

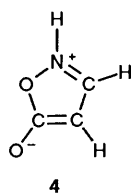
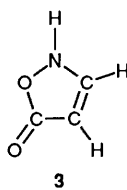
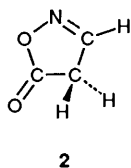
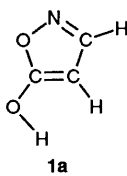
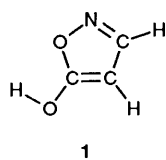
Modelling of Tautomeric Equilibria of 5-Hydroxyisoxazole in Aqueous Solution

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The structure and energetics of the three tautomers of 5-hydroxyisoxazole have been studied theoretically in the gas phase and in aqueous solution. The structures of the species have been optimised in the gas phase and in solution using the self-consistent reaction field model, with a multipole expansion up to $l = 7$, at the 6-31G**//6-31G** level. Electron correlation up to the MP4SDTQ level has been included in the gas phase calculations. The predicted solvation energies are consistent with those from the polarisable continuum model and from molecular dynamics simulations, and predict the CH tautomer to be dominant in water, in agreement with experiment. The NH tautomer is predicted to be the next most stable tautomer, although its energy separation from the CH form is larger than that suggested by experiment.

The tautomeric equilibria of heterocycles are frequently sensitive to solvation effects.¹ Many such equilibria are of importance in modelling interactions having biological implications and for this reason there have been many recent reports describing the prediction of solvation effects on tautomeric equilibria.²⁻⁵ A wide range of methods have been employed including explicit inclusion of the solvent *via* molecular dynamics simulations,² its implicit inclusion *via* continuum models,³⁻⁵ and the use of both semi-empirical³ and *ab initio* molecular orbital methods.⁴ We have previously reported calculations of the effect of water on the tautomeric equilibria of 5-hydroxyisoxazole, involving the four species 1, 1a, 2 and 3,



using continuum models and molecular dynamics calculations.⁵ We noted in that work, the need for more accurate treatments of the solvation effects. We here present more extensive calculations of the four species in aqueous solution by performing geometry optimisation both in the gas phase and in aqueous solution using a large basis set, and by including a more complete description of the solute charge distribution used in the continuum models.

Computational Methods

Free Molecule Calculations.—The structures of the four tautomers studied here were optimised at the 6-31G** level⁶ and characterised as minima by calculation of their harmonic frequencies. Subsequently, the effect of electron correlation was studied at this level (6-31G**//6-31G**) using Møller–Plesset perturbation theory⁷ to second and full fourth order (MP2, MP4SDTQ). Values of the free energy (G_{298}°) of the four structures were obtained by applying the standard corrections⁸ (evaluated at the SCF 6-31G**//6-31G** level) to the energies obtained at the 6-31G**(MP4SDTQ) level. These calculations were carried out using the program GAUSSIAN90.⁹

Modelling of Solvation Effects.—We have employed two continuum models, in which the solute is modelled in a cavity surrounded by solvent characterised by a relative permittivity (ϵ). The first is the self-consistent reaction field (SCRF) model developed by Tapia and Goscinski¹⁰ and by Rivail and co-workers.¹¹ Here the solute charge distribution is represented by a single-centre expansion in multipole moments. We previously truncated this expansion at the dipole term ($l = 1$) and employed a spherical solvent cavity. Here we extend the multipole expansion up to $l = 7$, and use an ellipsoidal cavity whose dimensions are determined by the atomic van der Waals radii as suggested by Rivail *et al.*¹¹ These calculations were carried out using the computer code of Rivail *et al.* implemented within the GAUSSIAN90 program. The calculations were carried out at the 6-31G** level, and the geometry of the solute was optimised starting from the gas phase optimal structure, although the resulting structures were not characterised as minima. However, the geometry changes upon hydration were small and in line with chemical intuition, so that the reported structures are believed to be minima.

An alternative approach of improving upon the use of the dipole approximation and a spherical cavity is the polarisable continuum model (PCM) of Tomasi and co-workers.¹² Here, a solvent cavity is generated from spheres centred at each atom in the molecule and virtual charges are generated on the cavity surface to represent the polarisation of the solvent. We have obtained the individual sphere radii from the Mulliken atomic charges of the gas phase wavefunction, using the parameters of Aguilar and del Valle.¹³ These calculations of hydration free energies were carried out using fixed geometries obtained from the gas phase species and were also carried out using a 6-31G** basis. The solvation free energies thus calculated, were then combined with the gas phase free energies to yield relative free energies of the four species in water.

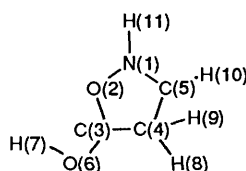
Table 1 Total energies (a.u.) and relative energies (kcal mol⁻¹) of tautomers

Tautomer	6-31G**//6-31G**	6-31G**(MP2)//6-31G**	6-31G**(MP4SDTQ)//6-31G**
1	-319.462 01 (6.8)	-320.368 74 (4.0)	-329.420 42 (6.8)
1a	-319.458 68 (8.9)	-320.365 78 (5.9)	-320.426 32 (8.8)
2	-319.472 80 (0)	-320.375 13 (0)	-320.440 30 (0)
3	-319.463 96 (5.6)	-320.364 91 (6.4)	-320.428 17 (7.6)

Table 2 Optimised geometry of tautomers^a

	1	1a	2	3
Bond lengths/Å				
1-2	1.3881	1.3824	1.3887	1.3876
	0.0032	0.0052	0.0121	0.0020
2-3	1.3098	1.3046	1.3466	1.3607
	0.0001	0.0042	-0.0057	-0.0098
3-4	1.3476	1.3508	1.5122	1.4636
	0.0035	0.0010	-0.0071	-0.0109
4-5	1.4210	1.4218	1.4901	1.3240
	-0.0048	-0.0046	-0.0020	0.0048
1-5	1.2835	1.2818	1.2547	1.3862
	0.0043	0.0046	0.0017	-0.0145
1-11				1.0010
				0.0039
5-10	1.0723	1.0721	1.0729	1.0722
	-0.0010	-0.0004	-0.0014	-0.0019
4-9			1.0841	
			0.0015	
4-8	1.0666	1.0680	1.0841	1.0679
	0.0010	-0.0004	0.0013	0.0009
3-6	1.3155	1.3170	1.1761	1.1810
	-0.0052	-0.0048	0.0076	0.0120
6-7	0.9463	0.9439		
	0.0026	0.0033		
Bond angles (deg)				
1-2-3	109.16	109.17	111.23	109.54
	0.02	-0.04	-0.01	0.12
2-3-4	111.46	111.41	107.04	106.23
	-0.17	-0.18	0.34	0.51
2-3-6	117.43	114.70	123.23	121.79
	0.64	-0.53	-1.08	-0.98
3-6-7	110.39	110.79		
	1.69	1.04		
3-4-5	101.46	101.47	99.27	106.32
	0.27	0.32	0.09	-0.26
4-5-1	113.22	112.85	113.38	111.34
	-0.03	0.01	0.32	0.09
2-1-11				107.26
				0.21
3-4-8	128.74	129.24	110.88	124.50
	0.11	0.00	0.28	0.76
3-4-9			110.88	
			0.45	
4-5-10	128.11	128.24	127.31	130.16
	-0.45	-0.63	-0.94	-0.60

^a See Fig. 1 for atom numbering. The bond lengths and angles are for the gas phase species (6-31G**//6-31G**) followed by the change upon hydration predicted by the SCRF (*l* = 7) model.

**Fig. 1** Numbering scheme for Table 2**Table 3** Relative free energies (G_{298}°) (kcal mol⁻¹)^a and dipole moments (μ /D) of gas phase tautomers

Tautomer	G_{298}°	μ
1	7.4	1.8
1a	9.4	4.7
2	0	5.1
3	8.5	5.7

^a Calculated from the electronic energy at the 6-31G**(MP4SDTQ)//6-31G** level, with corrections at the 6-31G**//6-31G** level.

Table 4 Solvation free energies (ΔG_{soln}), total relative free energies (ΔG_{tot}) (kcal mol⁻¹), and dipole moments (μ /D) of tautomers in water

Tautomer	ΔG_{soln}^a	ΔG_{tot}^b	μ
1	-6.4	10.7	2.5
1a	-8.1	11.0	5.9
2	-9.7	0	6.6
3	-10.9	7.3	7.3

^a Evaluated at 6-31G**//6-31G** level using SCRF (*l* = 7) method.

^b Evaluated with gas phase values at 6-31G**(MP4SDTQ)//6-31G** level.

Table 5 Relative free energies of solvation (kcal mol⁻¹) calculated by different models

Tautomer	SCRF (<i>l</i> = 7) ^a	Polarized continuum ^a model	Free energy perturbation method ⁵
1	4.5	4.1	3.9
1a	2.8	2.6	—
2	1.2	1.3	2.1
3	0	0	0

^a This work.

Computational Results and Comparison with Experiment

The results of the calculations on the isolated tautomer species (**1**, **1a**, **2**, **3**) are summarised in Tables 1 and 2. At both the SCF and correlated levels, the CH tautomer (**2**) is of lowest energy, whilst the ordering of the three higher energy species is dependent upon the level of correlation included. At the highest level of theory used (MP4SDTQ) the energy separation between these three species is only 2 kcal mol⁻¹.^{*} The optimised structures of **1**, **1a** and **2** were confirmed to be planar, whilst for the NH tautomer (**3**) the -NH hydrogen was 48.7° out of plane. In our previous study the energy of the planar form of **3** was reported, leading to a somewhat higher relative energy for this species. Application of the standard corrections, calculated at the 6-31G**//6-31G** level, to the MP4SDTQ results, leads to the relative gas phase free energies of the four species shown in Table 3. These corrections do not affect the ordering, the main effect being to increase the relative stability of the CH tautomer (**2**).

The results of the SCRF calculations, to model the hydration, are shown in Tables 2, 4 and 5. As far as the change in molecular

* 1 kcal mol⁻¹ = 4.184 J.

geometry and electronic structure are concerned, there is a significant increase in the dipole moment of all four species, upon hydration (compare the values in Tables 3 and 4). The predicted changes in bond lengths (Table 2) reflect the polarisation occurring upon solvation. These changes are most marked for **3**, and imply the importance of resonance structure **4**. It is noteworthy that in the hydroxy species (**1**) the C–O(H) bond length decreases upon solvation, whilst for the oxo-species (**2**, **3**) the C=O bond length increases. Thus the difference between the C–O(H) and the C=O bonds is reduced by hydration, an effect which might be detected *via* IR spectroscopy.

The trend of the calculated hydration free energies (Table 4) is in line with the molecular dipole moments. However, the differences are considerably less than those found when the charge distribution is approximated at the dipole level ($l = 1$), showing the importance of higher moments of the charge distribution. In particular, the solvation free energies of **1** and **1a**, which differ only in the conformation of the –OH group, are within 2 kcal mol⁻¹, although their dipole moments differ considerably. Such a result is certainly more reasonable from an intuitive viewpoint. These estimates of the solvation free energies have been combined with our best estimates of the free energies of the gaseous species (Table 3) to yield the relative free energies in water, shown in Table 4. The two oxo species (**2**, **3**) are predicted to be the more stable, with the hydroxy conformers (**1**, **1a**) being higher in energy. Thus, although the CH tautomer (**2**) is predicted to be the most stable species both in the gas phase and in water, solvation has reversed the ordering of the NH and hydroxy tautomers predicted in the gas phase.

The close agreement between the predictions of the SCRf and PCM models is encouraging (Table 5), with the relative hydration free energies differing by less than 0.5 kcal mol⁻¹. In addition, the predictions of these two continuum models are in accord with those from molecular dynamics simulations⁵ (free energy perturbation method) to within 1 kcal mol⁻¹, although the NH tautomer was taken to be planar in the latter study.

Our calculations thus predict that isoxazol-5-one exists in water as the CH form, with only $\sim 10^{-5}$ of the NH form being present, and the hydroxy form being essentially absent. No experimental data can be located for the unsubstituted species, although 3-substituted isoxazol-5-ones have been reported to exist in solvents of low dielectric constant overwhelmingly in the CH form, whilst in aqueous solution $\sim 30\%$ of the NH form is present.¹⁴ Clearly the former finding is in line with the results of our calculations, whilst the populations found in water suggest a free energy difference between **2** and **3** of less than 1 kcal mol⁻¹, a value considerably smaller than our prediction. Experimental data have been reported for the 3-methyl species. To provide a direct comparison with these data, we have carried out calculations on the two oxo tautomers (**2**, **3**) of 3-methylisoxazol-5-one. In brief, at the 6–31G**//6–31G** and 6–31G**(MP4SDTQ)//6–31G** levels, the gas phase energy differences between these two species are 5.7 and 8.2 kcal mol⁻¹ respectively, values little different from those for the unsubstituted species (Table 1). Solvation free energies calculated at the SCRf ($l = 7$) level, differ by less than 0.1 kcal mol⁻¹ from the values for the unsubstituted species (Table 4). Thus, at the level we have carried out our calculations, we find no evidence for 3-methyl substitution having any significant effect on the tautomer equilibria.

Conclusions

The calculations reported here extend our previous study⁵ of tautomerism in 5-hydroxyisoxazole by the use of a large basis (6–31G**) to predict the structures and energetics both in the gas phase and in aqueous solution, and by the use of a more complete description to model the solute charge distribution

within a self-consistent reaction field scheme. In all continuum models, the shape and size of the solvent cavity is somewhat arbitrary. In our previous study, we chose a spherical cavity of radius ($a = 2.5 \text{ \AA}$) following the value used in the semiempirical calculations of Karelson *et al.*³ The volume of the elliptical cavities used here corresponds to a spherical cavity of a somewhat larger radius (3.1 \AA). The value of the solvation energy depends upon a^{-3} and is thus extremely sensitive to this parameter. Indeed, in our previous study, with a cavity radius of 2.5 \AA and using the dipole approximation, the planar form of **3** is of lower energy than the non-planar form, so that we were consistent in studying the planar form of all four species. In spite of this arbitrariness in the cavity size, it is encouraging that both continuum models used here, and the MD simulations, predict consistent relative solvation free energies.

Although we predict the CH tautomer to be dominant in water, in agreement with experiment, our calculated energy separation of the CH and NH species is significantly overestimated. In view of its magnitude this discrepancy is probably not attributable to basis set effects or the level of correlation employed. We have estimated both the cavitation¹⁵ and dispersion energy¹⁶ contributions to the solvation energy and find that they differ by less than 0.3 kcal mol⁻¹ for the four species studied. It may be that the discrepancy arises from differences in the local structure of the water associated with the different tautomers, not considered in the continuum models. However, the consistency of the continuum and MD treatments argues against this explanation. Further experimental and theoretical studies of this system are clearly needed.

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