Tautomeric Equilibria of Maleic Hydrazide in the Gas Phase and in Aqueous Solution: An Experimental and Theoretical Study

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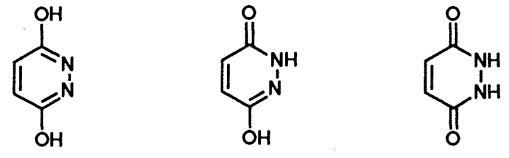
Theoretical predictions of the tautomeric equilibria in maleic hydrazide in the gas phase and in aqueous solution are presented. The use of pK_a data to obtain tautomer populations in aqueous solution is discussed and the values obtained compared with our theoretical predictions. *Ab initio* calculations of the gas phase species including a high level of electron correlation are combined with both molecular dynamics simulations and continuum methods, to model solvation effects. Both in the gas phase and in aqueous solution the monohydroxy-monoketo tautomer is predicted to be dominant. The effect of solvation is predicted to stabilize preferentially the diketo form so that both forms may be observed in solution, whilst the dihydroxy form is essentially absent. These conclusions are in agreement with available experimental data.

The tautomeric equilibrium in 2-hydroxypyridine has been exhaustively studied, both experimentally and theoretically, in the gas phase,[1] and in aqueous solution.[2] The corresponding tautomerism in maleic hydrazide (1,2-dihydropyridazine-3,6-dione) is more complex and less well-studied. Here, three tautomers may, in principle, be observed, the monohydroxy-monoketo form **B**, the dihydroxy form **A**, and the diketo form

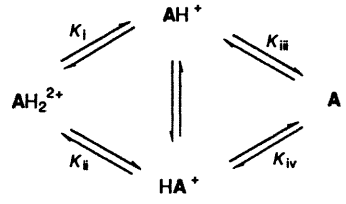


A **B** **C**

C. No experimental data are available to indicate the tautomer preference in the gas phase, whilst condensed phase studies indicate the predominance of the monohydroxy-monoketo form in the solid state and in solution.[3] In this system, we have tautomerism involving contiguous heteroatoms which has been studied in other molecules, such as 1,2,3- and 1,2,4-triazole.[4] Here, the strong presumption, due chiefly to Elguero,[5] that contiguous heteroatoms of the same hybridisation type are strongly destabilising is borne out by both experimental and theoretical studies. This argument leads to the prediction that tautomer **B** is preferred over **A** and **C**.

Recently, theoretical studies of tautomerism, involving structures **A**, **B** and **C** have been reported using *ab initio* methods,[6] involving the use of the polarisable continuum model due to Tomasi *et al.*,[7] to model solvation. In this paper, we report quantum mechanical studies of tautomerism in the gas phase and in aqueous solution using different continuum models of solvation and also report the results of molecular dynamics (MD) simulations of solvation of the tautomers. We also assess the experimental data which may be used to estimate the tautomer ratios in aqueous solution. We first discuss this latter problem, followed by the use of a number of models to predict the tautomer ratios in water.

Experimental Estimates of Tautomer Ratios.—The case of maleic hydrazide is of exceptional complexity, and it may help to outline some simpler situations first. If two or more tautomers share a common cation, as for the pyrazolones which we report elsewhere,[8] then the contribution of each deprotonation route to the overall proton loss equilibrium constant K_a is expressed as $K_a = \Sigma K_i$, where the i's are subspecies. If two successive deprotonation steps are involved we have the situation of Scheme 1, where the macroscopic



Scheme 1

(measured) constants K_{a1} and K_{a2} are related to the microscopic equilibria according to eqns. (1) and (2). The form of these

$$K_{a1} = K_i + K_{ii} \quad (1)$$

$$1/K_{a2} = 1/K_{iii} + 1/K_{iv} \quad (2)$$

equations is such that $pK_{a1} < (pK_i, pK_{ii})$ and $pK_{a2} > (pK_{iii}, pK_{iv})$ necessarily. Formally identical schemes and equations may be written for dianionic and amphoteric species.[9]

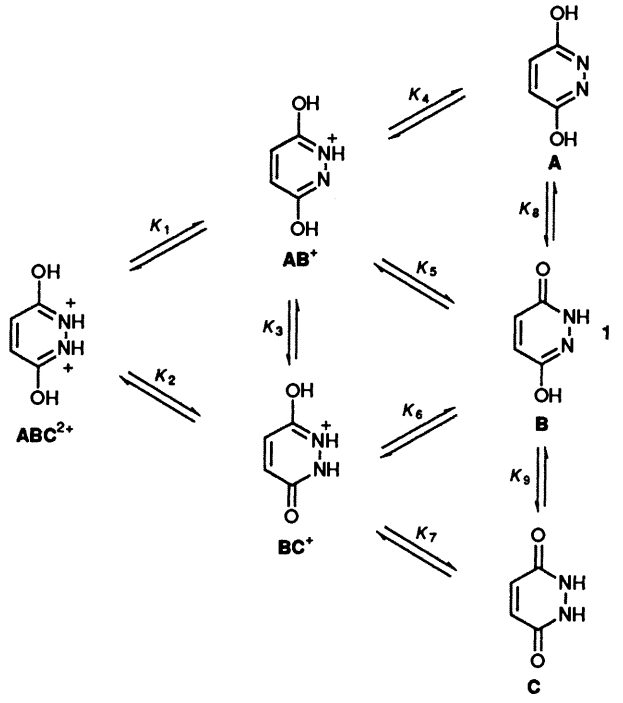
For maleic anhydride, a common dication $\mathbf{ABC}^{++}$ deprotonates to give the tautomeric monocations $\mathbf{AB}^+$ and $\mathbf{BC}^+$ which deprotonate in turn to give not one potential neutral species but three (Scheme 2). The relations between the macroscopic and microscopic constants for these two steps are now given by eqns. (3) and (4). While eqns. (1) and (3) are

$$K^{++} = K_1 + K_2 \quad (3)$$

$$K^+ = \{1/2(K_3 + 1)\}(K_4 + K_5) + \{K_3/2(K_3 + 1)\}(K_6 + K_7) \quad (4)$$

effectively identical, (4) differs from (2) in that the restriction $pK^+ > pK_i$ is removed.

The basicity method as applied to tautomeric ratio[10] consists in measuring the pK_a values of model *O*- or *N*-alkylated compounds in which the position of the otherwise mobile proton(s) is fixed. Use of these pK_a values to supply microscopic



Scheme 2

Table 1 Empirical correction factors for fixed tautomers[8]

Structural type	ΔpK_a
$HOC{=}NMe^+ - \rightarrow HOC{=}NH^+ -$	+0.43
$-NHNMe^+ = \rightarrow -NHNH^+ =$	+0.73
$MeOC{=}NH^+ - \rightarrow HOC{=}NH^+ -$	+1.0

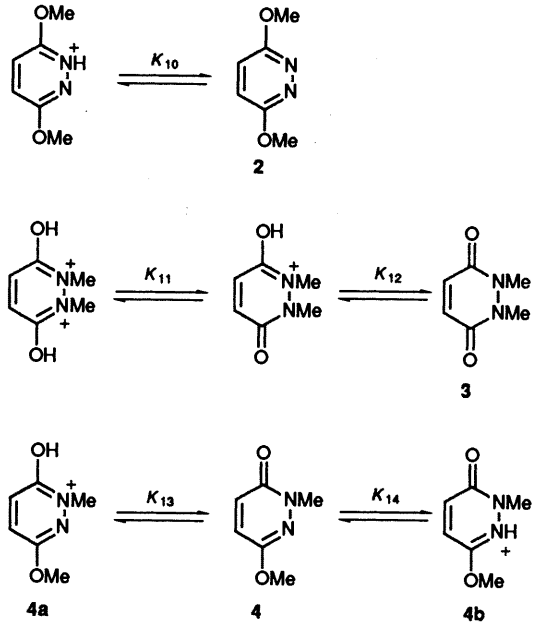
Table 2 pK_a Values for maleic hydrazide and some model compounds[a]

Compound		Charge type	Ref. 15	Ref. 16	Ref. 17
Pyridazine		+			2.29
		++			−7.78
1	pK^+	+	−0.99	> −1	−2.64
	pK^{++}	++	−3.28	< −4	−8.06
2	pK_{10}	+	1.61	≈1.5	
		++		≪ −4	
3	pK_{12}	+	−1.94	≈ −2	
	pK_{11}	++	−3.96	< −4	
4	pK_{13}[b]	+	−0.91	≈ −1	
		++		≪ −4	
6		+	−2.1		
		++		≪ −4	
7		+	−1.27	≈ −1.8	
		++	−2.42	< −4	

[a] See Scheme 2 and formulae for key to pK nomenclature. [b] Or pK_{14}; see text.

deprotonation constants has then to assume either that basicity is unaffected by alkylation, or that it is always affected to the same extent. We have described this as the 'naive basicity' hypothesis.[11] However, Spinner and Yeoh[12] point out that both *O*- and *N*-methylation are expected to be base-weakening since they lead to poorer solvation in the cation, and furthermore, this effect is expected to be greater in the former case.[13] Several failures of the 'naive basicity' hypothesis have been reported.[8,10,11,14] Recently, we have derived a number of empirical correction factors that appear to work for some pyrazolones;[8] these appear in Table 1.

Table 2 summarises the relevant pK_a values, most of which are due to Barlin[15,16] in two important papers on this topic. In the first,[15] a UV spectrophotometric technique was used to derive monocationic and some dicationic pK_a values, including pK^+ and pK^{++} for maleic hydrazide itself. This study also used UV evidence to demonstrate that **1**, **4** and **5**, as well as the

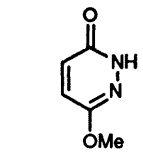


simpler pyridazinones **6** and **7**, all monoprotonate preferentially at carbonyl; *e.g.* **4** gives **4a**, not **4b**. The later paper,[16] following some disquiet at drifting isosbestics in the former study, used ^1H NMR spectroscopy to demonstrate the presence of discontinuities for certain compounds which throw doubt on some original conclusions. In particular, it is not now thought that diprotonation (down to $H_0 - 4$) was detected for any compound in this series, and some pK_a values in consequence need revision (Table 2). These discontinuities are confined to compounds containing mobile protons and may be caused by medium-induced variation in tautomeric composition.[16]

One result of the second study[16] has been to destroy any chance of solving eqn. (3), since no model for pK_1 or pK_2 exists.* We are forced to fall back on Barlin's observation[15] that **4** resembles maleic hydrazide with respect both to UV spectrum and pK_a, while **2** and **4** possess similar spectra. We take this resemblance to imply a maximum value of 0.1 for K_3 (Scheme 2).

We may now use our previous correction factors[8] (Table 1) to some limited extent in the present series. From pK_{10} 1.61, we have pK_4 *ca.* 2.6. From pK_{12} −1.94, we have pK_7 *ca.* −1.5. We have no previous model for the deprotonation of AB^+ to **B**, but the pK_a values for **6** and **7** provide some guide; ΔpK_a +0.3 will convert pK_{13} −0.91 to pK_5 *ca.* −0.6. It is possible that, in addition to these, further solvational corrections are required for the conversion of uncharged OMe and NMe to OH and NH, though these should be much smaller than for the charged species. On most electronic criteria,[18] OH is a better electron donor than OMe, so a positive correction is likely in that case. Given ΔpK_a +1.2 for OMe in **4** relative to **6**, and the relative σ_p^+ values for OMe and OH,[18] we may roughly estimate a

* Billes and Toth[17] report pK^{++} − 8.06, but a value as low as this is improbable, since it implies that two electron-donor (OH) groups substituted into pyridazine produce a base-weakening effect (Table 2). Nevertheless a dicationic pK_a value well below −4 may be anticipated for any compound in this set. Their value for pK^+ is certainly in error; they do not remark on, and have presumably missed, the complications reported by Barlin.[15,16]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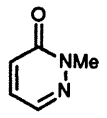
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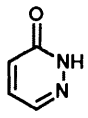
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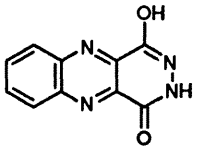
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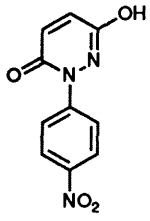
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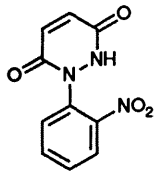
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Table 3 Possible microscopic equilibrium constants for the tautomerism of maleic anhydride in water, and their consequences for pK^+ and x_B

	Set (1)	Set (2)	Set (3)
K_3	0.1	0.1	0.03
pK_4	2.6	2.8	2.8
pK_5	−0.6	−0.4	−0.4
pK_6	−1.6	−1.4	−1.9
pK_7	−1.5	−1.5	−1.5
pK^+	−0.70	−0.57	−0.47
x_B	0.72	0.61	0.83

further rise of ΔpK_a 0.2 as likely. There are no systematic differences in σ-value between NMe and NH,[18] so correction here is probably not needed.

Given values for the above constants, the rest follow by difference. The result of taking $K_3 = 0.1$ and applying corrections for charged groups alone is to be found as set (1) of Table 3. Incorporation of the uncharged OMe → OH correction results in set (2), while a threefold lower value for K_3 then results in set (3). While none of these analyses is entirely satisfactory, let alone definitive, all agree on the salient points: that **B** is the favoured species but not by much; and that the fraction of **A** must be negligible ($x_A < 10^{-3}$). Concerning the predicted value of pK^+, the data of Barlin's later paper[16] suggest −1 as a minimum value, and one of approaching −0.5 would not be impossible.

Some qualitative attempt can be made to explain the preferences revealed by Table 3. Protonation of **B** to give $\mathbf{AB}^+$ converts NH to NH^+, both adjacent to imino-nitrogen to which each will be attracted. Its protonation to $\mathbf{BC}^+$ converts imino-nitrogen to NH^+, both adjacent to NH; *i.e.* an attractive force into a repulsive one. Whatever other factors enter into these equilibria, the former process should be far more favourable than the latter. Deprotonation of $\mathbf{BC}^+$ to give **B** relieves this repulsion whereas the normally favoured keto-form results if it goes to **C**; Table 3 suggests that preference for either route is not great. Nevertheless, there is suggestive evidence that the diamide **C** lies much closer to **B** in energy than does the dienolic tautomer **A**. For **8**, form **B** as shown still predominates, despite the potential formation of two intramolecular hydrogen bonds in the dihydroxy form.[19] By contrast, **10** switches to form **C** through just such a bond; this is not an electronic effect, since the *para*-isomer **9** does not show it.[20] And deprotonation of $\mathbf{AB}^+$ favours **B** over **A** by almost the same factor as is found for 2-pyridone.[10] Hence, we may conclude that, allowing for NH–NH repulsion, the normal hetero-aromatic preferences[10] are maintained.

Computational Methods

A theoretical prediction of the relative free energies of the three species in aqueous solution requires first a prediction of their relative energetics in the gas phase, followed by estimates of their solvation energies. We note that no experimental data are available to judge directly the accuracy of the free molecule calculations. We now discuss the methods used to model these tautomers in the gas phase and in aqueous solution.

Free Molecule Calculations.—In studies of the 2-pyridone, 2-hydroxypyridine system, and other tautomeric equilibria using *ab initio* methods,[1,21] it has been found that geometry optimisation using at least a double-zeta basis, followed by energy calculations using a large basis with polarisation functions and including electron correlation, are needed to obtain tautomer energy differences accurate to ~4 kJ mol^{-1}. Following this approach the structures of the three tautomers studied here were optimised at the 3-21G level and characterised as minima by calculations of their harmonic frequencies. Extended basis set (6-31G**) calculations were then carried out at these geometries (6-31G**//3-21G). To judge the stability of these results, geometry optimisation was also carried out at this high level of basis set (6-31G**//6-31G**). The importance of electron correlation in predicting the energetics of keto–enol tautomerism is well established. For the 2-pyridone–2-hydroxypyridine pair, a high level of electron correlation is needed to yield results of quantitative agreement with experiment. Using Moller Plesset (MP) perturbation theory at second order (MP2) gave results considerably inferior to those at the SCF level, and fourth order calculations (MP4) were needed to yield predictions consistent with experiment.[22] For this reason, we have carried out calculations of the energetics of the three tautomers at the MP4 level, using a 6-31G** basis. These values are finally corrected using zero point energies estimated from harmonic frequencies calculated at the 3-21G level, to yield the best estimates of the relative energies of the three tautomers given in Table 4. All these *ab initio* calculations were carried out using the program GAMESS,[23] except for the MP4 calculations which used the program GAUSSIAN 90.[24]

Modelling of the Solvent–Solute Interactions.—Two strategies have been employed to estimate the solvation energies of the three tautomers.

The first considered such interactions explicitly using a free energy perturbation (FEP) method in molecular dynamics simulations to obtain directly the contribution of solvation ($\Delta\Delta G_{solv}$) to the total free energy difference ($\Delta\Delta G_{tot}$) between pairs of tautomers. Such a method has been found to be successful in modelling the solvation of 2-hydroxypyridine and 2-pyridone.[25] For the maleic hydrazide tautomers studied here we use the same strategy, molecular mechanics parameters and parameters of the window growth method, as used by Cieplak *et al.*[25] The FEP calculations were carried out using the program AMBER.[26]

The second strategy employed two continuum models, in which the solute is modelled in a cavity surrounded by solvent characterised by a relative permittivity (ε). We first use the self-consistent reaction field (SCRF) model developed by Rivail and co-workers.[27] This model follows the work of Kirkwood[28] who derived the expression for the free energy of interaction of a charge distribution immersed in a cavity surrounded by a dielectric continuum. The solute charge distribution is represented by a single centre expansion in multipole moments and appropriate modification of the one-electron terms in standard SCF programs allows for minimisation of the sum of the molecular electronic energy and solvation free energy. The formalism may be extended from the spherical cavity model, to the case of an ellipsoidal cavity, which allows for the more

Table 4 Total energies (au) and relative energies[a] (kJ mol^{-1}) of tautomers of maleic hydrazide

	Tautomer		
	B	**A**	**C**
3-21G//3-21G	−410.0807 (0)	−410.0665 (37.3)	−410.0776 (8.1)
6-31G**//3-21G	−412.4080 (0)	−412.3986 (24.7)	−412.3996 (22.1)
6-31G**//6-31G**	−412.4111 (0)	−412.4025 (22.5)	−412.4050 (15.9)
6-31G**(MP4)//6-31G**	−413.6822 (0)	−413.6754 (17.8)	−413.6727 (24.8)
ZPE 3-21G//3-21G	(0)	(−4.0)	(−1.9)
Best estimate	(0)	(13.8)	(22.9)

[a] Relative energies are given in parentheses.

Table 5 Free energy differences (kJ mol^{-1}) of tautomers in water obtained from MD simulations

Tautomer pair	$\Delta\Delta G_{solv}$	$\Delta\Delta G_{tot}$
B ⇌ **C**	**B** → **C** −15.4 ± 0.4 **C** → **B** 14.4 ± 0.4	**B** → **C** +8.0 ± 0.4
B ⇌ **A**	**B** → **A** 4.2 ± 0.4 **A** → **B** −7.3 ± 0.8	**B** → **A** +20.0 ± 0.6

Table 6 Solvation free energies (ΔG_{solv})[a] and total relative free energies (ΔG_{tot}) (kJ mol^{-1}) obtained by continuum models

	SCRF[b]		PCM	
	ΔG_{solv}	ΔG_{tot}	ΔG_{solv}	ΔG_{tot}
B	−31.9 (−28.8)	0	−71.6	0
A	−25.7 (−23.4)	20.0	−66.1	19.3
C	−39.4 (−35.3)	15.4	−72.3	22.2

[a] All calculations at 6-31G**//6-31G** level. [b] The values in parentheses do not include solute polarisation.

realistic modelling of the shape of the solute molecule. In this work we use ellipsoidal cavities whose dimensions are determined by the atomic van der Waals radii as suggested by Rivail *et al.* and use a multipole expansion up to $l = 6$. The calculations were carried out using the computer code of Rivail *et al.* implemented within the GAUSSIAN 90 program.

The second continuum model employed was that due to Tomasi and co-workers,[7] in which the cavity is generated from spheres centred at each atom in the molecule and virtual charges on the cavity surface are used to represent the polarisation of the solvent. We have implemented this continuum model within the program GAMESS. The sphere radii in this Polarisable Continuum Model (PCM) were calculated in terms of the Mulliken atomic charges and basis set used, from the parameters of Aguilar and del Valle.[29]

Calculations of hydration energies using the SCRF and PCM treatments were carried out at the SCF (6-31G**//6-31G**) level, using geometries optimised for the gas phase molecules. A major difference between FEP and continuum models is that solute polarisation is included in the latter treatments.

Results

Gas Phase Calculations.—The results of the free molecule calculations are summarized in Table 4. Our results for the 3-21G basis (3-21G//3-21G) are in essential agreement with the published values of Hofmann *et al.*,[6] with all three structures predicted to be planar. The preferential stability of **B** is in line with the repulsion in the other two tautomers involving adjacent nitrogen atoms of the same hybridisation type. The expansion of the basis to include polarisation functions on all atoms (6-31G**//3-21G) does not change the predicted energy ordering of the tautomers (**B** < **C** < **A**). However, it is seen (Table 4) that preferential stabilisation of the hydroxy forms (**A**, **B**) (particularly the di-hydroxy form, **A**) occurs, so that forms **A** and **C** are now close in energy, and some 20–25 kJ mol^{-1} higher in energy than the hydroxy–keto form, **B**. The use of polarisation functions on all atoms has previously been found to be needed to model accurately the tautomer energetics in cytosine.[21] When geometry optimisation is carried out using the 6-31G** basis (6-31G**//6-31G**), the relative energy of **A** and **B** is essentially unchanged, whilst the diketo form **C** is preferentially stabilised. This is associated with the predicted non-planarity of the molecule (compared to planarity at the 3-21G level), with the HNNH dihedral angle being 62°. We note that this geometric change is essentially the same as that reported by Hofmann *et al.*[6] for the optimisation of tautomer **C** at the 6-31G* level. However, these authors report that the relative energy of **C** is close to that found with a 3-21G basis, in contrast to our 6-31G** results.

Turning to the effect of electron correlation at the MP4 level, we find that the ordering of the tautomers is altered from that given at the SCF level, due to the predicted preferential stabilisation of the hydroxy forms **A**, **B**. The ordering is now **B** < **A** < **C**. However, it is clear that the relative energies of the keto forms **B**, **C**, which are expected to be preferentially hydrated, will be crucial in determining the population of the tautomers in aqueous solution. We now discuss the combination of these free molecule results, with estimates of the solvation free energies of the three tautomers.

Solvation Free Energy Calculations.—It is generally considered that in systems similar to those studied herein, hydration favours the oxo-, compared to the hydroxy-form. Thus, for the 2-hydroxypyridine, 2-pyridone system, a FEP calculation[25] predicts the free energy of solvation to be ~ 20 kJ mol^{-1} greater for the 2-pyridone. A similar trend is shown by our FEP calculations (Table 5) with the monohydroxy-monoketo form **B** being predicted to be more strongly solvated than the dihydroxy form **A** by ~ 5 kJ mol^{-1}, and less strongly solvated than the diketo form **C** by ~ 15 kJ mol^{-1}. When we include the predicted gas phase energy differences (Table 4), we see that the magnitude of these differential solvation effects will be crucial in determining the populations of the three tautomers in aqueous solution. In particular, a preferential solvation of **C** compared to **B** of ~ 15 kJ mol^{-1} will result in **B** and **C** being close in energy, but with **B** being the dominant tautomer. It is clear from qualitative arguments that **A** will not be observed in aqueous solution unless our gas phase calculations are grossly in error. When we consider the pair of tautomers **B** and **C**, and combine our predicted solvation energy difference (Table 5) with the gas phase energy difference (Table 4), we predict that **B** is preferred to **C**, in aqueous solution (by ~ 8 kJ mol^{-1}).

Turning to the results of the two continuum models (Table 6), we see that both the SCRF and PCM treatments predict the expected order of solvation, **C** > **B** > **A**. The results of the SCRF model are perhaps more credible with the progressive replacement of an hydroxy by a keto group increasing the solvation energy by ~7 kJ mol^{-1}. The results of the PCM treatment are rather less satisfactory, with only a small (< 1 kJ mol^{-1}) difference in the solvation energy of **B** and **C**, although the difference in solvation energy between **B** and **A** is similar to the results of the SCRF calculations. It is clear from all our solvation studies, using both MD and continuum models, that the dihydroxy tautomer **A** will not be observed in aqueous solution. The differential solvation between the diketo **C** and monohydroxy-monoketo form **B** is critical in predicting their energy difference in aqueous solution. Here the MD results appear to yield superior results to the continuum models.

Discussion

We have presented computational estimates of the gas phase energetics (Table 4) and of the tautomer populations in aqueous solution derived from experimental data. When taken together, these can lead to estimates of the relative free energies of solvation that can be compared to the predictions of different theoretical treatments.

Our analysis of the pK_a data suggests a small free energy difference between tautomers **B** and **C** in aqueous solution. A value in the region of 5 kJ mol^{-1} would seem appropriate. When combined with our gas phase calculations this leads to a greater solvation of **C** compared to **B** of 15–20 kJ mol^{-1}. The value predicted by MD simulations is close to this, whilst those given by the continuum models are somewhat smaller. All models predict that the population of the dihydroxy tautomer is very small in aqueous solution (~10^{-4}), a value consistent with the limited experimental data available.

Acknowledgements

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