

Molecular dynamics study of the tautomeric equilibrium in the Mannich base

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Abstract

The density functional theory ab initio quantum mechanical and molecular dynamics thermodynamic integration methods have been used to study the intramolecular proton transfer equilibrium in 2-[N,N-dimethylaminomethyl]-3,4,6-trichlorophenol. The model of slow proton transfer reaction was applied, where the geometry and charge data were linearly interpolated between two states calculated at the Becke3LYP 6-31G(d,p) level. This avoids the difficulties connected with the different time scales of proton transfer reaction and solvent relaxation processes. The calculated free energy differences obtained from ab initio calculations including the Tomasi model of the solvent reaction field ($1.16 \text{ kcal mol}^{-1}$) and from ab initio plus molecular dynamic thermodynamic integration calculations ($1.7 \pm 1.8 \text{ kcal mol}^{-1}$) are in agreement with the experimental value $0.12 \pm 0.02 \text{ kcal mol}^{-1}$. © 1998 Elsevier Science B.V.

1. Introduction

The properties of hydrogen bonded systems and particularly the conditions for the proton transfer reaction are important in materials science as well as in the understanding of most key functions of living organisms [1,2]. Proton transfer reactions in biological systems typically proceed in fluctuating aqueous or macromolecular environments [3,4]. The study of the nature of such processes appears to be complicated by the variety of species existing in the equilibrium due to the different stoichiometry of the complexes formed, association and dissociation reactions.

Products of the condensation of formaldehyde, secondary amines and derivatives of phenol at an ortho

position to the OH group were found to be convenient model systems for studying intramolecular proton transfer processes [5,6]. These so-called Mannich bases were extensively studied [7,8]. The high stability of the intramolecular hydrogen bond in Mannich bases was demonstrated by IR spectroscopy; for example in the gas phase no free OH groups exist even at an elevated temperature of 150°C [9]. It was shown experimentally that the intramolecular proton transfer equilibrium constant depends on the intrinsic and external contributions [10]. The intrinsic contribution - means here the energy difference between the neutral and the ionic form of the isolated species, while the external contribution is the change in free energy of solvation upon the intramolecular proton transfer.

The intrinsic contribution can be calculated by quantum mechanical methods. It was found that the more acidic the phenolic part of the complex and the more basic the amino part of the complex, the lower is the difference in energy between the ionic and neutral forms [11]. Results of the experimental studies show in all studied Mannich bases, where the proton transfer equilibrium was observed, that the ionic form has a lower energy and a decrease in the temperature leads to the increased population of this form [6]. Let us define ΔH^0 as the enthalpy difference between the ionic and the neutral form. ΔH^0 of proton transfer reactions (ΔH_{PT}^0) was found within -2 to -4 kcal mol $^{-1}$ limits [12]. Interestingly it also appeared that the ΔS_{PT}^0 values were found to be negative and relatively high -5 to -15 cal mol $^{-1}$ K $^{-1}$ [12,13]. Proton transfer equilibrium constants were determined by UV spectroscopic techniques in temperature range from -15 to $+30^\circ\text{C}$. The molar absorption coefficients were determined separately for molecular (in CCl $_4$ solution) and ionic forms (in methanol with excess of KOH) at each studied temperature. For each temperature at least three concentrations were studied for at least four wavelengths. The slope of the log K against the $1/T$ plot allows for the determination of ΔH_{PT}^0 . ΔG_{PT}^0 was calculated from K_{PT} at each temperature.

The intramolecular proton transfer reaction is associated with the reorganization of solvent molecules [14,15]. The active role of the solvent was clearly demonstrated by the experiment [16]. It was shown that lowering the temperature below the freezing point of the solution stops a further equilibrium shift in the direction of the ionic form. Frozen solvent molecules are not able to take place in the orientational reorganization.

With the aim of constructing a theoretical model of proton transfer equilibrium in solutions, we have applied a combined quantum mechanical and molecular dynamical approach in this Letter [17,18]. It is known that a quantum-mechanical treatment of solute plus many hundred solvent molecules is not possible because an ab initio treatment of such a huge system would be computationally intractable [19].

In our approach the solute molecule is treated at the ab initio level, while the solvent dynamics is described by molecular mechanics (GROMOS96

force field) [20]. Ab initio calculations yield the intrinsic energy difference and in addition the force field parameters (in particular the solute charges) that are later used in the simulation. A simplified model of solute-solvent interactions based on the atom to atom potentials, is computationally inexpensive and allows for thermal averaging using molecular dynamics. Using thermodynamic integrations, the difference in the free energy of solvation was calculated. With such a model we intend to reproduce the experimental thermodynamic characteristics of the proton transfer reaction in methanol solutions of Mannich bases, in particular ΔG^0 for the proton transfer. Calculations will be performed for the case of 2-[N,N-dimethylaminomethyl]-3,4,6-trichlorophenol (Fig. 1). Its proton transfer equilibrium in methanol solution at room temperature is experimentally determined ($\Delta G_{PT}^0 = 0.12 \pm 0.02$ kcal mol $^{-1}$) [13], indicating that the neutral form is slightly more favourable in terms of free energy than the ionic form.

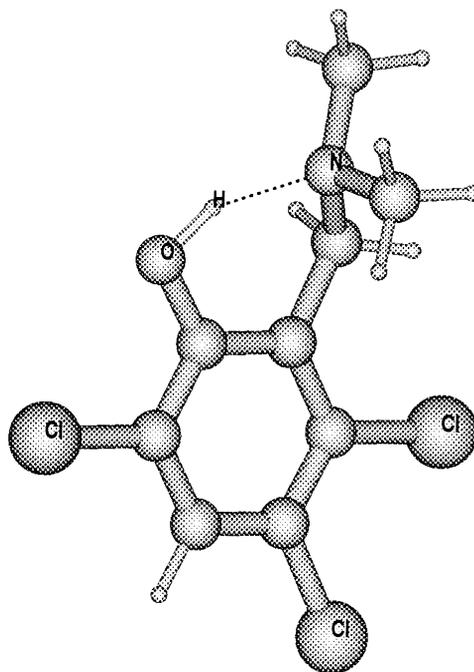


Fig. 1. Neutral form of 2-[N,N-dimethylaminomethyl]-3,4,6-trichlorophenol.

2. Computational

In our study we have used a combination of ab initio quantum chemical calculations and molecular dynamics/thermodynamic integration method (MD/TI) to calculate the free energy difference between two given forms. Methodologically related calculations are reported elsewhere [21].

The computational procedure consists of two stages. In the first stage, we performed ab initio geometry optimizations of the ionic and the neutral form in vacuo at the Becke3LYP 6-31G(d,p) level [22,23]. The applied valence basis set augmented with polarization functions is flexible enough to faithfully reproduce the energetics of the proton transfer processes. The calculations were carried out by using the GAUSSIAN94 suite of programs [24]. When we carry out geometry optimization for the ionic form, the proton moves into the neutral form position. For this reason we have frozen the N–H distance at 1.05 Å for the ionic form.

The frequency calculations in the harmonic approximation at the Becke3LYP 6-31g(d,p) level using the in vacuo optimized geometries were done for both forms in order to obtain the difference in the zero point energy (ΔZPE). The fact that N–H distance for the ionic form was not optimised can lead to an erroneous force field. However, it concerns mostly the high frequency $\nu(N-H)$ vibrations and the ΔZPE error should not be large for this reason. Additionally, the calculations did not show any imaginary frequencies also for the ionic form which suggests that the frequency calculation was performed for the stationary state.

Moreover, we have performed ab initio calculations including the model of solvation proposed by Miertus and Tomasi [25], which gave us the atomic charges calculated using the Merz–Kollman scheme [26]. This scheme gives rise to the atomic charges that reproduce the electrostatic potential in the vicinity of the molecule. When calculating the Merz–Kollman charges for the reaction in methanol, we modeled the effect of the polar environment by placing the molecule in to the cavity composed of interlocking spheres, which was immersed in the dielectric continuum. The radii of interlocking spheres were standard van der Waals radii scaled by

a factor of 1.2. It was shown that in this way the calculated free energies of solvation reproduce experimental values for a large number of molecules and ions [27].

Molecular dynamics/thermodynamic integration calculations (MD/TI) were performed in methanol solution and in vacuo to obtain the free energy difference ΔG between the two forms [28,29]. This method has been implemented in the molecular simulation suite of programs GROMOS96 [20]. The atomic charges derived from the ab initio calculations were used in the MD/TI. For simulations in the methanol solution one solute molecule was placed into a cubic box with an edge of 24.4 Å containing 232 methanol molecules. The system was equilibrated under constant pressure (1 atm) with a pressure coupling constant [30] of 0.2 ps using periodic boundary conditions with a cutoff radius of 10.0 Å at several temperatures. Next the MD/TI simulation at $T = 298$ K and 1 atm of pressure was carried out from the neutral form to the ionic one and also in the backward direction in order to obtain the hysteresis that is the best measure of the accuracy of the free energy difference obtained by performing thermodynamic integration in the forward and the reverse directions under the same conditions. The hysteresis reflects the systematic error associated by time lag between the Hamiltonian and the actual configuration at every step. We have used the GROMOS96 force field model for methanol.

The transformation between the neutral and ionic forms was performed by a smooth variation of a coupling parameter λ . The functional dependence of the molecular mechanical energy function on the parameter λ is given in Ref. [20]. All the bond length, bond angle, dihedral angle and improper angle values were chosen to correspond to the ab initio optimized values.

The thermodynamic integration was carried out by the thermodynamic integration slow growth method in the molecular dynamics simulation. The coupling parameter λ was gradually changed from 0 to 1 in a 100 ps simulation. The time step for integration was 0.5 fs. The system was coupled to the temperature bath of 298 K by using Berendsen's method with a coupling constant of 50 fs [30] and a spherical cutoff radius of 10.0 Å. We have collected

4000 succeeding values of $\partial V/\partial\lambda$, and integrated them numerically according to Eq. (1).

$$\Delta G = \int_0^1 \left\langle \frac{\partial V}{\partial \lambda} \right\rangle d\lambda \quad (1)$$

The free energy difference between the two forms in solution ΔG_{tot} can be estimated according to Eq. (2).

$$\Delta G_{\text{tot}} = \Delta E_{\text{ab initio}} + \Delta \text{ZPE} + \Delta G_{\text{solv}} \quad (2)$$

where ΔZPE is the difference in zero point vibrational energies, $\Delta E_{\text{ab initio}}$ is the difference in ab initio energies for the isolated system and ΔG_{solv} is the difference of free energy of solvation between the ionic and neutral form. Note that the latter value was obtained as the difference between the free energy for the proton transfer in the Mannich base in methanol solution and in the gas phase. The gas phase value was obtained by the ab initio calculations, since the molecular dynamics method is inadequate to model intrinsic energetics.

Table 1
Geometry and dipole moment data from ab initio calculations

| Atoms | Neutral form | Ionic form |
|--|-------------------|-------------------|
| bond length (\AA) | | |
| H–O | 0.967 | 1.496 |
| H–N | 1.82 | 1.05 ^a |
| C _{AR} –O | 1.35 | 1.29 |
| N–O | 2.68 | 2.48 |
| C _{AR} –Cl | 1.68 ^b | 1.76 ^b |
| bond angle (degree) | | |
| C _{AR} –O–H | 107.2 | 101.0 |
| N–H–O | 146.9 | 153.7 |
| C _{CH₂} –N–H | 98.2 | 91.6 |
| dihedral angle (degree) | | |
| C _{AR} –C _{AR} –O–H | –12.2 | –21.2 |
| C _{AR} –C _{AR} –C _{CH₂} –N | 32.5 | 43.2 |
| C _{AR} –C _{CH₂} –N–C _{CH₃} ^c | –151.3 | –159.6 |
| C _{AR} –C _{CH₂} –N–C _{CH₃} ^d | 81.6 | 71.8 |
| dipole moments (Debye) | 4.6 | 9.2 |

^a This distance was frozen during optimization.

^b All three C_{AR}–Cl bond lengths are the same.

^c Methyl group in the plane of the phenyl ring.

^d Methyl group out of the plane of the phenyl ring.

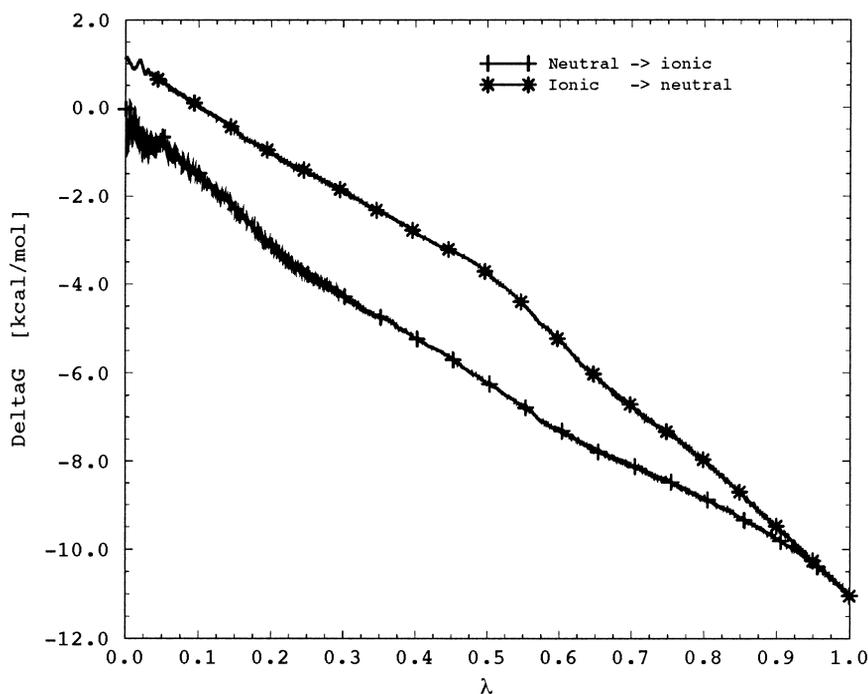


Fig. 2. Difference of the free energy in methanol solution obtained from MD/TI calculations. λ is the coupling parameter.

3. Results

In Table 1 we list the most important optimized geometry data obtained after the proton transfer when the N–O distance decreases for 0.2 Å. It means that the entire bulky N,N-dimethylamino group moves towards the oxygen atom connected to the phenyl ring and the main part of the other geometry changes were caused by this movement.

For the calculations which use the solvent reaction field method, we also need the static dielectric constant for the solvent. For methanol we used the experimental value 32.66. Solvent reaction field approach is an alternative method that can be used in the estimation of the free energy of solvation. This approach is in general less reliable than the all atoms models for solvent and we calculated the free energy difference between both tautomeric forms at the Becke3LYP 6-31g(d,p) level using the model of Miertus and Tomasi [25]. The difference of the free energy obtained from the Tomasi model of solvation $\Delta G = 1.16 \text{ kcal mol}^{-1}$ is in fairly good agreement with experimental value $\Delta G_{\text{exp}} = 0.12 \pm 0.02 \text{ kcal mol}^{-1}$.

Table 2
MD/TI results

| | Neutral to ionic | Ionic to neutral |
|----------------------------|------------------|------------------|
| ΔG_v^O | -1.6 | 1.3 |
| ΔG_s^O | -11.0 | 12.2 |
| ΔG_{solv}^O | -9.4 | 10.9 |

ΔG_v^O , in vacuo; ΔG_s^O , in methanol; ΔG_{solv}^O , free energy of solvation in methanol. All data in kcal mol^{-1} .

The difference in ab initio total energy $\Delta E_{\text{ab initio}}$ between the ionic and neutral form in the gas phase is equal to $11.6 \text{ kcal mol}^{-1}$. The corresponding ΔZPE equals to $0.3 \text{ kcal mol}^{-1}$.

The profiles of ΔG of MD/TI calculations on the coupling parameter λ are depicted in Fig. 2 (in methanol solution) and in Fig. 3 (in vacuo). Both curves show relatively small hysteresis between the TI performed in the forward and backward directions. The MD/TI free energy values are given in Table 2. Combined with ab initio calculations the difference in the free energy between the ionic and neutral form is $1.7 \pm 1.8 \text{ kcal mol}^{-1}$, which is in agreement with the experimental value of $0.12 \pm 0.02 \text{ kcal mol}^{-1}$.

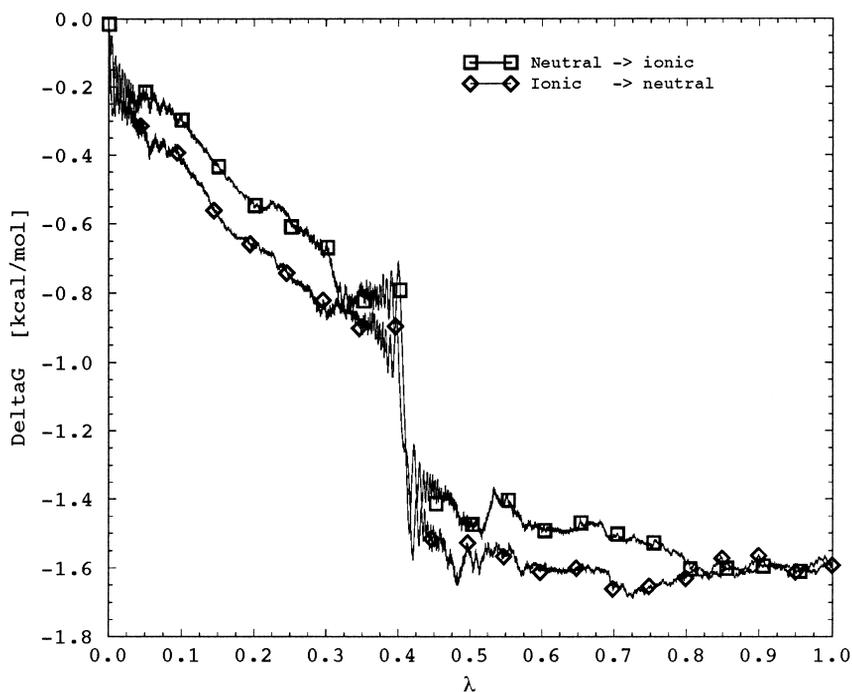


Fig. 3. Difference of the free energy between two forms in vacuo obtained from MD/TI calculations. λ is the coupling parameter.

4. Conclusions

We have calculated the free energy difference associated with the intramolecular proton transfer in the Mannich base (2-[N,N-dimethylaminomethyl]-3,4,6-trichlorophenol) in methanol solution. We obtained the free energy difference using the DFT ab initio method with an included solvent reaction field and a combination of ab initio energy difference and free energy of solvation provided by an all atom representation of solvent. In the latter case the thermal averaging was performed by molecular dynamics and the free energy was calculated with thermodynamic integration. Experimentally the neutral form is more favourable by 0.12 ± 0.02 kcal mol⁻¹. The ab initio calculations at the Becke3LYP 6-31g(d,p) level with the solvent reaction field of Miertus and Tomasi [25] predicted the neutral form to be more stable by 1.16 kcal mol⁻¹. Combined ab initio and MD thermodynamic integration results gives rise to the free energy difference of 1.7 ± 1.8 kcal mol⁻¹. The calculations presented in this Letter do not address the question of proton transfer dynamics, which in general requires a quantum-dynamical treatment. Methods for a quantum-dynamical treatment of proton transfer processes are developed [4,19] and ready to use. We hope to perform the quantum-dynamical study of the proton transfer in this system in the near future.

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