Tautomerism in Alloxan

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Ab initio STO-3G, 3-21G and 6-31G calculations have been used to investigate the energetics of the tautomerism in alloxan. The geometries of the tautomers have been fully optimized at STO-3G level. The results indicate that tautomerism in alloxan in the vapour is highly unlikely, the trioxo structure being by far the most stable structure. The population analysis of the alloxan anion gives evidence that the preferred protonation site is offered by the central oxygen atom, and rules out the opposite oxygen atom as a possible protonation site.

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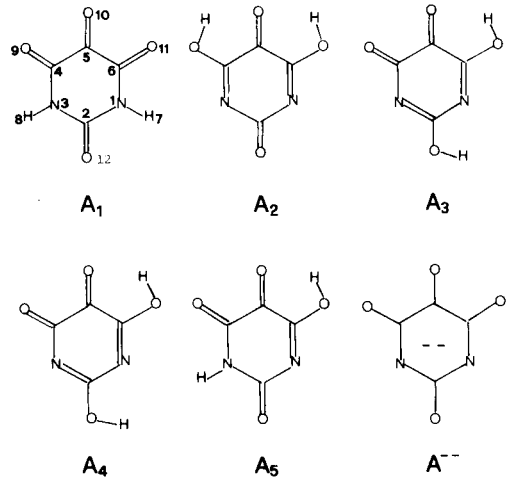
Alloxan is a "barbiturate". Interest in these compounds is related to their biological and pharmaceutical importance. The molecular structure of alloxan is known from an X-ray analysis [1], which indicates that in the solid the compound exits as the oxo structure **A1**, as does indeed barbituric acid itself [2]. Theoretically alloxan may exist in the tautomeric forms **A1-A5**. The energetics of the lactim-lactam tautomerism is of great importance in chemistry and biochemistry [3], accordingly many recent theoretical studies have dealt with this topic [4-8]. Information on the possible **A1-A5** tautomeric equilibria are absent. In the present paper we report the results of theoretical calculations on the enol/exo tautomerism of alloxan. The molecular geometries of the tautomers were fully optimized with the minimal STO-3G basis set by assuming planarity in all molecules and within C_{2v} contraints for the geometry of **A1**, **A2** and $\mathbf{A}^{--}$. To estimate the dependence of the relative energies on the quality of the basis set, single point calculations were performed with the 3-21G and 6-31 bases on the STO-3G geometry. The calculated geometries are shown in Figure 1. The largest mean absolute deviation from the experimental X-ray structure of alloxan is 0.035 Å and 1.5° for bond lengths and bond angles, respectively. As expected, the most significant changes in the molecular geometry, following the enol/exo tautomerism, are associated with the C-N and C-O bond lengths and with the internal carbonyl carbon valence angle. Deprotonation of alloxan produces significant changes in the O = C-N-C = O framework, living less affected the remaining part of the molecule. The calculated total and relative energies of the **A1-A5** tautomers are reported in Table 1. The ordering of stability of alloxan tautomers is invariably **A1 > A4 > A5 > A3 > A2** in the tree series of calculations. The 3-21G and 6-31G relative energies differ greatly from the STO-3G ones. This is very probably due to an overestimation of the stabil ity of the enol tautomer in the STO-3G calculations, as found in other enol/exo equilibria [4-8]. In the uracil tau tomeric system [7], for instance, the relative stabilty of the enol form (U3) with respect to the oxo form (U1) is



greater by *ca.* 12 kcal/mole in STO-3G//STO-3G than in 3-21G//3-21G calculations. When STO-3G//3-21G calculations were carried out the above figure becomes *ca.* 16 kcal/mole [7]. By comparing our STO-3G//STO-3G results with the more accurate 3-21G//3-21G results in uracil we may infer that our 3-21G data very probably overestimate the relative stability of the oxo forms by *ca.* 3-5 kcal/mole. This figure cannot change the predicted order of stability of the alloxan tautomers. Furthermore the above trend is even more emphasized by the 6-31G data. Therefore we decided not to carry out very expensive 3-21G//3-21G calculations on alloxan tautomers. Thus, by referring to Table 1, the conclusions follow: i) the trioxo structure is by far the most stable structure of alloxan in the vapor; ii) no evidence of tautomerism is predicted for alloxan in the vapour.

Interestingly, also no evidence of tautomerism was observed in the related compound 5,5-dihydroxybarbituric acid in the solid state [9]. Alloxan can be easily reduced in aqueous solutions, as well as in aprotic media, to the corresponding radical anion [10,11]. At low *p*H values the anion may be protonated [10]. On the basis of epr ex-

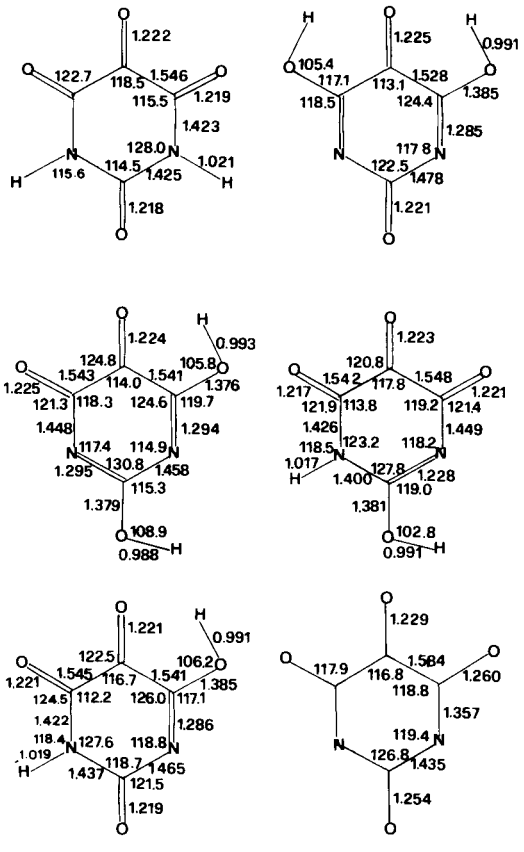


Figure 1. STO-3G molecular geometries of alloxan tautomers.

periments [12,13] the protonation site is postulated to be at O10. However, owing to the symmetry properties of the resulting neutral radical, it is not easy to differentiate between protonation at the O10 and O12 atoms [10]. The protonation site can be thought to be determined by the charge distribution of the unpaired electron. On this basis previous HMO [14] and INDO [11] calculations gave preference to protonation at O10. However, the formation of the neutral radical involves drastic electron redistribution at the related C=O bond. Thus it is more correct to consider the overall population at this bond. We may first look at the structure of the lowest unoccupied molecular orbital (LUMO) of the neutral alloxan, which is the orbital primarily involved in the electron transfer process. This orbital shows (Figure 2) great localization on the C5-O10 bond and it is expected to suffer major variations on passing from **A1** to **A1**$^-$. In fact by considering now the results of the population analysis in the alloxan ion (Table 2) we may note that information on the protonation site in **A1**$^-$ cannot come from the analysis of the charge distribution on the oxygen atoms; these all being almost equally charged. In contrast, it is quite evident that the C5-O10 bond is the best site for protonation. It gains 0.319 e$^-$ on passing from **A1** to **A1**$^-$ and its overlap population is reduced significantly with respect to the other C=O bonds in the molecule. By contrast the C2 = O12 bond shows in **A1**$^-$ a positive charge density and an increased overlap population. It may be safely ruled out as a protonation site in the alloxan anion. In the case of positive ionization of alloxan, charge density is principally (*ca.* 36%) removed from the C2-O12 bond, in line with the structure of the HOMO.

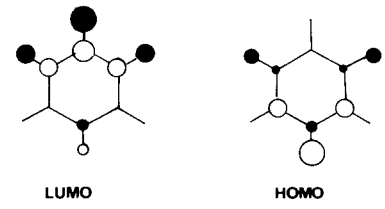


Figure 2. Lowest unoccupied (LUMO) and highest occupied molecular orbital (HOMO) of alloxan (STO-3G).

Table 1

Energies (E, a.u.) and Relative Energies (E_R, kcal/mole) of Alloxan Tautomers

	STO-3G//STO-3G		STO-3G//3-21G		STO-3G//6-31G	
	E	E_R	E	E_R	E	E_R
A1	−553.59300	0	−557.26126	0	−560.72502	0
A2	−553.54496	29.9	−557.17346	54.9	−560.62615	61.9
A3	−553.55079	26.4	−557.18105	50.2	−560.63324	57.4
A4	−553.57552	10.9	−557.22522	22.6	−560.68227	26.7
A5	−553.56940	14.8	−557.21905	26.4	−560.66850	35.4
A^{--}	−552.00161		−555.89770		−559.46414	

Table 2

Population Analysis of Alloxan and Alloxan Ions (STO-3G Basis)

	A1	**A1**$^+$	**A1**$^-$	**A**$^{--}$
Charges				
N1	−0.378	−0.287	−0.386	−0.174
C2	0.417	0.455	0.377	0.320
C4	0.290	0.313	0.217	0.240
C5	0.160	0.180	0.065	0.234
O12	−0.271	−0.016	−0.366	−0.208
O9	−0.219	−0.096	−0.360	−0.195
O10	−0.144	−0.074	−0.368	−0.089
H7	0.226	0.297	0.176	
Overlap population				
N1-C2	0.700	0.746	0.716	0.534
N3-C4	0.690	0.664	0.644	0.720
C4-C5	0.682	0.692	0.732	0.544
C2-O12	0.882	0.812	0.850	0.886
C4-O9	0.882	0.872	0.836	0.816
C5-O10	0.876	0.882	0.798	0.930
N1-H7	0.694	0.678	0.684	

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