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Theoretical Study of the Keto-Enol Tautomerism in Aqueous Solutions

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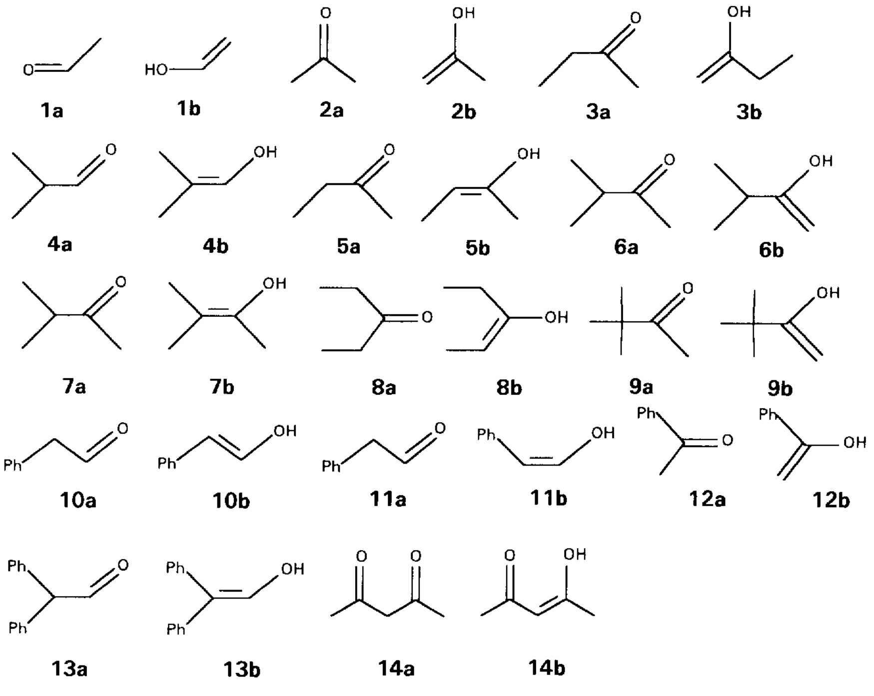
Abstract: The tautomeric equilibrium constants for a series of aliphatic ketones in aqueous solution are quantitatively predicted using the quantum chemical self-consistent reaction field approach.

The importance of understanding the nature of tautomeric equilibria has long been recognised for the study of the processes of both organic chemistry and biochemistry.[1,2] The tautomerism of organic compounds has been the subject of extensive theoretical studies using various quantum-mechanical and statistical-physical approaches.[3] The solvation energies of tautomers may vary significantly and therefore such systems are also of special interest as test cases for theoretical models of solvation as variations in dispersion energy, in cavity formation, and solvent restructurization entropy effects are all expected to be small for different tautomers of a given compound.[4,5] As a result, in many cases electrostatic reaction field models lead to the correct order of stability of tautomers in solution and, in some cases, even to quantitative agreement between calculated and experimental tautomeric equilibrium constants.[6-9] Comparative studies have shown that the simple self-consistent reaction field model (corresponding to a single spherical solute cavity in the solution[10,11]), implemented into *ab initio* or semiempirical MO theory, gives adequate tautomeric equilibrium constants for heterocyclic compounds in aqueous solutions.[4-9]

Notably, previous theoretical investigations of the solvent effect on the tautomeric equilibria have almost exclusively involved cyclic and mainly heterocyclic compounds. The molecular frame of cyclic molecules is rather compact and rigid and consequently, the spherical representation of the solute cavity is a good approximation for these systems, whereas the reaction field of conformationally flexible aliphatic molecules is expected to be significantly more complex. We believe that this is a main reason for the lack of an accurate description of the tautomeric equilibria of such systems in solution by the simple single-cavity SCRF (SCa SCRF) approach. Here we report the results using the SCa SCRF and the multi-cavity self-consistent reaction field (MCa SCRF) methods of the quantum-chemically calculated tautomeric equilibrium constants for a series of 11 aliphatic ketones (Scheme). As three of the ketones each participate in two equilibria (**3a** and **5a**; **6a** and **7a**; **10a** and **11a**), altogether 14 tautomeric equilibria were studied.

The MCa SCRF method was developed by us especially for the description of the electrostatic solvation of conformationally flexible molecules in high dielectric constant media[12]. In this method, individual reaction fields are developed for all rotationally or inversionally flexible fragments of the solute molecule, and the solute-dielectric continuum interaction energy is calculated as a sum of the interaction energies of the fragment charge distributions with their own reaction fields and the reaction fields of other fragments. The MCa SCRF method has been successfully applied for the prediction of the relative solvation energies of small organic molecules[12] and for the absolute hydration energies of inorganic ions in aqueous solution[13]. It has been also applied to model S_N2 reaction paths and transition states in solution[14].

In the present calculations, the solute molecules were partitioned into fragments, each of which corresponds to a conformationally flexible group. The cavity radii for individual molecules and molecular fragments were calculated from the mass densities ρ and molecular masses WM of the compounds as given in Ref. 12. Two dielectric media were modelled as surrounding the molecules, one with the macroscopic dielectric constant $\varepsilon = 1$, which corresponds to the gas phase (isolated molecules) and another with $\varepsilon = 80$, corresponding to an aqueous solution at 20°C. All calculations were performed using Dewar's Austin Model 1 (AM1)[15] parameterization.



Scheme

The AM1 calculated heats of formation, and the respective tautomeric equilibrium constants pK_T for molecules in different media are given in the Table. The tautomeric equilibrium constants were calculated according to the equation

$$\log K_T = \frac{\Delta G_T}{2.303RT} \approx \frac{\delta \Delta H}{2.303RT}$$

where ΔG_T is the free energy of the tautomeric equilibrium and $\delta\Delta H$ is the difference in the calculated heats of formation of the tautomeric species participating in this equilibrium.

Table. AM1 Calculated Heats of Formation ΔH_f^o (*kcal/mol*) and Tautomerization Equilibrium Constants $\log K_T$ of Aliphatic Ketones and Enols. Experimental Data are from Ref. 16 and 17.

Molecule	ΔH_f^o			$\log K_T$			
	$\varepsilon = 1$	$\varepsilon = 80$		$\varepsilon = 1$	$\varepsilon = 80$		
		SCa SCRF	MCa SCRF		SCa SCRF	MCa SCRF	experiment
1a	-41.56	-44.24	-45.33				
1b	-33.53	-33.82	-37.25	5.91	7.67	6.09	6.23
2a	-49.19	-51.59	-53.66				
2b	-39.53	-39.65	-42.59	7.10	8.78	8.13	8.33
3a	-55.15	-56.62	-60.07				
3b	-45.20	-45.30	-47.50	7.35	8.32	9.07	8.76
4a	-53.05	-54.66	-56.72				
4b	-50.13	-50.44	-52.05	2.15	3.09	3.44	3.86
5a	-55.15	-56.62	-60.07				
5b	-48.41	-48.55	-49.72	4.96	5.93	7.61	7.51
6a	-59.27	-60.86	-63.90				
6b	-49.05	-49.11	-52.32	7.51	8.64	8.52	8.61
7a	-59.27	-60.86	-63.90				
7b	-52.93	-53.57	-54.28	4.66	5.27	7.07	7.33
8a	-61.00	-62.57	-64.82				
8b	-53.71	-53.87	-55.52	5.36	6.40	6.84	7.43
9a	-61.49	-61.85	-65.35				
9b	-50.87	-50.85	-53.92	7.79	8.05	8.40	8.79
10a	-15.42	-16.53	-20.33				
10b	-8.30	-11.64	-16.49	5.23	3.60	2.82	3.07
11a	-15.42	-16.53	-20.33				
11b	-7.23	-11.00	-14.50	6.02	4.73	4.28	3.35
12a	-15.01	-16.47	-16.74				
12b	-4.76	-5.19	-5.71	7.53	8.28	8.10	7.96
13a	16.18	16.19	14.91				
13b	16.47	16.28	16.07	0.21	0.03	0.85	0.98
14a	-81.54	-88.04	-90.62				
14b	-84.90	-86.83	-89.43	2.47	-0.89	-0.88	-0.74

$\log K_T$ values calculated for $\varepsilon=1$ and for $\varepsilon=80$ by the SCa and MCa methods are plotted against experimental $\log K_T$ for aqueous solution in Fig. 1, 2 and 3, respectively. In most cases, the reaction field accounts for important effects. The calculated $\log K_T$ ($\varepsilon=1$) absolute values for compounds **4**, **5**, **7**, **8**, **10**, **11**, and **14** deviate more than 2 logK units from the experimental values in the aqueous solution and Fig. 1 shows no correlation. By contrary the following regression equations were obtained for the SCa and MCa plots:

$$\log K_T(\mathrm{SCa}) = (0.03 \pm 0.61) + (0.95 \pm 0.09)\log K_T(\exp) \qquad R^2 = 0.896; \quad s = 1.06$$

$$\log K_T(\mathrm{MCa}) = (-0.03 \pm 0.22) + (0.99 \pm 0.03)\log K_T(\exp) \qquad R^2 = 0.986; \quad s = 0.39$$

The MCa SCRF results are significantly superior to those obtained using the SCa SCRF method (cf. Figures 2 and 3) and provide a satisfactory explanation for the variation found.

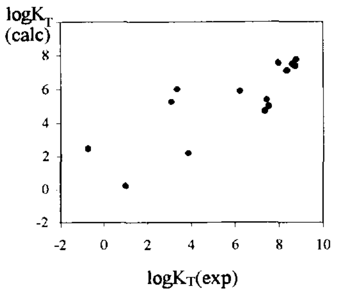


Fig. 1 **K$_T$(ε=1)**

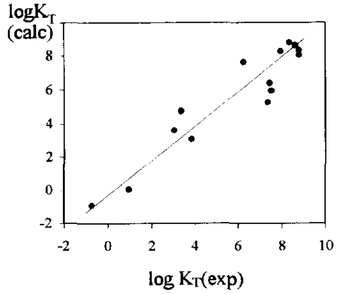


Fig. 2 **K$_T$(ε=80) by SCa**

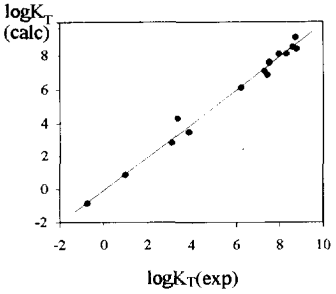


Fig. 3 **K$_T$(ε=80) by MCa**

In conclusion, we have demonstrated that the self-consistent reaction field approach in combination with the AM1 semiempirical quantum-chemical parameterization can give confident predictions of the tautomeric equilibrium constants of aliphatic ketones in aqueous solution.

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