydrogen bond for the keto-enol form of cyclohexane-1,3-dione due to the arrangement of the oxo-groups on a ring, in contrast to the conformationally flexible acetylacetone.

Zwitterionic amino acids: A zwitterion comes into existence if a proton relocates in a molecule resulting in the emergence of two formally ionic sites. Aliphatic amino acids are prototypical systems for this kind of transformation. The α-amino acids, especially glycine, have been studied in this respect in a number of papers (see, e.g. [194,195]). The importance of the studies by Nagaoka et al. and Tuñón et al. [196,197] is to be emphasized, where the dynamic aspects of the proton transfer were investigated. Alanine and serine were studied by Tortonda et al. [198,199] at the B3PW91/6-31+G** level combined with a contiunuum solvent SCRF method. The latter paper includes a discussion related to the glycine zwitterion formation and the observed contradictions between experiment and theoretical calculations. A recent study [200] deals with the problem of the proton transfers between amino acid side chains in solution.

The possibility and energetics for the intramolecular proton transfer have been investigated [196-199]. In all these studies the

neutral amino acid takes an anti -COOH structure, which must be higher in energy than the syn for a simple acid, as acetic acid [201,202]. A water-assisted mechanism involving the participation of 1-2 water molecules is still possible, as found by Alagona et al. [65] for the keto-enol tautomerization of the pyruvate anion and acetylacetone. By involvement of catalytic water molecules, the neutral glycine need not turn into the anti –COOH conformation.

Our review in this section concentrates on less widely studied problems, namely the zwitterion formation for β- and γ-amino acids, heteroaromatic acids, and hydrogen-bonded complexes.

Since aspartic acid is a dicarboxylic acid, this molecule can be considered both as an α- and β-amino acid. Two zwitterionic forms are possible in equilibrium in aqueous solution. Nagy and Noszál [40] studied the problem by optimizing gas-phase zwitterion dihydrates (the zwitterion itself is not stable in this phase). The relative internal free energies for three conformers of the pure zwitterion were calculated up to the QCISD(T)/6-31G* and MP2/6-311++G** levels and the solvent effects were considered at the SCI-PCM/HF/6-311++G**//HF/6-31G* level. Relative solvation free energies were also calculated by the FEP/MC method using ELPO-fitted charges. The relative protonation constant for the $HAsp^{-}+H^{+} \leftrightarrow$ Asp (zwitterion) equilibrium with reference to α- and β-zwitterions was calculated in the range of 0.97 ± 0.42 to 1.07 ± 0.36, in comparison with the experimental value of 1.26. The good agreement was achieved only by considering the corresponding ΔG_{th} terms, with special attention to the frequency-dependent contributions.

Alanine as an α-amino acid was reviewed above. The β-amino isomer, as the simplest molecule for this type of amino acids has been studied recently by Nagy in water and chloroform solvents [123]. A basic structural difference between α- and β-amino acids is that the isomers could form five- and six-member rings with intramolecular hydrogen bonds, respectively, with considerably smaller strain in the latter case.

β-alanine exhibits a combined conformational/tautomeric problem. The H_2N-CH_2-CH_2-COOH molecule can adopt NCCC gauche and trans conformations with possible zwitterionic structures in both cases. The N…H…O intramolecular hydrogen bond is feasible only in a gauche conformation. In aqueous solution all four conformers/ tautomers were identified. No zwitterionic form was found for the gauche conformer in chloroform, where the molecule can only create a strong intramolecular hydrogen bond as H_2N…HOCO with anti carboxylic group. IEF-PCM/B97D/aug-cc-pvtz relative free energies predicted the preference of the neutral form over the zwitterion for β-alanine in aqueous solution by 1.7 kcal/mol. As a result of a more negative solvation term of 2.6 kcal/mol by FEP/MC, the final prediction is 0.9 kcal/mol in favor of the zwitterion, as found for all α-amino acids.

The simplest γ-amino acid is the γ-aminobutyric acid. This molecule exhibits a large conformational flexibility, which was discussed above. The theoretical calculations by Ramek and Nagy [163] and Crittenden et al. [63] concluded in accord that an extended zwitterionic conformer is the most stable species in aqueous solution. The zwitterion hardly exists in chloroform and dichoromethane [162].

Carboxylic derivatives of N-heterocycles also exhibit the zwitterionic tautomerism. Equilibria for pyridine 3-COOH and 4-COOH acids (nicotinic and isonicotinic acids, respectively) were studied by Nagy and Takács-Novák [203]. In addition to the tautomeric equilibrium, the 3-COOH derivative shows a conformational equilibrium regarding the orientation of the syn carboxylic group with reference to the ring nitrogen. Relative free energies in the gas phase were calculated up to the MP2/6-311++G**//MP/6-31G* level. The solvent effects were calculated through FEP/MC simulations in water, methanol, and tetrahydrofuran for both solutes, and in mixtures of water and the organic solvents at different compositions for nicotinic acids. Total relative free energies were obtained as $\Delta G_{tot}=\Delta G_{gas}+\Delta G(solv)$. Calculated ratios for the zwitterion and the neutral form were compared with experimental values. The trend in the shift of the component ratio as a function of the solvent composition was predicted in accord with the experiment for the studied equilibria of nicotinic acid.

Zwitterionic alkylaminophenols: The tautomeric/conformational equilibria for the neutral and zwitterionic tyramine (4-(2-aminoethyl) phenol) was investigated by Nagy et al. [48]. Experimentally [48,126], the zwitterion/neutral form ratio was obtained at 3.8-5.9:1, corresponding to a free energy difference of 0.8-1.1 kcal/mol at T=298 K. PCM calculations were unable to point out the existence of the zwitterionic form in aqueous solution. Using the FEP/MC explicit solvent approach, the calculated relative zwitterion/neutral form solvation free energy depends very strongly on the accepted atomic charge set as the Coulomb parameter in the OPLS 12-6-1 intermolecular pair-potential. Use of in-solution charges for the polarized solute is necessary for pointing out the existence of the zwitterion in aqueous solution, but use of PCM/B3LYP/6-31G* ELPO fitted charges provide exaggerated ΔG(solv).

For dopamine, the measured zwitterion/neutral form ratio is 0.1 in aqueous solution [126]. PCM calculations point out both at the B3LYP/6-311++G** and MP2/6-31G* levels the predominance of the neutral form. Nonetheless, two kinds of zwitterions are still possible in the equilibrium, depending on the OH group left by the proton. Explicit solvent models in FEP/MC calculations predict the exclusive presence of the dopamine zwitterions and the preferred side-chain conformation is trans. The results suggest that PCM and FEP/MC inherently favor the neutral and the zwitterionic form, respectively, as can be concluded upon comparison of the calculation results for tyramine and dopamine.

Hydrogen-bonded complexes: An important class of the neutral form/ion-pair equilibrium was recently studied by Nagy and Erhardt for hydrogen-bonded complexes of amino acid mimics. Using the IEF-PCM method up to the CCSD(T)/CBS level, the possible proton jump was investigated for the R-COOH…H_2N-CH_3 and R-COOH… guanidine/methyl-guanidine systems (R=H, CH_3) in dielectric solvents with ε=5.0 and 15.0 [49]. The neutral hydrogen-bonded structure was predicted in the case of the H_2N-CH_3 acceptor, whereas the ion-pair exists with guanidine/methyl-guanidine bases.

IEF-PCM/CCSD(T)/CBS//MP2/aug-cc-pvdz and IEF-PCM/B97D/CBS//B97D/aug-cc-pvtz relative free energies were calculated for the hydrogen bonded tautomers of the neutral, CH_3COOH…$H_xN(CH_3)_{(3-x)}$ and ion-pair, CH_3COO^{-}…$^{+}H_{x+1}N(CH_3)_{(3-x)}$ (X=0-2) systems in aqueous solution [204]. The continuum approach predicted the preference of the neutral form for the in-solution optimized species. Only consideration of the FEM/MC relative solvation free energy contribution resulted in prediction of the ion-pair preferences for the complexes in aqueous solution, whereas the separated components must be ionic at pH=7. The solvent effect in chloroform cannot stabilize the ion-pair form for the CH_3COOH…H_2NCH_3 complex, which was considered as the simplest model for a bound muscarinic agonist to an aspartate/glutamate residue in the binding pocket of the receptor.

Different protonations: For a molecule with two protonable sites, equilibrium exists for the differently protonated species. If the system has both protonable and deprotonable sites, cationic, anionic and zero-net charge forms, including zwitterions, may be present in complicated equilibria.

Histamine is a famous example for a system with two protonable sites. The experimental protonation macroconstants for the first and second site is 9.80 ± 0.01 and 6.08 ± 0.01, respectively (see above). Although the experimental values can be determined, assignment to the corresponding protonation site is still to be identified. From analogies with ethylamine (more basic) and imidazole (less basic), the assignment seems to be straightforward, confirmed upon theoretical calculations by Raczyńska et al. [136]. Histamine is protonated 95.1% at the amine site, 4.6% is diprotonated, and 0.4% remains unprotonated at pH=7.4 [119].

In other cases, however, when experimental data are not available, theoretical calculations could explore the equilibrium ratio for the differently protonated species for non-symmetrical systems. Nagy et al. [41] studied the protonation of N-methyl piperazine at the N (tertial) vs N (secondary) atom in aqueous solution, acetonitrile, and dichloromethane. Subtle equilibria were concluded on the basis of IEF-PCM/B3LYP/aug-cc-pvtz and IEF-PCM/QCISD (T)/CBS levels. The continuum approach predicts increasing preference for the N (t) protonation with decreasing solvent dielectric constant. If a correction due to fractional solute association was considered, the calculated N(s) prot/N(t)prot ratio increases from 47/53 to 78/22 for the aqueous solution, whereas the experimental value was estimated at about 80/20 upon the interpretation of the NMR results.

Ratios of differently protonated species for six-member aliphatic heterocycles with two nitrogen atoms in different ring positions were calculated in water and dichloromethane [42]. Calculated IEF-PCM/B3LYP/aug-cc-pvtz and IEF-PCM/ QCISD(T)/cc-pvtz relative free energies predict the same preference for the compared species. For the isomers with relative ΔG_{tot} values up to 0.6 kcal/mol, the results are similar by the two methods. The deviations, however, increase with ΔG_{tot}>0.6 kcal/mol. Relative free energies do not change dramatically in dichloromethane solvent. With the exception of the N-methyl piperazine solute, relative solvation free energies from FEP/MC calculations considering a counterion and IEF-PCM calculations modeling the infinitely dilute aqueous solution with a pure solute differ by less than 1 kcal/mol.

Induced tautomeric equilibria

In the end, some special tautomeric process will be considered. The stable form of the nucleotide base adenine is the amino form: an NH_2 group connects to the pyrimidine ring. A thermodynamically less stable tautomer is the imine form, where a proton of the indicated NH_2 group jumps over to the neighboring ring nitrogen. This thermodynamic preference could be theoretically proved by calculations of the isolated structures. In fact, the amino adenine form appears in the DNA base pairs in the healthy humans, confirming that this tautomeric form is preferred under normal biological conditions.

Ai et al. [205] studied the conditions favoring the amino-imino transformation. They found that some metal ions and/or water or ammonia could catalyse the proton jump, and the imino form in these complexes is thermodynamically more stable than the amino tautomer. The conclusion is important and may be threatening: metal ions in humans, but even only so simple chemicals as ammonia or the always present water could trigger biological transformations, which easily leads to point mutation and concommittant mispairang. On the other hand, the authors expressed their hope that their results would also help understand and then control the biologically dangerous processes.

The thermodynamic possibility for a double-proton transfer reactions in spontaneous, non-catalyzed way has been studied in several papers [9-12]. Cerón-Carrasco and Jacquemin [206] considered the influence of the Mg^{2+} on the double proton transfer for the guanine-cytosine pair. According to these authors, the connecting Mg^{2+} ion drastically alters the natural equilibrium between the canonical and rare forms. The predicted equilibrium constant is in the order of 10^{-3} in comparison with 10^{-10} to 10^{-8} for natural mutations. Still the Mg^{2+} catalysis may not be dangerous for humans, because this ion also reduces the barrier for the reverese process. The calculated resulting rate constant is 10^{10}-10^{11} s^{-1}, which hints at a short lifetime of the induced rare tautomer.

All equilibria surveyed in this review were accepted as having been reached in the electronic ground state. Processes may go through, however, in the excited state, or only in some excited state. This possible distinction led to the Nobel Prize for Hoffmann, who, in company with Woodward, discovered and explained on the basis of the molecular orbital theory that electronic excitation could influence the opening path of cycloolefins, and thus the reaction could be directed as obtaining one or another product.

There have been speculations recently that excited state chemical transformations of DNA could be related to some sort of human cancer. Study of the excited state behavior of a model system, chemically resembling to some nucleotide could provide useful information regarding the possible proton transfer in the excited state of DNA.

Related studies, referred in former sections of this review, aimed at exploring the thermodynamic conditions of a proton transfer/double proton transfer in the ground state. Fang and Kim [207] systematically studied the excited state tautomerization of 7-azaindole-$(H_2O)_n$ (n=1,2) both in the gas-phase and in solution. The modeled process is a typical example for a solvent (water) assisted proton relocation in a condensed aromatics like adenine and guanine.

Electronic structures and energies for the reactant, Transition State (TS), and product were computed using the time-dependent density functional theory (TDDFT) and complete active space self-consistent field (CASSCF) levels with 6-31G (d,p), 6-311G(d,p), and 6-311þG(d,p) basis sets. The authors found that the dynamic electron corrections are very important for predicting the energetics of the excited-state tautomerization. Complete geometry optimization was carried out in the S1 state. The transition structure and the barrier height strongly depend on the applied basis set and the solvent effect at all studied TDDFT level. Accordingly, the authors conclude that further investigations are necessary whether the current TDDFT methods and consideration of the solvent effects are capable to correctly interprete the excited-state proton transfer reactions.

Concluding Remarks

Theoretical studies surveyed in this review were published mostly in the past twenty years. This time period was selected, because computer resources allowing satisfactorily high-level theoretical calculations for in-solution processes became available for a large fraction of the research community only in about the nineties. Although the theoretical basis was established 10-15 years prior to this period, computer powers

were not enough for routine calculations for small molecules even with only 8-10 C, N, O atoms and of similar number for the hydrogens.

This survey indicates that the calculated relative free energies for conformers/ tautomers are sensitive to the applied level of theory, the basis set used both in geometry optimization and highest-level single-point calculations, consideration of the thermal corrections for the local-energy-minimum structures and the way of calculating the relative solvation free energy. None of them is surprising for subtle equilibria.

If one optimizes the structure of a small molecule in the gas phase, experimental data (bond lengths, bonds angles and perhaps torsion angles) are available for comparison in many cases. Thus, one can assess the relevance of the applied method and its predictive capacity. For in-solution structures there are very few direct geometric data available in the literature. Accordingly, validation of the theoretical level could be carried out on gas-phase tests, although one cannot be ever sure that the method works equally well for gas-phase and in-solution molecules.

Regarding chemical equilibria, it is important to emphasize that relative instead of absolute free energy data are to be considered. This opens the chance that good relative free energies may be obtained even on the basis of theoretical methods with limited accuracy. Nonetheless, there is no guarantee for error cancellation, and the validation of the level of theory (method + basis set) should be checked at least against similar systems with available experimental equilibrium compositions. Unfortunately, such data are also rare for many classes of molecules.

In many of the surveyed papers the approach $\Delta G_{tot}=\Delta G(gas)+\Delta G(solv)$ was applied. $\Delta G(gas)$ accounts for the relative internal free energy of the pair of the molecules in the gas phase, which could remarkably differ form $\Delta G(internal)$ in solution. The solvent can differently stabilize the partners in solution, and a deviation of about 0.5 kcal/mol could be dramatic for subtle in-solution equilibria, frequently based on free energy differences less than 1 kcal/mol. Recently, more and more studies are based on in-solution optimized structures.

Source of the calculated $\Delta G(solv)$ is crucial for polar molecules with possible intramolecular hydrogen bonds. Polarizable continuum dielectric methods may underestimate their relative importance, and the predicted preferred conformer, tautomer could be in contrast to the experimentally known structure. Calculations of $\Delta G(solv)$ by means of the free energy perturbation or thermodynamic integration methods as implemented in a Monte Carlo or molecular dynamics simulation may correct the results.

Finally, most calculations have been performed for models implicitly considering infinitely dilute solutions. The derived ΔG must be valid under such circumstances. Real solutions are, however, always of finite concentration. In such solutions, different degrees of solute association are expected. Furthermore, the equilibrium constant expressed by concentration, K_c, should include activity coefficients or can be calculated upon relative chemical potentials for the standard state of 1 M solution. Such solutions must differ from an infinitely dilute model, whereas experiments have proven concentration dependent equilibrium ratios. This finding makes the theoretical predictions of solute compositions even more difficult. In order to reach a better agreement with the experimental values, concentration dependence and its possible effect on the solute geometry and interaction free energy must be at least studied in future research works.

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