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A THEORETICAL STUDY ON THE PROTONATION OF BENZAMIDE

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Abstract—We have performed an *ab initio* study of the protonation of benzamide, using a STO-3G minimal basis set. According to our results, benzamide is an oxygen-base in the gas-phase. Rotation of the $-CONH_2$ group respect to the aromatic ring does not affect the basicity of the molecule. If the presence of the solvent causes pyrimidization of the $-NH_2$ group, the intrinsic basicity of the O atom decreases, while that of the N atom increases and the interaction of this center with the solvent is stronger, favoring nitrogen protonation in solution.

The protonation of benzamide, and, in general the protonation of amides, has been the subject of a considerable number of studies, in which the protonation site was one of the most conflictive points. The earlier work concluded that the mechanism of hydrogen exchange in amides proceeds by protonation on the N atom,[1] according to experimental evidences,[2,3] since the hydroxide-catalysed reaction is faster than the hydronium-catalysed one.

Katritzky *et al.*[4] studying the protonation of benzamide in sulphuric acid media found that the points obtained to evaluate the corresponding pK_a yield a straight line, with a slope less than unity, when fitted to the Henderson-Hasselbach equation. Similar results were reported by Yates *et al.*[5,6] for protonation in perchloric acid. However, these results were interpreted as evidence of protonation at the O atom.[7] Results from NMR spectroscopy studies[8] seemed to ratify that amides undergo protonation at the O atom, under these conditions.

Paul and Schulman[9] indicate that the pK_a values reported by Katritzky *et al.*[4] and Yates *et al.*[5,6] (−2.10 and −2.0, respectively), are not consistent with the pK_a values (~ −7.0) of other carbonyl derivatives of benzene, and they conclude that protonation of benzamide in moderately concentrated H_2SO_4 occurs at the $-NH_2$ group. More recently,[8] from a UV and NMR study of protonation of benzamide in concentrated sulphuric acid and pure fluorosulphuric acid, Liler concluded that benzamide presents a tautomerism, with a changeover from N-protonated benzamide in aqueous acid to O-protonated in concentrated or anhydrous acid. Unfortunately, the problem seems not to be completely settled; Perrin proposed[10] a different mechanism to explain the hydrogen exchange in primary amides, which implies protonation at the O atom, since the different rate of exchange of the two N–H hydrogens can be explained, only if O-protonation is favored.

The aim of this paper is to present some "*ab initio*" calculations on the protonation of benzamide, as a contribution to clarify this problem. We have found[11–14] good linear correlations between gas-phase proton affinities and calculated C_{1s}, O_{1s} and N_{1s} orbital energies for those benzene derivatives that protonate on the aromatic ring, or which are oxygen or nitrogen bases, respectively. These correlations allow an economical evaluation of the intrinsic basicity of any position of these kind of compounds and, therefore, the prediction of the most basic site of the molecule under investigation. In order to consider the effect of the solvent, not included in such correlations, we will extend our treatment to consider electrostatic effects, that are probably involved in the solvation mechanism, by evaluating the corresponding molecular electrostatic potentials.

Gas-phase basicity

We have adopted for our study of benzamide its experimental geometry[15] to avoid very expensive geometry optimisations.

The corresponding O_{1s} and N_{1s} orbital energies were calculated using a STO-3G minimal basis set.[16] From these data, and using eqns (2) and (3) of Ref. [13] the intrinsic proton affinities of both positions were obtained. The results indicate that, in the gas-phase, benzamide is clearly an oxygen-base, being the intrinsic P.A. of the O atom (224.2 kcal/mol), 22.5 kcal/mol higher than that of the N atom (201.7 kcal/mol). These results agree with those obtained with the corresponding molecular electrostatic potentials. In Fig. 1 we show the molecular electrostatic potential map, calculated using the same basis set indicated above and the equations of Ref. 17, at the oxygen and nitrogen regions.

In the first case (Fig. 1(a)) this map was calculated on the plane defined by the carboxylic group and the N atom. In the second case (Fig. 1(b)) it was evaluated on a plane which bisects the HNH angle and is perpendicular to the $-NH_2$ group.

Study of possible solvation effects

It is well known that the key index of basicity in aqueous solution is the free energy of protonation of the base in water,

$$\Delta G^\circ \text{prot, s} = \Delta H^\circ \text{prot, s} - T\Delta S \text{ prot, s} \qquad (1)$$

(or the pK_a of the conjugated acid, since $\Delta G^\circ \text{prot, s} = -RT \ln K_a$).

According to this, benzamide would behave as a nitrogen base in solution, if solvation effects would introduce a noticeable change on either (or both) the

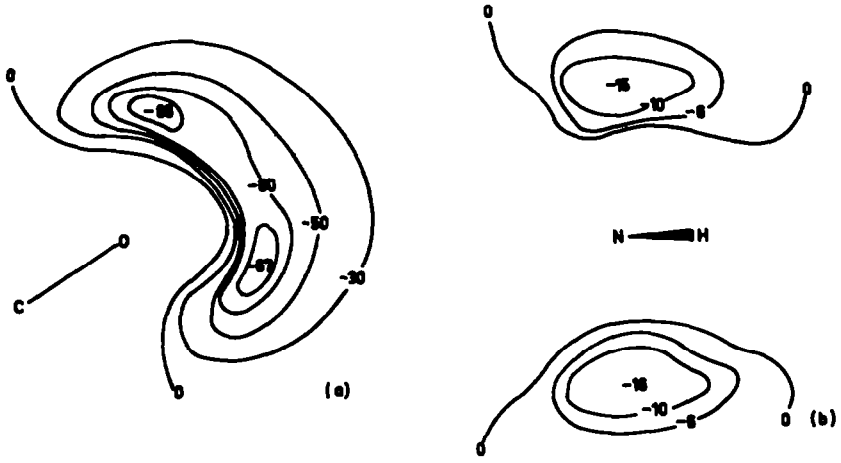

Fig. 1. Molecular electrostatic potential map for benzamide: (a) in the plane defined by the carboxylic group and the nitrogen atom. (b) in a plane which bisects the HNH angle and perpendicular to the $-NH_2$ group.

enthalpy ($\Delta H°$ prot, s) and the entropy ($-T\Delta S°$ prot, s) terms.

Aue *et al.*[18] have shown that there is very good correlation between the enthalpies of protonation of alkylamines in gas-phase and in aqueous solution. It would be reasonable to assume that such a correlation also holds for amides. Therefore, our determination of gas-phase P.A.'s is a form of measuring the enthalpy term of eqn (1). On the other hand, entropy changes are usually produced by symmetry alterations on protonation. We will now discuss some possible structural changes which could take place in solution, and therefore modify ΔH prot, s, $\Delta S°$ prot, s or both, simultaneously.

Both experimental determinations[15] and theoretical calculations,[19] show that the $-CONH_2$ group of benzamide is not coplanar to the aromatic ring, but twisted so that the dihedral angle (ϕ) between these two planes is about 24 deg. In principle, we expected a situation similar to that found in anisole,[20] i.e. that the conformation of the $-CONH_2$ group relative to the aromatic ring affects, not only the absolute value of the proton affinity of this compound, but also the site of protonation. To investigate this point we have carried out calculations on this molecule going from $\phi = 0°$ (planar conformation) to $\phi = 90°$ (orthogonal conformation). We have found benzamide to behave in quite different way from anisole: the intrinsic basicity of either center (oxygen and nitrogen atoms) does not change with ϕ. In consequence, the corresponding $\Delta H°$ prot, s should remain also unchanged. On the other hand variations of the corresponding molecular electrostatic potentials are so small that it is hard to believe that the rotation of the $-CONH_2$ group could introduce significant changes in the entropic term.

In the gas-phase the $-NH_2$ group of benzamide is practically planar. Another possible structural change produced by the intervention of the solvent, could be a certain pryimidization of the amino group. As this molecule is too big to study the influence of this effect on the intrinsic basicity of the N and O atoms, we have studied this point using a simpler molecule: formamide.

Our results, using the experimental geometry,[21] show that the P.A. of the O atom (evaluated from its O_{1s} orbital energy[15]) is 6.6 kcal/mol higher than that of the N atom. Similarly, the absolute minimum of the molecular electrostatic potential at the O atom (−61.6 kcal/mol) lies 25.8 kcal/mol below that at the N atom (−35.8 kcal/mol). Therefore, formamide, as benzamide, is an oxygen base in the gas phase.[13,22]

We have next carried out a full geomatry optimisation of this molecule (at the STO-3G level) for different values of θ (Fig. 2 for definition), from $\theta = 0$ (planar conformation) to $\theta = 55°$ (which corresponds approximately to a tetrahedral conformation). We have found that the difference between the P.A. values of O and N decreases gradually with increasing θ; at $\theta = 55$ this difference is 4.7 kcal/mol, i.e. 27% smaller than in the equilibrium conformation.

A similar result is found when the molecular electrostatic potential is evaluated. In this case the effect is stronger. For $\theta = 55°$, the absolute minimum at the O atom is −55.7 kcal/mol, i.e. 5.9 kcal/mol shallower than in the equilibrium conformation; but the one at the N atom is deeper (−68.6 kcal/mol) than in the equilibrium conformation, and lower than that at the O atom.

Therefore, pyrimidization of the amino group decreases the basicity of the carboxylic group and increases that of the amino group. In consequence, if this structural change takes place in solution, the difference between the enthalpy terms for both centers is smaller than in the gas-phase. The variations in this term are essentially of electrostatic nature, in agreement with the suggestions of Aue *et al.*[18]

However, this is not the only effect that occurs when pyrimidization of the $-NH_2$ group takes place. The same authors[18] indicate that the base interacts less strongly with the solvent, when there is a high degree of charge delocalisation. In our case it is evident that pyrimidization of the $-NH_2$ group makes more localised the nitrogen lone pair and therefore, a stronger interaction with the solvent should be expected. As no significant changes take place on the oxygen, this effect could favor nitrogen protonation. Also the contribution of the entropy term is in the same direction, because of the

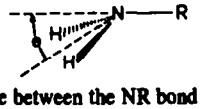

Fig. 2. θ is the angle between the NR bond and the NH_2 plane.

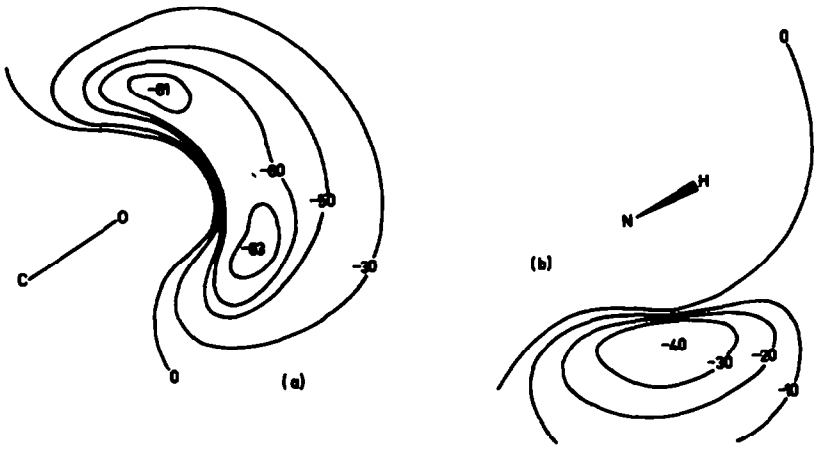

Fig. 3. Molecular electrostatic potential map for benzamide with $\theta = 30$ (a) and (b) as in Fig. 1.

unsymmetrical charge delocalisation introduced by pyrimidization.

To corroborate these conclusions in the particular case of benzamide, we have carried out just one calculation with $\theta = 30°$. Our results are parallel to those discussed for formamide. For instance, the corresponding molecular electrostatic potential (Fig. 3) shows that the minimum at the O atom is shallower, and the one at the N 2.5 times deeper, than those corresponding to the equilibrium conformation (Fig. 1).

We can conclude that benzamide is an oxygen base in the gas-phase being remarkable the difference between the P.A. of O and N atoms. Rotation of the $-CONH_2$ group respect to the aromatic ring does not affect the basicity of the molecule.

If the presence of the solvent causes pyrimidization of the amino group, the intrinsic basicity of the O atom decreases while that of the N atom increases and the interaction of this center with the solvent is stronger. This would explain the tautomerism with a changeover from O-protonated benzamide to N-protonated, proposed by Liler.[8]

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