THE EFFECT OF PROTONATION ON THE THERMAL ISOMERIZATION OF STILBAZOLIUM BETAINES

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MNDOC calculations have been carried out on the protonated and unprotonated forms of a stilbazolium betaine. The results show (1) a strong increase by 24 kcal/mol of the torsional barrier around the central bond upon protonation, (2) polar structures for the protonated as well as the unprotonated forms, and (3) strong alterations of the polar structure of the latter during isomerization, and predict a higher *pK* value for the cis isomer, particularly, in the case of less polar and less protonic solvents.

1. Introduction

Protonation can thoroughly change the valence structure of conjugated π-electron systems. For the case of the Schiff base of retinal, we have recently shown [1,2] that, in a protein environment, protonation can partially revert the structure of alternating single and double π-bonds and can allow isomerization around a double bond to proceed in the ground state. In the light-driven proton pump cycle of bacteriorhodopsin [3], such an acid-catalyzed reaction reconverts the retinal chromophore from an intermediate 13-cis configuration to its initial all-trans-configuration.

Other prominent examples of a change of valence structure upon protonation are provided by the merocyanine dyes of the stilbazolium betaine type M (see fig. 1). For these compounds, protonation of the oxygen can change [4] the quinonoid structure M_a into the polar structure M_b, which is essentially analogous to stilbene with two benzenoid rings and a central ethylenic C–C double bond. The π-bonding pattern of the stilbazolium betaines is easily influenced by external charges. In fact, the bond pattern can be rearranged to a large degree even by incomplete protonation of the oxygen, such as by hydrogen bonding with solvent molecules [4,5]. This rearrangement is spectroscopically witnessed by a strong negative solvatochromy [6,7]. The work of Bayliss and McRae [8] has established that the solvent shifts of the merocyanine dyes, indeed, are mainly due to the hydrogen-bonding capability of the solvent rather than to its bulk dielectric properties. Assuming specific interactions with both the nitrogen and oxygen atoms, the extreme solvatochromic effect observed for the stilbazolium betaine M in polar protonic solvents has been explained by Benson and Murrell [5] on the basis of a π-electron theory. From their calculations, which included a bond-length optimization, these authors also predicted that in a non-polar solvent the dye should have the quinonoid structure M_a, whereas in a highly polar solvent is should assume the benzenoid structure M_b. It should be stressed at this point that, in the π-electron model of Benson and Murrell, the limiting case of the stilbazolium betaine M in a highly polar solvent is represented essentially by the protonated molecule MH^+ in the vacuum. The stilbenoid structure M_b leads to the expectation that stilbazolium betaines like many stilbene derivatives

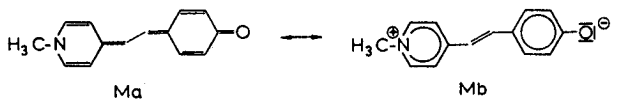

Fig. 1. Quinonoid (M_a) and benzenoid (M_b) resonance structures for the stilbazolium betaine M.

should exist in a cis as well as in the trans configuration and that the cis isomer, although thermodynamically less favourable due to steric hindrance, should be sufficiently stable for at least spectroscopic identification.

Recently, Steiner et al. [9,10] have shown that the strengthening of the central C–C bond induced by a highly polar solvent, in fact, leads to the existence of a fairly stable cis isomer of the stilbazolium betaine M. This isomer had been prepared in aqueous solution by photochemical trans → cis isomerization of the protonated compound MH^+ and subsequent deprotonation. In contrast to the thermally stable cis isomer of MH^+, the unprotonated merocyanine M exhibited a strongly temperature-dependent thermal cis → trans isomerization with an activation enthalpy of 27.9 kcal/mol and a rather large positive entropy of activation of 45.4 cal/mol K [11]. An investigation of the dependence of these activation parameters of the nature of the solvent has demonstrated that they both decrease with decreasing solvent polarity. In chloroform, for instance, values of 18.1 kcal/mol for the enthalpy and of 11.3 cal/mol K for the entropy of activation have been measured [11]. The existence of a cis-stilbazolium betaine had been observed previously only by Schulte-Frohlinde and Güsten [12] as an intermediate in the termal cis → trans isomerization of a hydroxystyryl-quinolinium cation, i.e. the O-protonated form of the betaine.

In order to obtain some more insight into the torsional stability of the central C–C bond of the stilbazolium betaine M and into its dependence on the protonation state, we have carried out quantum-mechanical all-valence-electron MNDOC [13] calculations. The next section presents the computational results on equilibrium geometries, charge distributions and isomerization potential curves for the unprotonated and protonated molecules M and MH^+.

2. Results

Figs. 2a and 2b show the calculated bond lengths of the molecular backbone of the merocyanines M and MH^+, respectively. The data result from MNDOC calculations [13] in which all bond lengths and bond angles have been optimized and planar conformations of the molecules are assumed. The pattern of bond

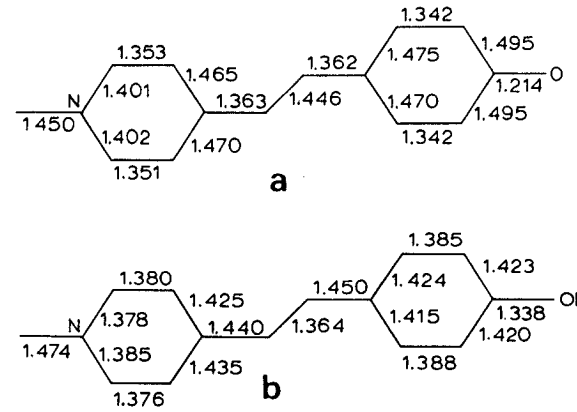

Fig. 2. Bond lengths of the carbon skeleton of the (a) unprotonated and (b) protonated stilbazolium betaines M and MH^+, respectively, resulting from MNDOC calculations. The distances are given in Å.

lengths in fig. 2a for the stilbazolium betaine M clearly corresponds to the quinonoid valence structure M_a (cf. fig. 1), whereas the geometry of the protonated compound MH^+ shown in fig. 2b matches the benzenoid structure M_b. Upon protonation, the central C–C bond length is reduced from a value of 1.466 Å, corresponding to a polyene-type single bond, to a value of 1.364 Å, which is typical of a polyene double bond. Conversely, protonation transforms the neighbouring double bonds into single bonds by stretching them from 1.36 to ≈1.45 Å. Correspondingly, in the two ring systems the dintinct quinonoid bond-length alternation predicted for M is found to shift towards a benzenoid structure upon protonation (compare figs. 2a and 2b).

According to the simple resonance picture shown in fig. 1, protonation stabilizes the migration of a π-electron charge from the pyridine ring towards the protonated oxygen. In fact, our MNDOC results corroborate to some extent this concept as can be concluded to a comparison of figs. 3a and 3b, which show the atomic partial charges of the stilbazolium betaines M and MH^+, respectively. We also indicated the total charges appearing in certain areas of the molecules.

Fig. 3a shows that the unprotonated merocyanine M is characterized by strong dipoles localized in the regions of the double bonds. The molecule has an overall dipole moment of 8.4 debye. The pyridinium moiety carries a positive charge of $+15 \times 10^{-2} e$ and the phenoxy moiety a negative charge of $-16 \times 10^{-2} e$. Hence, the vacuum structure of M is rather

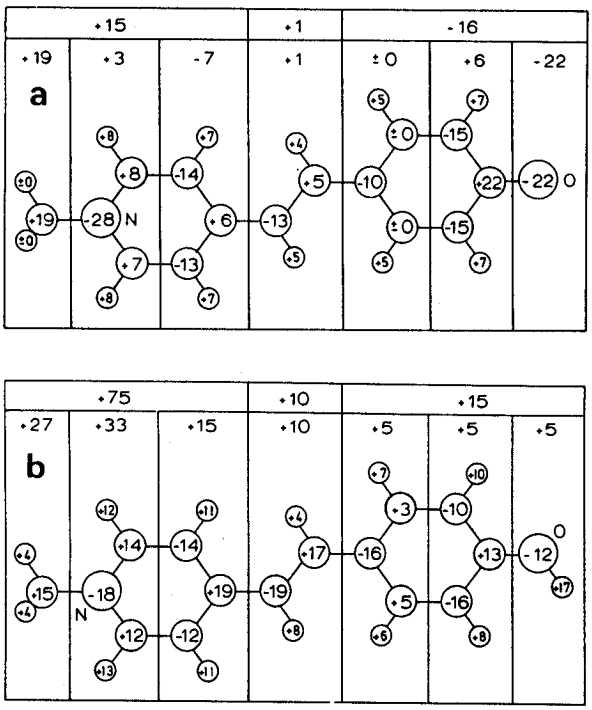

Fig. 3. MNDOC atomic partial charges of (a) M and (b) MH^+. The charges are given in units of 10^{-2} e.

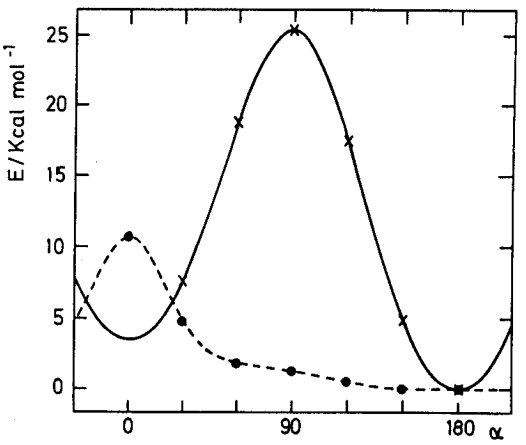

Fig. 4. Effect of protonation on the isomerization potential curve of the stilbazolium betaine X; X = MH^+ (—); X = M (– – –). The curves represent a cubic spline interpolation of the numerical values calculated at 30° intervals; trans is at a torsion angle α of 180°, cis is at 0°.

polar, although the correspondence of its geometry to the non-polar valence structure M_a suggests the opposite.

In the protonated dye, the alternation of positive and negative partial charges along the molecular skeleton, which generates the local dipoles, is even more distinct than in the unprotonated compound (see fig. 3b). The positive charge is delocalized over the whole molecule. However, 75% of this charge is situated in the region of the pyridine ring. In this respect, our MNDOC results resemble the charge distribution which can be deduced from the valence structure M_b in fig. 1.

Fig. 4 presents the effect of protonation on the potential curve for the ground-state trans → cis isomerization around the central C–C bond. For the calculation of the molecular energy along the reaction coordinate α (see the caption to fig. 4), the bond lengths and bond angles as well as various torsional angles have been optimized. The latter included, in particular, the torsional angles of the C–C bonds adjacent to the central C–C bond. Upon protonation, the activation energy increases from 1.3 to 25.3 kcal/mol. The activation energy is defined here as the difference of the molecular energies in the transition state ($\alpha = 90°$) and in the all-trans configuration ($\alpha = 180°$). The corresponding data on polyene-type bonds are 5 kcal/mol (experimentally) and 1.1 kcal/mol (MNDOC) for isomerization around the central single bond of butadiene and ≈50 kcal/mol (experimentally and MNDOC) for double-bond isomerization (see the discussion in ref. [1]). Hence, according to our description, the central C–C bond of M is predicted to have the torsional stability of an ordinary polyene-type single bond.

Our calculations show that, due to steric hindrance, the cis state of the unprotonated merocyanine M, assumes an energy of 10.7 kcal/mol above the trans state. The cis state is found to be non-planar. The steric interaction of the two arene rings enforces a twist of the two strong π-bonds adjacent to the central C–C bond by ≈12°, which appears to be the reason for the rather high energy of the cis state of M. Fig. 4 shows that M is lacking an activation barrier and, hence, the cis conformer described should not be stable in a non-polar environment.

The torsional stability of the central C–C bond is strongly increased for the protonated compound MH^+. Although the bond does not assume the stability of a true double bond, the protonation effect of 24

kcal/mol is large enough to allow the existence of a fairly stable cis isomer. The barrier increase determined here is about twice as large as a related effect predicted by us recently for the Schiff base of retinal [1]. In this case, the single bond most sensitively influenced by protonation of the Schiff base nitrogen is the 14–15 bond and, according to MNDOC, its rotational barrier in the protonated form is predicted to be 13 kcal/mol.

The equilibrium geometry calculated for the cis isomer of MH^+ deviates much more from planarity than the corresponding conformation of M. In the case of MH^+, the torsional angles of the weak π-bonds neighbouring the central bond are predicted to be $\approx 50°$. Thus, in contrast to M, the protonated molecule MH^+ can avoid a strong steric interaction of the arene rings by twisting around these two single bonds. Consequently, the energy of the cis state is raised above the trans state by only 3.5 kcal/mol. This energy may be slightly underestimated by our calculation because of the deficiency of the MNDOC method in determining torsional barriers of single bonds [1].

The distribution of partial charges in the cis isomer of MH^+ is similar to that in the trans configuration. 85% of the positive charge is located in the region of the pyridine ring and only 4% in the phenoxy moiety. However, along the reaction coordinate of cis → trans isomerization, a transient but major rearrangement of charges takes place. In the transition state ($\alpha = 90°$) the interrupted conjugation of the π-system prevents the migration of the π-electron towards the protonated oxygen such that the pyridine ring carries only 11% of the positive charge. Corresponding to this charge distribution, the transition-state geometry is characterized by a quinonoid alternation of single and double bond lengths. Therefore, in terms of the valence structures of fig. 1, the transition state of MH^+ corresponds to the non-polar valence structure M_a. In contrast to MH^+, the unprotonated merocyanine M does not show any major alterations of geometry and charge distribution during isomerization.

3. Summary and discussion

Our all-valence-electron MNDOC calculations have demonstrated that equilibrium geometries, charge distributions and stereochemical properties of stilbazolium betaines depend sensitively on the protonation state. In particular, no barrier for thermal cis → trans isomerization around the central C–C bond exists for the unprotonated compound whereas this barrier is 22 kcal/mol for the protonated molecule. This effect of protonation on the torsional stability of a π-bond is much larger than those calculates in the related case of the protonated retinal Schiff base [1].

Although we did not attempt to provide a description of the strong solvent effects observed for the stilbazolium betaines and although our results do not pertain directly to the properties of these molecules in solution, they still explain why the merocyanines are ideally suited for strong interactions with polar protonic solvents. Because of the very polar character even of the unprotonated merocyanine M, it appears plausible that a solvent by stabilizing the local dipoles and by forming hydrogen bridges to the oxygen can transform M into a structure which resembles that of MH^+ [4,5]. Hence, one expects the existence of a metastable cis isomer of the unprotonated compound in polar protonic solvents. According to our calculations, the non-polar transition state of the cis → trans isomerization renders such a strong solvent–solute interaction impossible. This implies an increased solvent disorder in the transition state and rationalizes the observation [9,11] of a large positive entropy of activation for the thermal isomerization of M as well as its decrease in less polar solvents. Furthermore, because a major intramolecular rearrangement of positive charge is predicted to accompany the isomerization of the protonated compound MH^+, the extraordinary thermal stability of its cis-isomer in water [9] has to be expected.

Our calculations clearly indicate to what extent the existence of stable cis isomers observed for the unprotonated stilbazolium betaines [9,12] depends on the nature of the solvent. It has been demonstrated that in a non-polar environment the central C–C bond of these merocyanines should exhibit only the torsional stability of a polyene-like single bond, whereas in a protonic environment it should gain considerable double-bond character. Therefore, the experimental value of 27.9 kcal/mol measured for the activation energy of thermal cis → trans isomerization

of M in aqueous solution, besides containing contributions due to solvent–solute interactions, is predicted to decrease sharply upon reduction of the solvent polarity and hydrogen-bonding capacity. In fact, this behaviour has been observed recently [11].

The rather low energy of 3.5 kcal/mol of the protonated cis isomer as compared with the 10.7 kcal/mol of the unprotonated cis conformer implies that the pK of stilbazolium betaine should increase upon trans → cis isomerization. The measurements of Steiner et al. [9] yielded indications that this appears to be the case. From the above considerations, it is apparent that the increase of pK should be larger in less polar and less protonic solvents. Further measurements to corroborate the increased basicity of stilbazolium betaines in the cis conformation would be of importance for the explanation of the proton pump activity of the retinal Schiff base in bacteriorhodopsin. In the latter case, a steric hindrance rendering an isomerization around a single bond incomplete may induce a strong decrease of the pK of the Schiff base [2,14,15]. Stilbazolium betaines could represent the first "in vitro" example of a stereochemical steering of acid–base properties mediated through the protonation-induced change of π-bond stability.

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