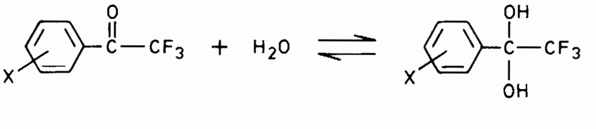
Trifluoromethyl Ketone Hydration. Substituent Effects of Amino-groups and the Hydrating Properties of Aqueous Dimethyl Sulphoxide

Robert S. McDonald,*,† Khay-C. Teo, and Ross Stewart *
Department of Chemistry, University of British Columbia, Vancouver, Canada V6T 1Y6

The equilibrium constants for hydration of the 4-amino-, 4-methylamino-, and 4-dimethylamino-derivatives of ααα-trifluoroacetophenone have been determined in mixtures of dimethyl sulphoxide (DMSO) and D_2O (or H_2O) using ^{19}F n.m.r. spectroscopy. The dimethylamino-compound follows the pattern observed earlier for the 4-methoxy-compound, *i.e.* in mixtures up to 80 mol % DMSO these compounds are more highly hydrated than in pure water. The extent of hydration of the amino- and methylamino-compounds, on the other hand, decreases steadily as the water content of the mixture is decreased. The difference in behaviour of the two groups of compounds is attributed to the presence of acidic protons in the unhydrated forms of the amino- and methylamino-compounds, which are able to form strong hydrogen bonds to DMSO. The results indicate the strong solvent dependence to be expected for σ^+ substituent constants for the three kinds of amino-group. A sampling of other carbonyl compounds that undergo hydration revealed a considerable variation in the response of such compounds' equilibrium constants to changes in DMSO–water composition, with only one compound, 2-nitrobenzaldehyde, showing the sort of response that is shown by the 4-dimethylamino- and 4-methoxy-derivatives of trifluoroacetophenone.

In connection with studies of carbonyl reduction by various hydride donors we had occasion to prepare the 4-amino- and 4-methylamino-derivatives of ααα-trifluoroacetophenone.[1,2] Other derivatives of this compound had been studied previously with regard to their hydrating properties,[3,4] which are strongly substituent dependent [equation (1)].


(1)

Electron-withdrawing groups increase the degree of hydrate formation in water and electron-donating groups decrease it, as expected, the equilibrium constants being correlated by σ^+ substituent constants. The equilibrium constants are also solvent dependent. Addition of tetramethylene sulphone (sulpholan) as cosolvent shifts the equilibrium (1) to the left for all compounds. Surprisingly, when X = 4-MeO, the only derivative that could be thoroughly studied in the previous work, addition of dimethyl sulphoxide (DMSO) up to about 80 mol % was found to shift the equilibrium to the right; *i.e.*, DMSO–water mixtures appear to be better hydrating media towards this ketone than is water itself. The purpose of the present work was two-fold. First, to determine whether or not the unusual hydration behaviour of the 4-methoxy-compound in aqueous DMSO is also shared by the corresponding amino-, methylamino-, and dimethylamino-compounds. Secondly, to compare the substituent effects of the three amino-groups. There appears to be no σ^+ value in the literature for the 4-methylamino-group and the values reported for the 4-amino- and 4-dimethylamino-group vary considerably.[5-9] A determination of the equilibrium constants for hydration of the three ketones appeared to be an attractive means of assessing the substituent effects of these three groups.

Experimental

The 4-substituted trifluoroacetophenones were prepared as described previously.[1-3] D_2O (minimum 99.8% D) and [$^2H_6$]DMSO (minimum 99% D) were obtained from Merck, Sharp and Dohme of Canada and used without further purification. DMSO was Fisher reagent-grade. The aqueous DMSO solutions (D_2O–DMSO and H_2O–[$^2H_6$]DMSO) were prepared by volume and solvent composition calculated accurately by mass.

Where solubility permitted, solutions were 2—5 wt % (*ca.* 0.1—0.25M). Otherwise, saturated solutions were prepared. Solutions were allowed to equilibrate for at least four days before spectra were recorded and then rerun one week later. No decomposition of any of the solutions was observed during this time period and duplicate determinations of K_h normally agreed to within 10%. The experiments were conducted at 35 ± 2 °C, depending on the probe temperature of the instrument being used at the time. Fortunately, the heats of hydration of these compounds are low and so the equilibrium constants are relatively insensitive to variations in temperature (refs. 3 and 10 and Table 3).

To facilitate signal-locking in the n.m.r. D_2O–DMSO was used as the solvent mixture in most cases, although a number of experiments were also conducted using H_2O–[$^2H_6$]DMSO. There appeared to be no significant difference in the results obtained using the two different solvent systems.

Hydration equilibrium constants were calculated by taking the ratios of the average of multiple integrations of the two resonances in the ^{19}F n.m.r. spectrum due to the free carbonyl compound and its hydrate. Spectra were recorded on a Varian EM-360L spectrometer (single sweep mode) for the more concentrated solutions or on a Varian XL-100 instrument in the Fourier transform mode for the dilute solutions. For the latter spectrometer the acquisition time was 2 s per pulse on a sweep width of 2 000 Hz. The final spectra were the result of 400—30 000 transients.

Results and Discussion

Table 1 lists the values of the equilibrium constants for hydration of the ketones containing the three amino-groups as a function of solvent composition, and the values for the D_2O–DMSO system are plotted in the Figure. It can be seen that the effect previously observed with the 4-methoxy-compound is also present in the case of the 4-dimethylamino-compound but not in the cases of the compounds containing

---

† *Present address:* Department of Chemistry, Mount Saint Vincent University, Halifax, Nova Scotia, Canada B3M 2J6.

Table 1. Equilibrium constants for hydration of the 4-amino-, 4-methylamino-, and 4-dimethylamino-ketones in D_2O–DMSO as a function of solvent composition: T35 ± 2 °C; K_h = [hydrate]/[ketone] [a]

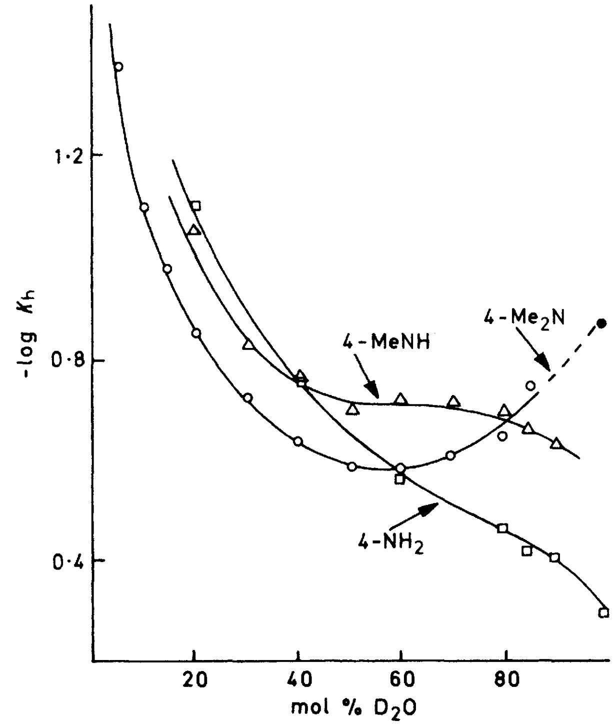
mol % D_2O	4-NH_2	4-MeNH	4-Me_2N
100	0.51		
90	0.39	0.24	
85	0.38	0.22	0.18
80	0.34	0.21	0.23
70		0.20	0.25
60	0.28	0.19	0.26 (0.26) [b]
50		0.20	0.26 (0.25)
40	0.18	0.17	0.24 (0.23)
30		0.15	0.19 (0.18)
20	0.079	0.090	0.14 (0.14)
15			0.11
10			0.081 (0.07)
5			0.043

[a] The equilibrium constants K_d previously reported were for the reverse reactions in H_2O.[3] [b] Values in parentheses refer to mixtures of H_2O and [$^2H_6$]DMSO.

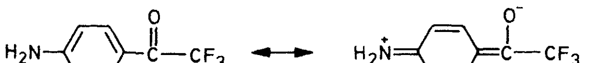
Table 2. Relationship between the hydration constants of the 4-dimethylamino- and 4-methoxy-ketones in aqueous DMSO

mol % water [a]	log K_h [a]		log K_{MeO} − log K_{Me_2N}
	4-MeO [b]	4-Me_2N [c]	
80	1.15	−0.64	1.79
60	1.26	−0.58	1.84
40	1.20	−0.63	1.83
30	1.11	−0.71	1.82
20	0.95	−0.85	1.80
10	0.69	−1.09	1.78
5	0.38	−1.37	1.75

[a] H_2O used for the MeO compound, D_2O for the Me_2N compound. [b] Data from ref. 3. [c] Present work.



Logarithm of the hydration constants of the amino-ketones as a function of solvent composition in aqueous DMSO. The point for Me_2N in pure water (H_2O) is an earlier independent estimate [3]


$$\mathrm{H_2N{-}C_6H_4{-}\overset{O}{\overset{\|}{C}}{-}CF_3 \longleftrightarrow H_2\overset{+}{N}{=}C_6H_4{=}\overset{O^-}{\overset{|}{C}}{-}CF_3} \qquad (2)$$

the amino- or methylamino-groups. Indeed, the ordering of the three compounds changes as the solvent composition is changed. In aqueous solution the order appears to be ' normal ', that is the ketone containing the dimethylamino-group is the least hydrated and that with the amino-group the most hydrated. This order corresponds to electron-donating ability being greatest for the dimethylamino-group and least for the amino-group, the order found in most previous determinations of σ^+ values for these two groups.[5-9] (Lack of solubility prevents measurements in water being made for the dimethylamino- and methylamino-compounds; however, the previously published value for the equilibrium constant of the dimethylamino-compound in water, determined using an indirect u.v. spectroscopic method,[3] is in reasonable agreement with the extrapolated curve shown in the Figure.)

As the water content of the mixture is reduced the curves cross and the amino-compound becomes the least hydrated ketone in solutions containing <40 mol % water.

What is the cause of the behaviour shown in the Figure and what are the consequences with respect to the two matters addressed in the Introduction? We attribute much of the effect to the ability of the amino- and methylamino-groups in the unhydrated ketones to form strong hydrogen bonds to DMSO and the lack of ability of dimethylamino (and methoxy) to do so. The sort of resonance interaction present in all three unhydrated ketones is shown in equation (2); only in the amino- and methylamino-cases, however, are there acidic protons that can be expected to interact strongly with the exposed negative end of the DMSO dipole, thus providing additional stabilization of the unhydrated ketone relative to its hydrate, as is observed. (The *gem*-diol unit of the hydrate can also form hydrogen bonds to DMSO and to water but this factor is presumably present to about the same degree in all three compounds.)

It is clear that the σ^+ substituent constants of the three amino-groups are strongly solvent dependent, with the expected order of electron release, $Me_2N > MeNH > NH_2$, being reversed in mixtures rich in DMSO.

The close similarity between the behaviour of the 4-dimethylamino- and 4-methoxy-groups can be seen by the results given in Table 2. There the logarithms of the equilibrium constants for hydration of the two ketones are listed for solutions varying in composition from 5 to 80 mol % water. It can be seen that the logarithmic quantities differ by an amount that is nearly constant despite the equilibrium constants themselves undergoing large changes in this solvent range.* (The values for the methoxy-compound refer to H_2O, whereas for the dimethylamino-compound the more extensive data available in D_2O has been used. The data in Table 1 indicate that the effect of replacing H_2O by D_2O is minimal.)

---

* An alternative treatment involves plotting the logarithm of the hydration constant for the dimethylamino-compound against the W_0 function derived originally using as the principal indicator the methoxy-compound.[3] For all eleven data points given in Table 1 for D_2O an excellent straight line relationship was obtained, correlation coefficient 0.9987, slope 0.91.

Table 3. Equilibrium constants for hydration of a number of carbonyl compounds, K_h = [hydrate]/[ketone] [a]

No.	Compound [b]	K_h (D_2O)	K_h (50 mol % D_2O–DMSO)	Ratio
1	Pyridine-2-carbaldehyde	0.42	0.13	3.2
2	Pyridine-4-carbaldehyde [c]	1.12	0.57	2.0
3	Phthalaldehyde	6.3	2.4	2.6
4	Propionaldehyde	1.0	0.44	2.3
5	αα′-Dichloroacetone	4.1	2.6	1.6
6	4-Nitrobenzaldehyde	0.27	0.16	1.7
7	2-Nitrobenzaldehyde	0.28	0.29	0.97

[a] Experiments conducted with an EM-360 instrument at 31—32 °C, except for 2- and 4-nitrobenzaldehydes which were done using a WP-80 instrument (Fourier transform mode) at 25 °C. [b] Previous literature values: 1, 0.50 (H_2O, 25 °C);[11] 2, 1.53 (H_2O, 25 °C)[11] (ref. 4 comments on the wide variations in reported values for this compound); 3, 7.7 (D_2O, 25 °C);[12] 4, 0.71 (H_2O, 25 °C);[13] 5, 9.7 (H_2O, 25 °C),[14] 6.3 (H_2O, 25 °C);[15] 6, 0.11 (H_2O, 25 °C);[16] 0.25 (H_2O, 25 °C);[17] 7, 0.11 (H_2O, 25 °C),[16] 0.43 (H_2O, 25 °C).[18] [c] ΔH (hydration) -3.8 kcal mol^{-1}.[11]

Other Carbonyl Hydrates.—We have briefly examined a number of other carbonyl compounds to see if they are hydrated to a greater or lesser extent in aqueous DMSO than in water itself. Table 3 shows a comparison of the equilibrium constants for hydration of a number of compounds in D_2O in 50 mol % D_2O–DMSO. Though the ratios of equilibrium constants in the two media vary from case to case most compounds exhibit ' normal ' behaviour in that they are somewhat less hydrated in the mixed solvent than in water. 2-Nitrobenzaldehyde is the exception and, though its degree of hydration is only slightly more in 50 mol % D_2O than in water, a more extensive study of this compound showed a clear minimum appearing in the range 80—90 mol % D_2O.

We have attributed the striking difference between the dimethylamino- and methoxy-compounds on the one hand and the amino- and methylamino-compounds on the other to the presence of acidic protons in the unhydrated forms of the latter compounds. It appears from the results shown in Table 3 that there are a number of other structural factors that can determine the response of carbonyl groups and their hydrates to changes in solvent composition and that the nature of these factors is not at all obvious.

Acknowledgement

The financial support of the Natural Sciences and Engineering Council of Canada is gratefully acknowledged.

References

1 R. Stewart and K. C. Teo, *Can. J. Chem.*, 1980, **58**, 2491.
2 R. Stewart, K. C. Teo, and L. K. Ng, *Can. J. Chem.*, 1980, **58**, 2497.
3 R. Stewart and J. D. Van Dyke, *Can. J. Chem.*, (*a*) 1970, **48**, 3961; (*b*) 1972, **50**, 1992.
4 W. J. Scott and P. Zuman, *J. Chem. Soc., Faraday Trans. 1*, 1976, **72**, 1192.
5 A. J. Hoefnagel and B. M. Wepster, *J. Am. Chem. Soc.*, 1973, **95**, 5357.
6 O. Exner in ' Correlation Analysis in Chemistry,' eds. N. B. Chapman and J. Shorter, Plenum, New York, 1978.
7 J. Hine, ' Structural Effects on Equilibria in Organic Chemistry,' Wiley, New York, 1975, p. 72.
8 L. M. Stock and H. C. Brown, in ' Advances in Physical Organic Chemistry,' ed. V. Gold, Academic Press, London, vol. **1**, 1963.
9 S. Clementi and P. Linda, *J. Chem. Soc., Perkin Trans. 2*, 1973, 1897.
10 R. P. Bell in ' Advances in Physical Organic Chemistry,' ed. V. Gold, Academic Press, London, vol. 4, 1966.
11 S. Cabani, P. Gianni, and E. Matteoli, *J. Phys. Chem.*, 1972, **76**, 2959.
12 R. S. McDonald and E. V. Martin, *Can. J. Chem.*, 1979, **57**, 506.
13 L. C. Green and P. T. McTigue, *J. Chem. Soc.*, 1963, 5217, 5224.
14 R. P. Bell and A. O. McDougall, *Trans. Faraday Soc.*, 1960, **56**, 1281.
15 P. Greenzaid, Z. Luz, and D. Samuel, *J. Am. Chem. Soc.*, 1967, **89**, 749.
16 R. P. Bell and P. E. Sorensen, *J. Chem. Soc., Perkin Trans. 2*, 1976, 1594.
17 J. M. Sayer, *J. Org. Chem.*, 1975, **40**, 2545.
18 E. Laviron, H. Troncin, and J. Tironflet, *Bull. Soc. Chim. Fr.*, 1962, 524.

Received 8th July 1982; *Paper* 2/1154