A Theoretical Treatment of Solvent Effects on the Tautomeric Equilibria of Five-membered Rings with Two Heteroatoms

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The tautomeric equilibrium constants of nine oxo and hydroxy derivatives of five-membered heterocycles containing two ring heteroatoms (nitrogen or oxygen) as calculated by the AM1 quantum chemical model agree well with literature gas-phase data. The inclusion of solvent effects through a self-consistent reaction field technique into these calculations yields results in full agreement with experimental data obtained for these systems in aqueous solution. It is not possible to use the calculated energies for isolated molecules to predict the relative stabilities of these tautomers in solution.

Solvent effects are specific, and differentially lower the energy of one tautomer over another demonstrating in some cases a strong solvent effect on tautomeric equilibria. In general, dielectric media favour charge separation and preferentially lower the energy of species with the greater degree of charge separation. In the species studied solvent reaction field effects favour ionic resonance forms of the carbonyl tautomers and hence a greater degree of aromaticity.

The tautomeric equilibria of various heterocycles have been studied extensively by quantum-chemical methods of different degrees of accuracy.[1–6] Almost all such calculations refer to isolated molecules and, therefore, most of the results are directly comparable to experimental observations made in the gas phase at low pressures, and not necessarily with dense systems such as solids, liquids and solutions upon which measurements are made. Most of the available experimental data on tautomeric equilibria have been obtained in solutions in which intermolecular interactions between the solute and solvent molecules can cause substantial changes in the geometry and electronic structure of the substrates in comparison with isolated gas phase species. These changes may change the reactivity and the stability of molecules in different media. Thus, it is of primary importance to estimate the magnitude of the possible errors which result from comparisons of the results of the gas-phase quantum-chemical calculations with the corresponding experimental results in solution.

According to current models, the effects of a surrounding medium can be incorporated into an effective Schrödinger equation.[7] The specific interactions (hydrogen bonding, electron donor–acceptor complexes and strong dipole–dipole complexes formed between solute and solvent molecules) are often treated by the superposable approximation.[7a,8] The incorporation of Onsager's reaction field model in molecular orbital calculations allowed consideration of non-specific interactions and brought the theory of solvent effects to a simple and useful level of approximation.[7a,9,10] The charge density anisotropy, as revealed by the dipole moment, μ, plays a central role. A modified Hamiltonian, H' is used in the Schrödinger equation for the polar solute molecules in the form of equation (**1**), where p is the electronic wave function of the molecule and H_0 is the Hamiltonian for the isolated molecule.

The multiplier g (the reaction field tensor) in equation (1) is

$$H' = H_0 + g\langle p|\mu|p\rangle^2 \qquad (1)$$

$$g = \frac{2(\varepsilon_r - 1)}{(2\varepsilon_r + 1)r_c^3} \qquad (2)$$

a function of the dielectric properties of the solvent and the size of the solute molecule. According to the Kirkwood–Onsager theory, g is given by equation (2), where ε_r denotes the relative permittivity of the medium and r_c is the radius of the cavity into which the solute molecule is embedded. The use of the macroscopic relative permittivity of the solvent in equation (2) is justified for time-averaged orientation polarization of the solvent molecules in the field of the solute molecules. If the process studied is characterized by lifetimes shorter than the orientation relaxation time of the solvent, diminished values of ε_r and g should be used. In the limit of purely electronic polarization of the solvent, the relative permittivity ε_r should be replaced in equation (2) by the square of the refractive index.

$$f_i y_i = \varepsilon_i y_i \qquad (3)$$

The electronic energy of a solute molecule in a particular dielectric medium is calculated by solving the respective one-electron Fock equations [equation (3)] using the self-consistent reaction field (SCRF) procedure.[11,12] Here y_i denotes a molecular orbital of orbital energy ε_i, and f_i is the one-electron Fock operator corresponding to H'.

$$E_{el} = \sum_{ij} P_{ij}H_{ij} + \tfrac{1}{2}\sum_{ijkl} P_{ij}P_{kl}(\langle ij|kl\rangle - \tfrac{1}{2}\langle ik|jl\rangle) \qquad (4)$$

The electronic energy of the molecule is given by equation (4), where P_{ij} denote the corresponding density matrix elements, H_{ij} is the one-electron modified core-Hamiltonian element which, for a closed-shell system are given by

$$P_{ij} = \sum_{a}^{mo} 2C_{ia}C_{ja}$$

and $\langle ij|kl\rangle$ are two-electron electron repulsion integrals. The total energy is calculated using equation (5), where the sums are

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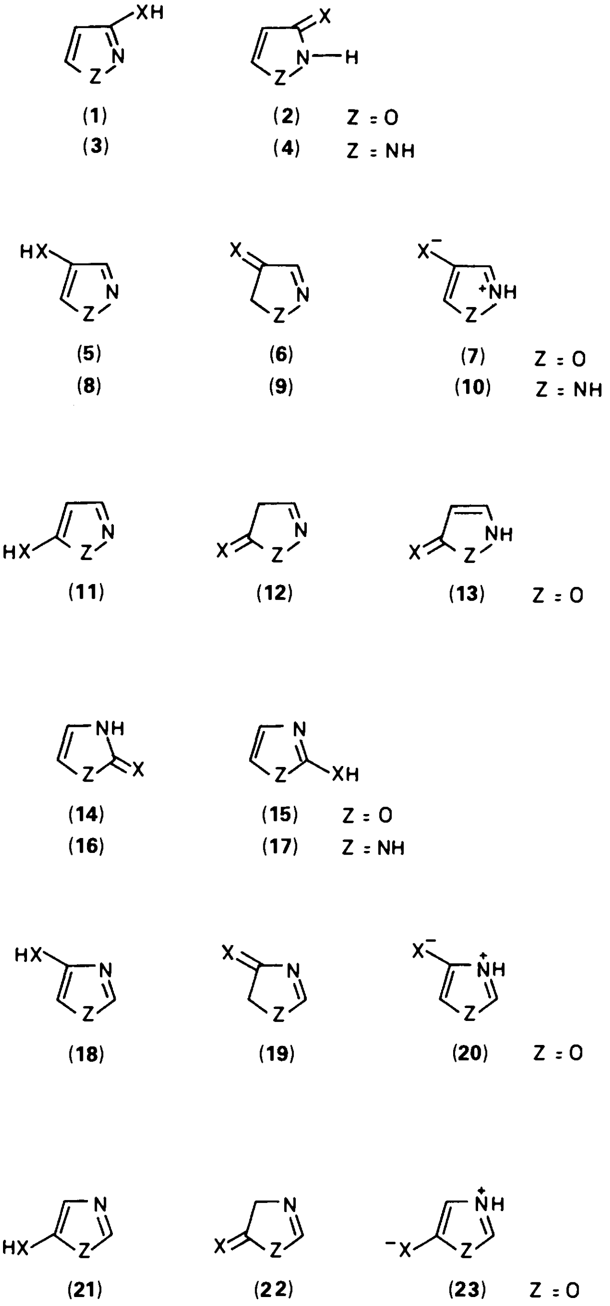

Scheme.

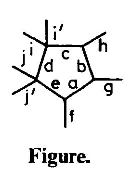

Figure.

taken over all the nuclei in the molecule, Z_k and Z_l are the charges of the nuclei at the distance R_{kl}, and R_k denote their radius vectors.

$$E_{\text{tot}} = E_{\text{el}} + \sum_{k+l}\left[\frac{Z_k*Z_l}{R_{kl}} + g_kZ_kR_k*\langle p|\mu|p\rangle\right] \qquad (5)$$

We have shown earlier that the solvent polarization effects discussed above play a key role in the determination of the directional and energetics of various chemical processes.[12–14] In the present work the results of a quantum-chemical investigation of the solvent reaction field influence on the relative energies of the tautomers of five-membered heterocycles with two heteroatoms (Scheme) are discussed. A semiempirical SCRF LCAO MO approach based on MNDO and AM1 models[15,16] was used. The original MNDO/AM1 code was modified to include reaction field effects.[18]

Results and Discussion

In the present paper, nine five-membered heterocycles containing two ring heteroatoms (oxygen or nitrogen) were investigated: the compounds and the calculated heats of formation ΔH_f and dipole movements of each of the corresponding tautomers are given in Table 1. Calculations have been made for two different states of the molecules: (i) in the gaseous phase (isolated form) and (ii) in an isotropic medium of the relative permittivity of water ($\varepsilon_r = 78.4$).* All the heterocycles investigated are approximately of the same size and a constant value was used for the cavity radius ($r_c = 2.5$ Å). A full geometry optimization taking account of the molecular symmetry was carried out for each individual tautomer studied. The optimized bond lengths and bond angles are presented in Tables 2 and 3. Bonds and angles are denoted by letters given in the Figure.

3-Hydroxyisoxazole.—The experimentally observed tautomer in aqueous solution is the hydroxy form.[19] The AM1 calculations predict a ratio of oxo/hydroxy forms of *ca.* 1 in the gas phase, but in a medium of higher relative permittivity ($\varepsilon_r = 78.4$), the hydroxy tautomer should be more favoured by 2.6 kcal mol^{-1} which corresponds to $pK_T = 4.4$ at room temperature (if $\Delta S = 0$ is assumed); for details see ref. 17, equation (9). Thus, the inclusion of the dielectric effect in the quantum-chemical model enables the prediction of the correct tautomer of 3-hydroxyisoxazole in aqueous solution.

The calculated bond lengths and angles of both tautomers are little changed by the relative permittivity of the medium around the molecules. However, the calculated dipole moments are substantially higher in a medium of high relative permittivity, mainly due to major charge redistribution in the molecule, rather than by changes in the distances between the charge separations. The dipole moment of the oxo-tautomer (**2**) varies more with the change of the dielectric medium than that of the hydroxy tautomer (**1**) (relative changes in moving from gas phase to the medium of $\varepsilon_r = 78.4$ are 52.2 and 27.7%, respectively). This leads to the important but not surprising conclusion that the magnitude of the influence of the solvent reaction field on electronic structure is different in different tautomers. In general, solvent effects tend to favour charge separation, but, as shown in this case, the dipole moment alone cannot always be used as a measure of charge separation.

4-Hydroxyisoxazole.—4-Hydroxyisoxazole predominates in aqueous solution.[19] The SCRF calculations correctly indicate that in a solution of high relative permittivity the energy of hydroxy tautomer (**5**) is *ca.* 0.3 kcal mol^{-1} lower than that of the 5*H*-oxo form (**6**). The 4*H*-oxo form has little intrinsic polarity, and in the gaseous phase it is by far the more stable.

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* The AM1 method overestimates hydrogen bonds and reproduces correctly Onsager's reaction field effect for an associated liquid, *e.g.* water; see ref. 17.

Table 1. The calculated AM1 heats of formation, ΔH_f, and dipole moments for the tautomeric forms of the five-membered heterocycles.

Heterocycle	Tautomeric form	Index[a]	ΔH_f/kcal mol^{-1}		μ/D	
			$\varepsilon_r = 1$	$\varepsilon_r = 78.4$	$\varepsilon_r = 1$	$\varepsilon_r = 78.4$
3-Hydroxyisoxazole	oxo	**(2)**	5.02	−3.13	3.32	5.05
	hydroxy	**(1)**	5.08	−5.76[b]	4.21	5.39
4-Hydroxyisoxazole	2*H*-oxo	**(7)**	39.03	13.44	6.31	9.56
	5*H*-oxo	**(6)**	−7.44	−7.71	0.68	0.90
	hydroxy	**(5)**	2.97	−8.05	2.83	4.56
5-Hydroxyisoxazole	2*H*-oxo	**(13)**	0.98	−26.76	5.40	9.21
	4*H*-oxo	**(12)**	−14.44	−25.83	4.49	6.38
	hydroxy	**(11)**	0.42	−9.17	3.89	5.10
2-Hydroxyoxazole	oxo	**(14)**	−40.53	−56.39	4.77	6.88
	hydroxy	**(15)**	−27.91	−33.04	2.86	3.72
4-Hydroxyoxazole	3*H*-oxo	**(20)**	−14.46	−37.92	5.47	9.01
	5*H*-oxo	**(19)**	−37.53	−45.82	3.33	4.83
	hydroxy	**(18)**	−23.69	−27.66	2.55	3.37
5-Hydroxyoxazole	3*H*-oxo	**(23)**	−24.02	−62.90	6.97	12.16
	4*H*-oxo	**(22)**	−43.03	−45.44[c]	1.95	2.69
	hydroxy	**(21)**	−30.65	−34.05	2.23	3.10
3-Hydroxypyrazole	oxo	**(4)**	36.89	9.79	5.58	10.36
	hydroxy	**(3)**	25.04	21.55	3.46	4.56
4-Hydroxypyrazole	2*H*-oxo	**(10)**	65.47	8.15	8.29	13.88
	5*H*-oxo	**(9)**	24.14	17.18	2.94	4.95
	hydroxy	**(8)**	25.03	21.35	2.79	3.76
2-Hydroxyimidazole	oxo	**(18)**	2.91	−8.08	3.80	5.86
	hydroxy	**(19)**	11.38	8.14	2.24	2.98

[a] Numbers refer to the structures given in the Scheme. [b] Experimentally observed form in the polar solvent (*cf.* ref. 19). [c] Experimentally observed in crystal.

5-Hydroxyisoxazole.—The 2*H*-oxo form **(13)** of 5-hydroxyisoxazole dominates in aqueous solution.[19] The results of the SCRF calculations indicate that this should indeed be the most stable tautomer in a medium of the relative permittivity of water: the energy of tautomer **(13)** is *ca.* 1 kcal mol^{-1} lower than that of the 4*H*-oxo form **(12)** (*cf.* Table 1). The 4*H*-oxo form is, however, far more stable in the gas phase where the stability of the 2*H*-oxo form is comparable to that of the hydroxy tautomer. This illustrates the qualitative errors which can be made by the use of quantum-chemical results corresponding to isolated molecules for the prediction of the relative stability of compounds in solution.

The geometries of tautomers **(12)** and **(11)** change only slightly with the relative permittivity of the medium. This is also true for the bond angles of tautomer **(13)**, but here the bond lengths do change quite significantly, *e.g.* the C(4)–C(5) bond length increases by 0.055 Å and the C(3)–C(4) bond length by 0.047 Å (*cf.* Tables 2 and 3). However, these changes are not the main reason for the large increase of the dipole moment (70.5%) of this tautomer on moving from the gas phase to a medium of $\varepsilon_r = 78.4$: a simple charge density analysis indicates that it is the redistribution of electronic charge which principally causes this effect. The dipole moments of the other tautomers are somewhat less sensitive to a change in relative permittivity [the calculated increases in the dipole moment values are 41.9% for **(12)** and 31.0% for **(11)**].

2-Hydroxyoxazole.—The SCF calculations corresponding to the gas phase and the SCRF calculations with $\varepsilon_r = 78.4$ both indicate that the oxo form **(14)** of 2-hydroxyoxazole should be the dominant tautomer in all media because of the large negative value of ΔH_f in comparison with the hydroxy form **(15)**. This conclusion is in agreement with experimental observations.[19]

The variation of the geometries of both tautomers is insignificant in different media (*cf.* Tables 2 and 3). However, the dipole moments increase significantly with the relative permittivity for both tautomers (*cf.* Table 1) [44.1 and 30.2% for **(14)** and **(15)**, respectively].

4-Hydroxyoxazole.—The 5*H*-oxo tautomer **(19)** of 4-hydroxyoxazole is predicted to be the most stable form of this compound in both the gas phase and in water. Indeed, only the 5*H*-oxo form is experimentally observed in the solution.[19]

The SCRF calculations predict significant changes in the bond lengths of the 3*H*-oxo tautomer **(20)** of 4-hydroxyoxazole. The C(4)–C(5) bond length decreases by 0.038 Å and the CO bond length increases by 0.047 Å in the medium of $\varepsilon_r = 78.4$ in comparison with the isolated molecule (*cf.* Tables 2 and 3). The bond angles are altered much less by the solvent reaction field. Again these geometry changes are not the main reason for the large increase of the dipole moment of this tautomer **(20)** (by 64.8%) in the high dielectric medium. Population analysis indicates that this effect is again caused by the redistribution of the electronic charge. The calculated changes in the geometry and dipole moments of the other tautomers of 4-hydroxyoxazole are much less than those for the 3*H*-oxo form **(20)**.

5-Hydroxyoxazole.—For 5-hydroxyoxazole, the most stable tautomer as calculated by the AM1 SCF method is the 4*H*-oxo form. This tautomer is experimentally observed in the solid state.[19] The results of the SCRF calculations for the different tautomers in the dielectric medium of $\varepsilon_r = 78.4$ indicate, however, that the zwitterionic 3*H*-oxo form **(23)** should be much preferred (by *ca.* 17.5 kcal mol^{-1}) in polar solvents.

The dipole moment of tautomer **(23)** is sensitive to the polarity of the medium since it increases by as much as 74.5% in a dielectric medium of $\varepsilon_r = 78.4$ in comparison with gas phase. This increase is accompanied by substantial changes in charge distribution and geometry (*cf.* Tables 2 and 3). The dipole moments of other tautomers are moderately changed by media of high relative permittivity [38.2 and 38.8% for **(22)** and **(21)**, respectively].

Table 2. The calculated AM1 bond lengths/Å of the five-membered heterocycle tautomeric forms[a] in the gas phase; differences between the gas phase and a medium of $\varepsilon_r = 78.4$ are given in parentheses.[b]

Compound	a	b	c	d	e	f	g	h	i,i′	j,j′	OH
(1)	1.350 (−9)	1.413 (9)	1.493 (0)	1.360 (−13)	1.416 (14)		0.989 (−2)	1.235 (−24)	1.085 (1)	1.088 (−4)	
(2)	1.325 (−4)	1.357 (−7)	1.468 (6)	1.376 (3)	1.407 (15)			1.364 (1)	1.083 (−13)	1.085 (−7)	0.971 (−24)
(3)	1.332 (6)	1.355 (−7)	1.484 (−26)	1.428 (24)	1.403 (6)		0.996 (−50)	1.091 (−12)	1.243 (−46)	1.082 (14)	
(4)	1.321 (1)	1.314 (0)	1.504 (0)	1.523 (1)	1.461 (−3)			1.093 (−98)	1.221 (1)	1.116 (−3)	
(5)	1.320 (−7)	1.339 (6)	1.468 (−2)	1.382 (−1)	1.414 (−2)			1.090 (0)	1.357 (19)	1.082 (−8)	0.970 (−117)
(6)	1.344 (−18)	1.382 (18)	1.383 (−47)	1.460 (55)	1.453 (10)		0.989 (−33)	1.094 (−58)	1.084 (2)	1.219 (−39)	
(7)	1.328 (−7)	1.317 (−19)	1.516 (−17)	1.510 (14)	1.432 (−38)			1.092 (−29)	1.118 (−7)	1.215 (−14)	
(8)	1.329 (−4)	1.343 (−5)	1.456 (3)	1.385 (5)	1.404 (−12)			1.091 (0)	1.081 (−20)	1.343 (5)	0.973 (−27)
(9)	1.406 (13)	1.401 (8)	1.409 (6)	1.370 (0)	1.412 (−32)		1,229 (−27)	0.984 (−18)	1.090 (−26)	1.084 (−11)	
(10)	1.404 (6)	1.339 (−1)	1.410 (−8)	1.385 (−2)	1.406 (0)		1.350 (−3)		1.090 (1)	1.082 (−10)	0.975 (−18)
(11)	1.354 (−3)	1.350 (−17)	1.467 (−9)	1.419 (−37)	1.398 (−12)		1.093 (−44)	0.989 (−21)	1.241 (−47)	1.078 (19)	
(12)	1.403 (16)	1.305 (−12)	1.450 (1)	1.545 (8)	1.437 (−3)		1.098 (−10)		1.225 (−14)	1.117 (−2)	
(13)	1.399 (5)	1.327 (−4)	1.420 (3)	1.392 (53)	1.399 (5)		1.091 (1)		1.365 (−6)	1.081 (−12)	0.972 (2)
(14)	1.361 (−57)	1.347 (20)	1.391 (−64)	1.426 (24)	1.470 (35)		1.090 (−17)	0.991 (−9)	1.083 (6)	1.222 (−77)	
(15)	1.412 (−6)	1.302 (4)	1.462 (6)	1.528 (0)	1.413 (3)		1.096 (−3)		1.122 (−4)	1.217 (−8)	
(16)	1.413 (0)	1.326 (−4)	1.405 (3)	1.390 (−4)	1.395 (−9)		1.089 (−3)		1.088 (8)	1.343 (5)	0.974 (−16)
(17)	1.364 (−17)	1.432 (29)	1.478 (29)	1.383 (−47)	1.394 (37)	0.987 (−78)	0.998 (5)	1.237 (−70)	1.083 (10)	1.092 (−29)	
(18)	1.337 (2)	1.374 (−6)	1.450 (−6)	1.402 (1)	1.394 (4)	0.992 (−13)		1.364 (−16)	1.082 (−4)	1.089 (−12)	0.971 (−4)
(19)	1.343 (3)	1.384 (2)	1.461 (2)	1.461 (79)	1.383 (−78)	0.993 (−78)	0.992 (−79)	1.087 (0)	1.245 (15)	1.087 (16)	
(20)	1.325 (−21)	1.327 (−83)	1.494 (30)	1.546 (75)	1.462 (45)	0.988 (−73)		1.091 (0)	1.223 (−87)	1.121 (44)	
(21)	1.329 (13)	1.360 (25)	1.448 (−32)	1.406 (−124)	1.401 (−68)	0.992 (−29)		1.088 (7)	1.361 (130)	1.086 (−41)	0.969 (−118)
(22)	1.416 (−3)	1.416 (27)	1.407 (80)	1.385 (−1)	1.407 (1)	0.983 (6)	1.247 (−33)	0.983 (5)	1.089 (−7)	1.089 (−20)	
(23)	1.402 (−7)	1.367 (2)	1.397 (−2)	1.405 (−3)	1.400 (−91)	0.984 (−11)	1.375 (5)		1.089 (−1)	1.087 (−9)	0.972 (10)

[a] Bonds are individually denoted by letters which refer to the bonds so labelled in the Figure. [b] Differences (× 10^3).

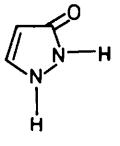
Table 3. The calculated AM1 bond angles/° of the five-membered heterocycle tautomeric forms[a] in the gas phase; differences between the gas phase and a medium of ε_r = 78.4 are given in parentheses.

Compound	ab	bc	cd	de	ae	af	ag	bh	ci(i′)	dj(j′)	XOH
(1)	111.6 (0.4)	104.2 (−1.0)	106.4 (1.2)	110.6 (−0.8)	107.2 (0.2)		115.0 (4.7)	123.9 (0.7)	122.9 (−3.1)	136.2 (3.6)	
(2)	107.4 (−0.8)	109.9 (1.4)	103.4 (−0.9)	108.4 (−0.3)	110.9 (0.6)			122.6 (−1.3)	126.4 (−0.9)	136.5 (2.2)	106.0 (1.0)
(3)	111.8 (0.3)	108.6 (1.0)	101.5 (0)	110.8 (−0.6)	107.3 (−0.7)		105.5 (30.7)	123.1 (5.4)	126.8 (−5)	135.2 (2.4)	
(4)	112.0 (0)	111.0 (0)	101.6 (−0.1)	104.2 (0.1)	111.2 (0)			124.2 (−0.7)	129.2 (0.7)	112.7 (−0.2)	
(5)	109.5 (−0.3)	108.3 (0.3)	104.9 (0.4)	107.0 (−0.4)	110.3 (0.6)			124.9 (−2.9)	122.4 (2.5)	137.6 (4.6)	107.2 (−13.3)
(6)	111.2 (2.4)	109.3 (0.2)	106.3 (−0.7)	106.1 (0.3)	107.1 (−2.2)		115.9 (−2.9)	120.5 (1.6)	129.3 (6)	140.4 (−3.5)	
(7)	111.1 (2.1)	111.6 (0.6)	99.8 (−3.0)	106.7 (3.4)	110.8 (−3.1)			124.0 (−7.4)	112.1 (1.8)	136.9 (−8.7)	
(8)	109.2 (0.3)	109.9 (−0.1)	102.7 (−0.6)	109.7 (0.5)	108.5 (−0.1)			123.2 (−2.5)	127.5 (0.4)	140.3 (−0.2)	106.8 (1.1)
(9)	107.6 (0.6)	108.4 (−2.0)	107.5 (0.8)	109.5 (0.6)	106.9 (−0.1)		119.2 (−0.3)	125.3 (−1.1)	121.3 (−2.1)	135.7 (5.9)	
(10)	114.0 (0)	104.0 (0)	110.2 (0.2)	107.7 (0)	104.0 (−0.3)		114.0 (0.4)		120.0 (−2.4)	137.2 (−0.6)	106.9 (1.9)
(11)	110.1 (−0.5)	109.3 (1.4)	102.7 (−0.9)	109.7 (−0.4)	108.1 (1.3)		118.6 (−0.5)	125.8 (10.8)	120.9 (−3.4)	134.4 (1.5)	
(12)	116.5 (0.9)	106.7 (−1.0)	106.3 (1.0)	104.0 (−0.9)	106.4 (−0.1)		114.1 (1.3)		127.2 (1.6)	111.9 (−0.6)	
(13)	113.1 (0)	104.8 (0)	109.7 (0.2)	106.7 (−0.1)	105.6 (−0.2)		116.2 (2.3)		125.7 (3.2)	136.9 (−0.2)	108.1 (5.1)
(14)	110.1 (0.9)	110.3 (0.7)	107.3 (−14.8)	105.0 (15.4)	107.4 (−2.3)		119.9 (−2.2)	125.8 (6.1)	123.7 (0.6)	142.3 (−1.9)	
(15)	115.1 (0.6)	108.0 (−0.9)	104.4 (0.5)	112.5 (5.7)	100.0 (−5.9)		114.6 (−2.3)		110.4 (1.2)	136.4 (−1.3)	
(16)	112.6 (0)	106.6 (0)	107.8 (−0.4)	109.3 (0.6)	103.7 (−0.2)		115.4 (0.9)		122.4 (−1.6)	135.3 (0.1)	107.7 (−25.1)
(17)	109.6 (1.2)	104.7 (3.0)	107.0 (2.5)	109.6 (−0.1)	109.1 (−0.6)	121.5 (−0.4)	120.6 (4.2)	122.0 (−6.8)	123.6 (0.3)	130.5 (3.5)	
(18)	105.3 (−2.7)	111.0 (2.4)	103.8 (−0.9)	106.9 (−0.7)	113.0 (1.9)	119.5 (−2.5)		126.8 (1.8)	126.8 (−1.2)	130.8 (3.7)	108.5 (6.6)
(19)	109.5 (−0.2)	109.3 (−1.2)	102.2 (−0.2)	109.3 (−1.0)	109.7 (3.6)	121.3 (−2.2)	129.1 (5.6)	121.3 (5.6)	128.9 (0.1)	121.4 (−2.1)	
(20)	109.9 (1.4)	111.3 (1.1)	102.2 (−5.5)	102.1 (1.3)	113.8 (1.0)	120.8 (6.4)		123.2 (7.1)	130.4 (−1.1)	110.9 (−1.5)	
(21)	107.1 (−3.1)	109.2 (−1.4)	105.7 (2.9)	105.0 (2.5)	113.0 (0.1)	120.6 (−1.7)		122.6 (0.8)	129.7 (4.2)	131.4 (16.4)	106.4 (−14.1)
(22)	106.1 (0)	108.8 (−1.4)	108.1 (2.0)	108.3 (−0.9)	108.7 (0.3)	124.6 (−0.9)	126.9 (−0.2)	124.5 (−1.6)	121.7 (−3.0)	130.1 (2.9)	
(23)	112.7 (0.5)	104.1 (−6.8)	111.0 (−0.9)	122.9 (20.7)	105.6 (3.8)	126.4 (8.8)	118.3 (0.8)		120.8 (−0.9)	131.5 (−0.1)	106.8 (−1.2)

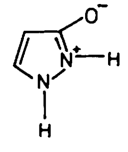
[a] Bonds are individually denoted by letters which refer to the bond angles so labelled in the Figure.

3-Hydroxypyrazole.—Contrary to the results of the gas phase SCF calculation, the AM1 SCRF calculation of the 3-hydroxypyrazole predicts the oxo form (**3**) to be the main tautomer in a solution of high relative permittivity, 11.7 kcal mol^{-1} more stable than the hydroxy form (**18**). This is in full agreement with experimental observations. Again, the calculated results for the isolated tautomers leads to qualitatively wrong conclusions.

The large increase of the calculated dipole moment of the compound (**17**) indicates that the neutral resonance form (**4a**) has a much smaller weight than the zwitterionic form (**4b**) in solution. This increase of dipole moment (by 85.8%) substantially exceeds the corresponding increase for the hydroxy tautomeric form (**3**) (31.9%) and it is also highest for all the compounds studied in this work.



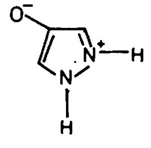
(**4a**)



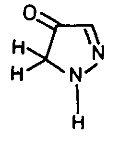
(**4b**)

4-Hydroxypyrazole.—The experimentally observable tautomer of 4-hydroxypyrazole in solution is the 2*H*-oxo form (**10**).[19] The AM1 SCF calculations for the isolated molecules give the energy of this form as the highest of the three possible forms by *ca.* 40 kcal mol^{-1}. The introduction of the solvent reaction field in the calculation enables prediction of the right order of tautomer stabilities in solution for this heterocycle (*cf.* Table 1).

This considerable extra stabilization of the zwitterionic tautomer (**10**) in aqueous solution results from the substantial increase of its dipole moment in highly polar media (84.6% in a solvent of $\varepsilon_r = 78.4$ in comparison with the gas phase). The optimized ring bond lengths and bond angles are rather insensitive towards the solvent reaction field, but the C–O bond length is characterized by a large increase in the medium of high relative permittivity (*cf.* Tables 2 and 3). Comparison with standard C–O bond lengths shows that in the gas phase it is essentially a double bond, whereas in the solution the value of the bond length is close to that of a C–O single bond. In other words, the zwitterionic form (**10a**) is calculated to have a much larger weight than the neutral form (**9b**) in solution.



(**10a**)



(**9b**)

2-Hydroxyimidazole.—For this heterocycle, both types of calculations (SCF and SCRF) predict the experimentally observed oxo form (**15**) in solution. The geometries of the two possible tautomers are influenced little by the solvent reaction field, but the dipole moment of the oxo form is altered substantially [by 54.3% in comparison with 32.9% for the hydroxy form (**14**)].

Conclusions

Four important conclusions may be drawn on the basis of the results of the quantum-chemical AM1 SCF and SCRF calculations presented in this paper.

(*a*) The solvent reaction field can have a strong differential effect on the electronic structures and relative energies of different tautomers. These calculated differences predict a change in the relative stabilities of the tautomers in different media and, consequently, in the predictions of the tautomeric equilibrium constants. In many cases quantum-chemical calculations on isolated molecules can lead to qualitatively incorrect results. These errors in prediction do not depend on the level of sophistication of the quantum-chemical model used, but rather on an incorrect or missing treatment of solvent effects.

(*b*) The solvent reaction field usually enhances significantly the importance of ionic resonance forms of the carbonyl tautomers studied. The presence of the aromatic $(4n + 2)$ π-electron ring structure is favoured in these resonance forms. Therefore, 'experimentally observable' resonance energies characterizing the aromaticity of the heterocycles studied should depend on solvent polarity, and are not independent from solvent stabilization.

(*c*) Solvent effects are predicted to favour charge separation and structural changes insofar as they support resonance forms with these charge separations. In general, but not always, tautomers with the largest dipole moments are stabilized the most by solvation. This is simply because tautomers with the largest dipole moments generally have the largest charge separation.

(*d*) Although the energy differences between the various individual tautomers are sometimes quite small, it is striking that in every case where comparison with experimental results is possible, these differences are found to be significant. For example, 4-hydroxyisoxazole predominates as tautomer (**5**) in aqueous solution and (**5**) < (**6**) by 0.3 kcal. Again the 2*H*-oxo form (**13**) predominates in aqueous solution and (**13**) < (**12**) by 1.0 kcal. Unfortunately, no quantitative experimental data (*i.e.* no K_t values) are available for these compounds to test further the quantitative significance of the calculated results.

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