A semiempirical SCF-MO study of the tautomeric forms of 3-acetyl tetronic- and tetramic acids

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SUMMARY

A number of tautomeric geometries of 3-acetyl tetramic acid and 3-acetyl tetronic acid were examined using the AM1 and PM3 methods. The results are compared with experimental data and with studies using MNDO and older methods, with the conclusion that both AM1 and PM3 provide satisfactory models of the behaviour of these species.

INTRODUCTION

The acyl tetronic and acyl tetramic acids are frequently found in nature [1], are versatile intermediates of considerable potential in the synthesis of other natural products [2], and, as highly stable acidic groups, also have potential as small anionic systems for use in drug design. Our interest in the ground state geometry of these molecules arose in the course of synthetic studies at that time being undertaken by Ley and coworkers. One of the natural products involved in these programs was to be made by a polyene cyclisation reaction, in the design of which the geometry of the acyltetronic acid unit was crucial; in another case the final product was an ionophore and the likely geometry of the tetronate unit was of interest both as an aid to understanding the process by which the ionophore bound to cations, and also to determine whether the synthetically reasonable substitution of a tetramic acid for the naturally-occurring tetronic acid would be expected to lead to substantial changes in the molecule's properties. Additionally, there were a number of complex features in the NMR spectra of intermediates in these programs that required explanation, and

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methylation of the natural products gave complex spectra which it was hoped would be more easily interpreted in the light of calculated expectations.

The 3-acyl tetronic- and tetramic acids contain a methine carbon bearing three chemically different carbonyl groups. The wide variety of possible enol tautomers in which one or two of these carbonyl groups are enolised makes these molecules an interesting test of theoretical techniques. If the exocyclic carbonyl group is enolised both E and Z isomers may be formed about the exocyclic double bond. There are also in some cases several possible hydrogen bonding patterns associated with a particular tautomer. Studies conducted in this area hitherto [3] have concentrated exclusively on the four simple monoenolic forms in which the highly acidic methine proton has undergone transfer to an oxygen atom. This superficially reasonable approach leaves a number of questions open, however. In particular, the location of the enol proton is not determined with any precision, and structural arguments that exist are founded largely on chemical shift data. Different authors have drawn opposite conclusions as to which is the major isomer and which the minor of the two species seen in $CDCl_3$ solutions, depending principally on interpretation of diamagnetic anisotropy effects by analogy with simpler systems. We felt that this was somewhat unsatisfactory, and in addition noted that there is no consideration of the possibility that a second enolisation could give rise to an 'aromatic' pyrrole (in the 3-acyl tetramic acid case) or furan (in 3-acyl tetronic acid). In the corresponding 2,5-diketopyrrolidines (succinimides) or with succinic anhydride, it has not proved possible to isolate the silyl monoenolethers, any enol ether-containing material being obtained as the doubly enolised pyrrole or furan [4]. This is particularly relevant in molecules related to the 3-acyl tetronic and tetramic acids by substitution at the 5 position since formation of a furan or pyrrole would cause racemisation of the chiral centre. Some attempts have been made by others to examine these difficult questions by theoretical means using CNDO, INDO, MINDO/2 and, in the most recent study on 3-acyl tetronic acids, MNDO semiempirical methods [3]; however, these methods are not well suited to the calculation of strongly hydrogen-bonded species, and even the results obtained in the 3-acetyl tetronic acids using MNDO fail to account quantitatively for the observed results. The presence of such strong hydrogen bonds may readily be inferred from the observation that NMR studies in polar solvents showed only one set of signals, consistent either with a stabilisation of one tautomer or, perhaps more probably, more rapid interconversion of tautomers as a result of the disruption of intramolecular hydrogen bonds by the more polar solvent. Finally, crystallographic methods have been applied to this problem [5] and may provide some guidelines regarding the structure of these species, but intermolecular hydrogen bonds are undoubtedly important in the solid state (two were detected, in addition to the expected intramolecular hydrogen bond) and other packing forces might also play a significant part in determining the observed crystallographic parameters.

Recent developments in semiempirical SCF/MO methods, in particular AM1, prompted us to examine these structures in an attempt to answer some of the above questions. The AM1 Hamiltonian has been used with considerable success in other examples of tautomerism [6]. We were also able to use the BFGS optimisation protocol which has been found to be more reliable in locating global minima in hydrogen bonded systems than the earlier DFP method [7]. We have therefore examined 12 geometries of 3-acetyl tetramic acid using both MNDO and AM1, while 13 3-acetyl tetronic acid geometries were studied using AM1, permitting comparisons with our 3-acetyl tetramic acid calculations and with literature MNDO studies. With the release of MO-PAC 5 we were also interested in exploring the results obtained using PM3.

MATERIALS AND METHODS

All the structures for MNDO or AM1 optimisation were preoptimised using the MODEL molecular mechanics program (available from K. Stelliou, Département de Chimie, Université de Montréal, C.P. 6128, succursale A, Montréal, Québec H3C 3J7, Canada), employing a modified version of the Allinger MM2 force field. The AMPAC [8] package was used for MNDO and AM1 calculations, and runs were carried out using the FPS-164 system at Imperial College Computer Centre, using BFGS optimisation. PM3 runs were carried out using MOPAC 5 [9] using a DEC MicroVAX 3200 workstation after preoptimisation of structures using SYBYL 5.2 [10]. Molecular mechanics calculations were performed on DEC VAX 8600 or microVAX machines attached to graphics terminals.

RESULTS AND DISCUSSION

In the molecular mechanics preoptimisation phase, three rotameric minima were found for the unenolised species. In the 3-acetyl tetramic acid case two of these converged on a single minimum after AM1 optimisation, while in 3-acetyl tetronic acid both methods showed three minima. These structures are shown in Table 1 as Newman projections along the exocyclic methine-carbonyl bond. The remaining tautomers are drawn in approximately the geometries in which they were obtained from the SCF/MO package AMPAC, with the enolic hydrogen atoms coplanar with the ring and in approximately the locations shown.

As can be seen from Table 1, results reached using AM1 clearly differ substantially from those obtained using MNDO. The latter are not in good agreement with experiment in that the two lowest-energy 3-acetyl tetronic acid geometries, with a heat of formation difference of 2.4 kcal/mol, should exist in a ratio of $\sim 60:1$. Two species are observed in solution, in a ratio of $\sim 4:1$. The difference between experimental observation and calculation is in accord with the expectation that MNDO will lack accuracy in calculating the energies of systems where strong hydrogen bonding is involved, and supports the view that earlier calculations using CNDO/2, INDO and MINDO/2 should be treated with caution. By contrast, the AM1 results are in excellent agreement with experimental data obtained from NMR studies in both the 3-acetyl tetramic acid study (calculated ratio $\sim 4:1$) and 3-acetyl tetronic acid calculations (observed ratio $\sim 1.5:1$, calculated ratio $\sim 1.4:1$), providing that the two observed tautomers are indeed those calculated to be lowest in energy by AM1. There are to our knowledge no published NMR [3] or other data which cannot be fully accounted for using this assumption, which seems to us to represent the simplest and most satisfactory explanation of existing observations and calculations. Previous studies have invoked solvent effects to explain the difference between calculated and observed ratios of tautomers, noting that a tautomer with a large dipole will interact more strongly with the solvent than one with a small dipole, and that therefore the use of the gas-phase heat of formation as a guide to free energy in solution will lead to an underestimation of the proportion of tautomers with relatively large dipoles found in the condensed phase. While this may be true, the addition of a further parameter to the description of the system is an undesirable complication, and one which appears to be unnecessary if the AM1 method is used: it is not possible to state with certainty that solvent effects could not affect the proportions of tautomers, but, since the lowest energy pair in each case had calculated total dipoles differing by less than 0.2, major effects seem unlikely.

TABLE 1

CALCULATED HEATS OF FORMATION USING MNDO AND AM1

	AM1 ΔH_f	MNDO ΔH_f			AM1 ΔH_f
	(Relative heats of formation : kcal/mol)				(Relative : kcal/mol)
1	0.0 (Absolute heat of formation −102.9991	0.0 −111.5822)	**13**		0.0 (Absolute H_f −149.3359)
2	0.8	2.4	**14**		0.2
3	3.8		**15**		5.4
4	5.1	2.8	**16**		5.8
5	7.4	5.9	**17**		6.3
6	7.8	4.1	**18**		6.9
7	15.0	6.8	**19**		9.6
8	15.4		**20**		19.7
9	15.6		**21**		19.9
10	15.7	5.0	**22**		20.2
11	18.8	10.0	**23**		23.8
12	19.2	9.2	**24**		24.3
			25		25.4

Confirmation that these results would not be drastically affected by the use of free energies was sought by free-energy calculations at 300K for the two geometries of each molecule found to have the lowest calculated heat of formation. The free energies computed for these geometries were in the same order as the calculated heats of formation, with (**2**) less stable than (**1**) by 1.2 kcal/mol

and (**14**) less stable than (**13**) by 0.02 kcal/mol; the results with 3-acetyl tetronic acid may be inaccurate since the gradient norm could not be reduced below the rather high value of 2.6 in the case of (**14**). In all other cases GNORM had a value < 1. Although these gas-phase results correlate slightly less well with solution-phase experimental results than those based on calculated heats of formation, they remain in much better agreement with experiment than any technique used prior to this work. Of particular note is the observation that the double bond geometry of the more stable tautomer in 3-acetyl tetramic acid is Z, whereas that in 3-acetyl tetronic acid is E. This is also true for the doubly-enolised species (**7**), (**9**), (**20**) and (**22**), in which the enol of the exocyclic carbonyl group is the hydrogen donor.

The ordering of the other higher energy tautomers also bears further analysis. Remarkably, the unenolised forms are apparently more stable than any of the remaining monoenolic forms of either species. This is at variance with the assumption used in previous studies, that the unenolised forms would be very minor intermediates in equilibria involving principally the compounds (**1**), (**2**), (**5**) and (**6**) (in 3-acetyl tetramic acid) or (**13**), (**14**), (**18**) and (**19**) (in 3-acetyl tetronic acid). The possibility that the higher-energy monoenolic species are involved to any significant degree must now be in doubt. The very substantial energetic requirement for enolisation at the ring methylene position is an accordance with the observed stability to racemisation of compounds with a chiral centre at this position, and it is clear that the very high energies associated with the pyrrole or furan forms rule out their presence under normal conditions. The greater degree of aromaticity expected for a pyrrole with respect to a furan may explain the observation that, while the furans are calculated to be the most energetic species in the series, the pyrrole (**10**) is calculated to have a heat of formation comparable with those calculated for (**7**), (**8**) and (**9**) which possess only one endocyclic double bond.

Having obtained broadly satisfactory results using AM1 we proceeded to examine the utility of the PM3 method on the unenolised and monoenolic species. The results of this study are summarized in Table 2, and show that the same trends are apparent using PM3 as with AM1. The method includes an option to apply a molecular mechanics correction to the amide rotational barrier: this was *not* used in these calculations (NOMM keyword applied). The heat of formation calculated using PM3 was a less good guide to expected ratios of tautomers than that obtained from AM1 for both tetronates and tetramates; interestingly, the range of heats of formation calculated for the various tautomers using PM3 was much less than that obtained using AM1. Gradient norms obtained using PM3 were much lower (<0.05) (after geometry optimisation using PRECISE) than in the corresponding calculations with AM1. The PM3 method located three rotameric minima for the unenolised forms of both substances; only one of the two forms in which the methyl group of the side chain lies outside the ring is illustrated in the table, since the calculated heats of formation for the rotamers corresponding to (**16**) were not significantly different from those corresponding to (**15**). The free energy differences between the lowest energy species were smaller when calculated using this method, leading to expected tautomer ratios in the region of 1.4:1 for 3-acetyl tetramic acid and 4:1 in the case of 3-acetyl tetronic acid.

CONCLUSION

We have studied a wide range of geometries for 3-acetyl tetramic and 3-acetyl tetronic acids, and conclude that the most stable forms are likely to be (**1**) and (**2**) for the former and (**13**) and

TABLE 2
COMPARISON OF CALCULATED HEATS OF FORMATION AND FREE ENERGIES USING AM1 AND PM3

		AM1 $\triangle H_f$ PM3 $\triangle H_f$	$\triangle G$ (kcal/mol)	
		(Relative heats of formation : kcal/mol)	AM1	PM3
1		0.0 0.0 (Absolute heat of formation -102.9991 -117.7425)		
2		0.8 0.5	1.2	0.2
3		3.8 1.9		
4		5.1 3.6		
5		7.4 3.8		
6		7.8 4.4		
13		0.0 0.0 (Absolute Heat of formation -149.3359 -156.4657)		
14		0.2 0.8	0.02	0.8
15		5.4 1.7		
17		6.3 2.9		
18		6.9 4.5		
19		9.6 5.9		

(14) for the latter. The use of the AM1 Hamiltonian results in predicted ratios for these structures which are more closely in accord with observed values than other methods used to date. These predicted ratios are largely unchanged by the use of free energies rather than heats of formation for those examples for which full thermodynamic data were calculated, and neither require nor suggest any importance for solvation effects in chloroform. Furthermore, while AM1 heats of for-

mation provide a rapid guide to the solution proportions of the various tautomers, it may be that the well characterised minima obtained with PM3 will provide a theoretically more satisfactory guideline, albeit at higher computational cost, at the free energy level. If the ability of the PM3 method to locate rotational minima which are not observed using other methods is a general phenomenon, this could also prove valuable in the study of tautomeric equilibria. Our results suggest that there is little reason to include (4), (5), (18) and (19) in any description of 3-acetyl tetronic and 3-acetyl tetramic acids as has been suggested by others studying these molecules. With regard to the original reasons for undertaking this study, the most interesting feature arises in the differences in double bond geometry expected as the major tautomer for the two compounds. On the basis of these calculations, it is reasonable to expect subtle differences in the binding modes of molecules containing tetramic as opposed to tetronic acids, a feature which could prove useful in the construction of both covalent interactions (such as in the proposed polyene cyclisation) and non-covalent interactions (such as those between an ionophore and its guest ion or an antibiotic and its biological target). The study also supports the NMR-based views of Gelin regarding which tautomeric form is the major one, and calls into question the opposite view, advanced by Saito.

ACKNOWLEDGEMENTS

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