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A study of amino-protecting groups using the polarizable continuum model (PCM)

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Abstract. In order to better understand the performance of 1,2-dimethyl-5-acetyl barbituric acid (DMB) as an amino protecting group relative to 5,5-dimethylcyclohexane-1,3-dione (DMD), ab initio calculations were performed. pK_a calculations using the PCM model indicated that both molecules are more acidic in the enol form. Therefore, the protecting reaction of these molecules should involve the anions formed from the loss of a proton from the enol compounds. Contrary to what would be expected, the larger efficiency exhibited by the DMB molecule cannot be attributed to an extension of the electronic conjugation effect. In the absence of any other noticeable effect that could be responsible for the greater efficiency of the DMB molecule, we are inclined to believe that the difference could be accounted for by the presence of two independent centers of conjugation.

Keywords: Dimedone – Dimethyl barbituric acid – pK_a calculations – Protecting groups

Introduction

Specific protecting groups play a key role in organic synthesis [1]. The strategy of using protecting groups allows the selective manipulation of poly-functional substrates. In order to be efficient, such groups must be easily introduced and removed from the substrate, and should not react during all of the intermediate reactions along the synthetic path prior to their elimination.

Along a synthetic route, there is often a need to protect primary amines [2, 3] as, for example, in the synthesis of spermidine [4]. In the course of our studies of the synthesis of this compound using selective protecting groups, we found that 1,2-dimethyl-5-acetyl barbituric acid (DAB) reacts with primary amines but is inert relative to secondary amines, sulfonamides, carbamates and alcohols. Preliminary tests involving the reaction of DAB with seven different primary amines showed an average yield of 86%. Besides that, the addition and elimination reactions of DAB can be conducted, in almost all cases, at room temperature [5].

Another protecting group generally used with primary amines is dimedone (5,5 dimethylcyclohexane-1,3-dione) (DMD) [6]. Comparing the performance of DMD and DAB in protecting primary amines, it was observed that DAB is a much more efficient agent. Apparently, the difference in efficiency can be related to the possibility of extending the electronic conjugation due to the presence of the N-(C=O)-N moiety in DAB. The protecting reaction could be viewed as a nucleophilic attack [6] of the anion (formed by the loss of a proton from the protecting group) on the nitrogen atom of the primary amine. Therefore, the presence of the N-(C=O)-N moiety would have an important role in stabilizing the anion. In order to check this hypothesis, one must investigate how easily DAB and DMD can lose a proton in solution to form the anions that would attack the amine. That is, we need to compute the pKa of these compounds in solution.

In this paper, the pK_a of DMD and 1,3-dimethylbarbituric acid (DMB), a substance closely related to

This paper is dedicated to Jacopo Tomasi in recognition of his outstanding contribution to the field of computational chemistry in solution. The authors are honored to contribute to this volume; especially so for two of them (COS and MACN) who have the privilege of his friendship.

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DAB, are calculated and compared. DMB was chosen for comparison because it is computationally simpler and exhibits the same structural characteristics as DAB.

The calculations presented are not intended to provide absolute pK_a values. However, as experimental pKa values, to the best of our knowledge, are not available for DMD and DMB, the calculations can at least furnish the relative ordering of the pKa values for these compounds. Based on these relative values, it might be possible to understand the experimental observations concerning the efficiency of these compounds as protecting groups.

Adopting a thermodynamic cycle whose advantages and shortcomings have been previously discussed [7, 8, 9], theoretical calculations were performed in order to obtain the p*Ka* values of DMD and DMB compounds in aqueous solution. Both structures are shown in Figs. 1 and 2, where the acidic hydrogen atom is identified in bold type.

These compounds show keto-enol tautomerism, and both forms can coexist in solution. Indeed, in aqueous solution, it is even more important to consider the enol form than for the gas-phase, due to the interactions that can be established between the solute and the solvent through hydrogen bonds [10, 11]. Therefore, any theoretical attempt at modeling the acid-base equilibrium must also include the keto-enol tautomerization. Taking both equilibria into account, schematic representations of the acid-base and tautomeric equilibria are given in Fig. 3 for DMD and in Fig. 4 for DMB.

The pK_a values were calculated for the keto and enol forms of both compounds (Figs. 3 and 4), where K^K stands for the acid-base equilibrium constant of the keto form, and K^E for the enol form.

The expression relating the pK_a and the variation of the standard Gibbs free energy of the acid-base equilibrium in aqueous solution is:

$$\Delta G^0(\text{kcal/mol}) = 1.36 \times \text{p}K_a + 2.36$$

where ΔG^0 is obtained from the respective thermodynamic cycle, built for each tautomeric form, and is given by the expression:

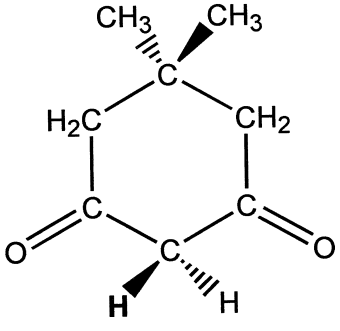

Fig. 1. DMD compound

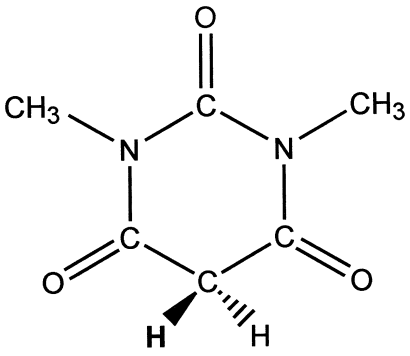

Fig. 2. DMB compound

$$\begin{aligned}\Delta G^0 = &-\Delta G_{\text{solv}}(\text{AH}) + \Delta E_{\text{relax}}(\text{AH}) + \Delta G^0_{\text{vap}}(\text{H}_2\text{O}) \\ &+ \Delta G^0_{\text{vac}} + \Delta E_{\text{relax}}(\text{A}^-) + \Delta G_{\text{solv}}(\text{A}^-) \\ &+ \Delta E_{\text{relax}}(\text{H}_3\text{O}^+) + \Delta G_{\text{solv}}(\text{H}_3\text{O}^+),\end{aligned}$$

where $\Delta G_{\text{solv}}(\text{X})$ and $\Delta E_{\text{relax}}(\text{X})$ are respectively the solvation energy and the relaxation energy calculated for any species X in the cycle, $\Delta G^0{}_{\text{vap}}(\text{H}_2\text{O})$ is the standard Gibbs free energy of vaporization of water at 298.15 K and 1 atm [7, 8, 9], and $\Delta G^0{}_{\text{vac}}$ is the standard variation of Gibbs free energy of the proton transfer process from AH to H_2O in gas-phase.

Computational details

Unless otherwise specified, all of the calculations were performed at Hartree Fock HF/6-31G+(d,p) level, and the geometries were optimized in gas-phase and in solution. The Integral Equation Formalism (IEF) [12, 13] formulation of the Polarizable Continuum Model (PCM) [14, 15] was used for computing the solvation effects. In this approach, the solvent is described as a dielectric continuum medium, polarized due to the presence of the solute. A cavity is opened in this dielectric continuum, built from interlocking spheres centered on the nuclei of the solute atoms. The van der Waals radii adopted for such spheres, proposed by Bondi [16], are 1.52 Å for oxygen, 1.55 Å for nitrogen, 1.7 Å for carbon and 1.2 Å for hydrogen, multiplied by a factor of 1.2 for all atoms of the neutral species (except for hydrogen atoms bound to oxygen atoms, when a factor of 1.0 was used). For all atoms of the anionic species, the radius of each sphere was multiplied by a factor of 1.1.

Another type of molecular cavity, parameterized for the calculation of solvation energies, the so-called United Atom Topological Model (UATM) [17], was used in some previous pK_a calculations. However, this kind of cavity was not adopted in the present study because of the large structural differences between the compounds used for its parameterization and those considered here.

The following components of the solvation energy were considered in the theoretical treatment: electrostatic, cavitation and dispersion-repulsion. The geometry of each system was optimized taking into account just the electrostatic component in the gradient calculations. The remaining non-electrostatic components were added to the final solvation energy through single point calculations at the geometry already optimized in the previous step.

The gas-phase calculations were performed using the Jaguar [18] code, while for the calculations in solution the Gaussian98 [19] package was used.

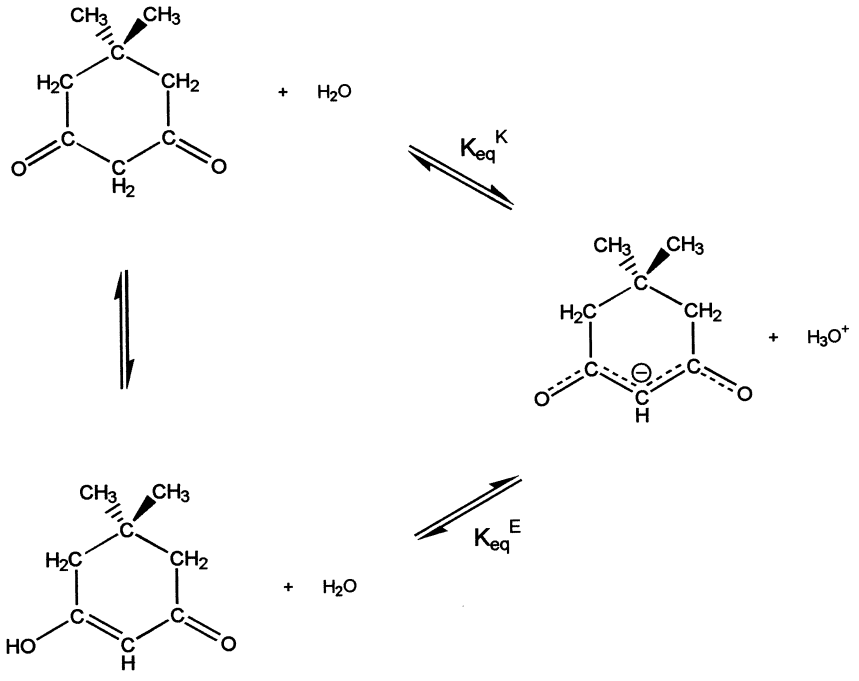

Fig. 3. Keto-enol and acid-base equilibria for DMD

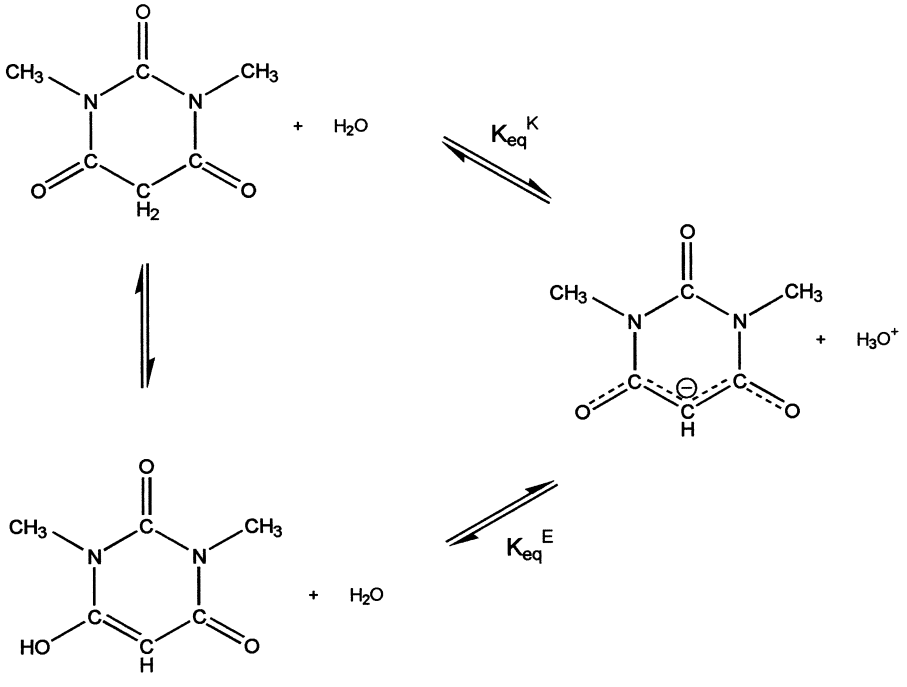

Fig. 4. Keto-enol and acid-base equilibria for DMB

Results and discussion

The pK_a values calculated for DMD and DMB are shown in Table 1. The results in this table indicate that the enol forms of DMB and DMD are more acidic than the respective keto forms in aqueous solution. Since the enol tautomer of DMB is more acidic than the other tautomers by a significant amount, in spite of adopting a theoretical model where some approximations were made, it is quite improbable that more sophisticated calculations would drastically change the ordering of the results obtained.

Due to the level of calculation employed along the thermodynamic cycle used in the pK_a calculations, we expect non-isodesmic acid-base equilibrium reactions to be more sensitive to the fact that electronic correlation effects were not taken into account [7, 8, 9]. In other words, the pK_a values obtained for the keto forms may be less reliable than those obtained for the enol forms. Since experimental pK_a measurements are not available

for such compounds, the model adopted was tested for its ability to furnish the relative pK_a ordering for 1,3 alkyl diketones whose experimental values are available in the literature [20]. Four compounds, with experimental pK_a values in the range from 5.86 to 19.0, were used. Although the resulting theoretical pK_a values were on average higher than the experimental ones, the correlation coefficient for experimental and calculated values was $r^2 = 0.9974$, indicating that the theoretical model can reliably predict the correct ordering of pK_a values.

Figures 5 and 6 show the geometries obtained for the species studied, and some relevant geometric parameters are given in Tables 2 and 3 for the systems in gas phase.

DMD has C_s symmetry, reflected in the geometric parameters in Table 2. Its ring assumes a chair conformation in the keto form, while being almost planar in the enol form, with the C-5 atom out of plane. There is a little distortion of the enol ring, as can be seen from the value of the C-1–C-2–C-3–C-4 dihedral angle. For DMD^- no more distortions are observed and the ring is practically planar, in order to favor the electronic conjugation, but the C-5 atom is still slightly out of the plane.

DMB has C_{2v} symmetry in its keto form (Table 3). The geometric parameters show that the N-1–C-1–N-2 angle is larger than the C-3–C-4–C-2 angle in the keto form. For the enol, the situation is reversed, and for the conjugate base the former angle is considerably smaller than the latter. The C-2–O-2 and C-3–O-3 distances can assume different values, depending on the character of the bond involved. They are shorter in the double bond (keto form), different in the enol form and present an intermediate value in the conjugate base, reflecting electronic conjugation. The N-1C-3 and N-2C-2 bonds are longer in the conjugate base than in the keto and enol forms. This is not what is generally observed in the presence of electronic conjugation effects. The increase in the N–C bond length in the anion, relative to its value in the other forms, was also reproduced by B3LYP/6-31G + (d,p) calculations, performed just for this case, in order to verify if this behavior could be related to any HF instability [21].

In the enol form of DMB, the methyl group close to the hydroxyl group is rotated in order to minimize repulsive interactions (Fig. 6, Table 3). In aqueous solution this methyl group has the same orientation as found in the keto form. The hydrogen atom of the hydroxyl group is out of the plane, as can be seen from the respective dihedral angle.

Table 1. Theoretical pK_a values calculated in this work

Compound	Enol	Ketone
DMD	15.5	18.24
DMB	5.77	16.79

Table 2. Geometric parameters for DMD. Distances are in Å and angles in degrees

Parameter	Keto	Enol	Conjugate base
C-1–C-2	1.519	1.331	1.409
C-2–C-3	1.519	1.467	1.409
C-3–C-4	1.514	1.518	1.531
C-1–C-6	1.514	1.505	1.531
C-1–O-1	1.192	1.342	1.231
C-3–O-2	1.192	1.200	1.231
C-1–C-2–C-3	113.91	120.96	123.66
O-1–C-1–C-2	120.94	119.53	125.24
O-2–C-3–C-2	120.94	121.98	125.27
C-1–C-2–C-3–C-4	−37.71	−6.60	−1.89
O-1–C-1–C-2–C-3	−143.82	177.82	−179.87
O-2–C-3–C-2–C-1	143.80	175.90	179.95
H-1–O-1–C-1–C-2	-	176.60	-

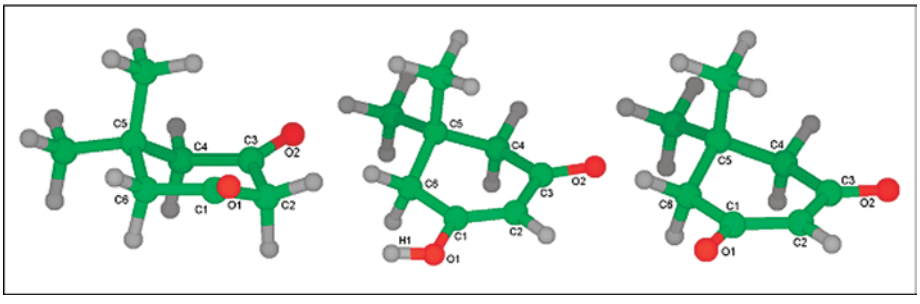

Fig. 5. Ketone (left), enol (middle) and conjugate base (right) structures of DMD, optimized in gas phase

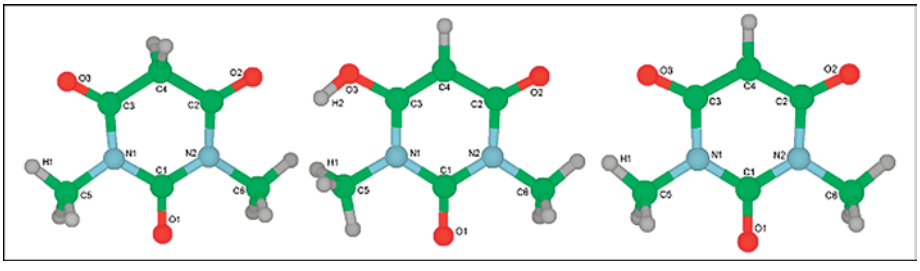

Fig. 6. Ketone (left), enol (middle) and conjugate base (right) structures of DMB, optimized in gas phase

Table 4 shows some intermediate quantities employed in the pK_a calculations. The solvation energy of the species involved is shown in the first column. From these values, it is clear that the interaction of the enol form, of both species, with the solvent is stronger than that of the respective keto forms. Also, both conjugate bases are strongly stabilized by the interaction with the solvent. However, the difference in stabilization brought about by the interaction with the solvent is much larger for the non-dissociated enol forms of DMD and DMB than for the conjugate bases.

Since pK_a is an equilibrium property, the main source of the large difference observed between the pK_a of DMD and DMB, in both tautomeric forms, may be related to the difference in the stabilization of the respective conjugate bases. Therefore, a more detailed structural study of both anions, the dimedonade (DMD^-) and the 1,3 dimethyl barbiturade (DMB^-), would be desirable. The stabilization of the conjugate bases should be mostly due to the electronic conjugation effect, and since this type of effect should be hardly affected by the presence of the solvent, its role in the relative stabilization of the conjugate bases can be well established by calculations in the gas-phase. These calculations are much less time consuming than the ones in solution for the size of the systems being investigated.

Figures 5c and 6c illustrate the chemical structures of the DMD^- and DMB^- anions, presenting C_s and C_{2v} symmetry, respectively. Both structures have π orbitals perpendicular to the ring plane. As the ability of the HF wavefunction to describe this kind of system has been questioned [22, 23, 24], MCSCF calculations were performed in π space. For DMD^-, a (6/6) MCSCF was performed, and a (12/12) for DMB^-; both calculations including all of the π electrons in the active space.

The GAMESS [25] computational code was used for the MCSCF calculations and for the successive localization steps of the MCSCF orbitals, according to the Edmiston-Ruedenberg procedure [26]. Some of the MCSCF orbitals relevant to our analysis are shown in Figs. 7 and 8. It is important to emphasize that these orbitals are all singly-occupied.

Table 3. Geometric parameters for DMB. Distances are in Å and angles in degrees

Parameter	Keto	Enol	Conjugate base
C-1–N-1	1.384	1.389	1.364
C-1–N-2	1.384	1.365	1.364
N-1–C-3	1.375	1.376	1.421
N-2–C-2	1.375	1.402	1.421
C-3–C-4	1.503	1.337	1.402
C-2–C-4	1.503	1.446	1.402
C-3–O-3	1.193	1.329	1.224
C-2–O-2	1.193	1.199	1.224
C-1–O-1	1.193	1.200	1.216
N-1–C-1–N-2	119.02	117.09	117.87
C-3–C-4–C-2	117.87	119.78	123.14
H-1–C-5–N-1–C-1	179.91	-123.31	179.12
H-2–O-3–C-3–N-1	-	17.96	-

Table 4. Quantities employed in the pK_a calculations (kcal/mol)

	X	ΔG_{solv}	ΔE_{relax}	ΔG^0_{vac}
Compound	Ketone	−3.83	−0.18	176.43
DMD	Enol	−7.58	−0.49	168.34
	Base	−62.26	0.20	-
	Ketone	−8.46	−0.26	167.45
DMB	Enol	−14.09	−2.09	158.95
	Base	−60.33	0.29	-

DMB^-

Figure 7 shows a π-type MCSCF orbital localized on the C-1 atom. Similar orbitals, localized on atoms C-2, C-3 and C-4, were also found. Likewise, two similar orbitals were found localized on each N atom and three similar orbitals on each O atom.

Among the remaining orbitals of the (12/12) MCSCF calculation, one is delocalized over the O-3–C-3–C-4–C-2–O-2 moiety, and another one over the N-1–C-1–(O-1)–N-2 moiety. However, none of the orbitals are delocalized over the entire ring. Therefore, it can be said that there are basically two centers of electronic conjugation in this molecule, each one with six π electrons.

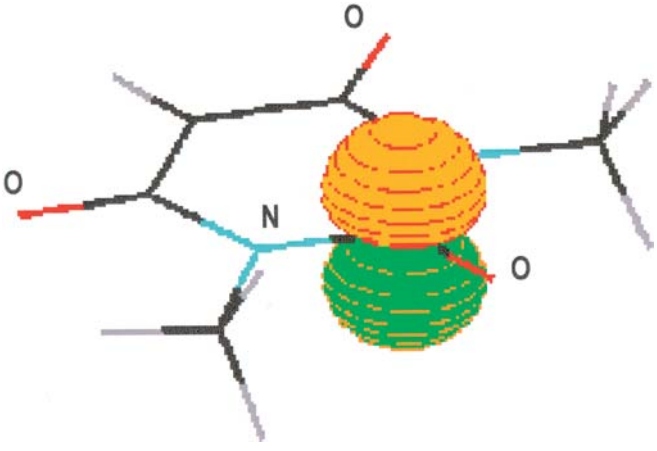

Fig. 7. 2*p*-like orbital localized on the C-1 atom of DMB compound

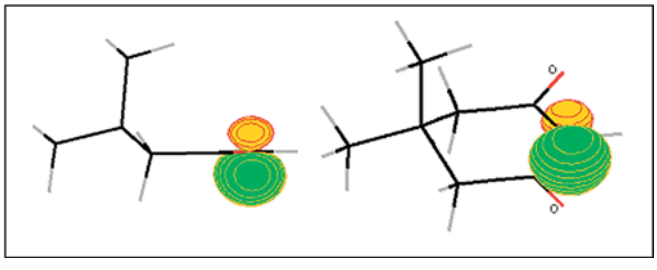

Fig. 8. 2*p*-like orbital localized on the C-2 atom of DMD compound

The first is formed by the O-3–C-3–C-4–C-2–O-2 moiety, and the second by the N-1–C-1–(O-1)–N-2 moiety. This is in agreement with the geometry changes observed in Table 3. The N-1–C-1–N-2 angle is reduced, and the N-1 and N-2 atoms are closer to each other in the anion than in the keto form. On the other hand, the distances N-1–C-3 and N-2–C-2 are larger in the anion, contrary to what would be expected in the presence of any electronic conjugation involving such centers.

DMD$^-$

Differently from the DMD$^-$ anion, there is just one center of electronic conjugation in this system.

For this molecule, five orbitals like the one shown in Fig. 7 were obtained, each one centered on an atom involved in the O=C–C–C–O$^-$ conjugation. Fig. 8 shows two views of a 2*p*-like orbital localized on the C atom. As the ring is not planar, one of the methyl groups bound to atom C-5 is located above the ring. The side view on the right of Fig. 8 illustrates the distortion of the π cloud due to the proximity of this methyl group.

From the analysis of the MCSCF calculation, it is clear that the better performance of the DMB molecule as a protecting agent cannot be attributed to the possibility of extending the electronic conjugation effect due to the presence of the N-(C=O)-N moiety. Also, it is quite improbable that the worse performance of DMD could be ascribed to steric effects. It is true that the DMD$^-$ ring is not exactly planar and that one of the methyl groups bound to the C-5 atom is projected inside the ring. However, assuming that the protecting reaction involves the attack of the DMD$^-$ species on the amine, through the O-1 atom outside the ring (see Figure 5c), the repulsive interactions between the methyl group above the ring and the approaching amine would not be strong enough to account for the much lower efficiency of DMD relative to DMB. On the other hand, for secondary amines, this effect could indeed be large enough to prevent the reaction, as observed experimentally. Therefore, the better performance of the DMB molecule can be only ascribed to an intrinsic stability of this molecule, due to the presence of two centers of electronic conjugation.

Conclusions

The pK_a calculations using the PCM model have shown that both the DMB and DMD molecules are much more acidic in the enol form. Therefore, the protecting reactions of these molecules should involve the anions formed from the loss of a proton from the enol compounds. Contrary to what would be expected, the larger efficiency exhibited by the DMB molecule cannot be attributed to an extending of the electronic conjugation effect. On the other hand, in the absence of any other noticeable effect that could be responsible for larger efficiency of the DMB molecule, we are inclined to believe that the difference could be accounted for by the presence of two (although independent) centers of conjugation.

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