

Steric Effects on the Solvation of Protonated Di-*tert*-butyl Ketone and Phenyl *tert*-Butyl Ketone

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The anomalously low basicity of two sterically hindered ketones (Bu₂CO and PhCOBu^t) stems from steric hindrance to the solvation of their protonated forms.

There is a long-standing question as to whether bulky groups near a site of ionization affect its strength.¹ For example, the assumption that the different ordering of acidities in the gas phase and in solution is due to 'steric hindrance to solvation' is an intuitive way of dealing with these effects. However, when the thermodynamics of transfer from gas phase to water of all species involved is completely characterized, a different picture emerges. The best known example is 2,6-di-*tert*-butylpyridine (2,6-DTBP), which is a weaker base than the 2,4-isomer by almost 2 p*K* units;^{2–6} similar effects have been observed for phenols,⁷ piperidines^{8,9} and anilines.¹⁰ The origin of such anomalies has been thoroughly investigated for the pyridines; thermodynamic and NMR results allowed the conclusion that the low basicity of 2,6-DTBP is not due to steric hindrance to solvation of 2,6-DTBP⁺, but to the fact that the water molecules solvating the NH⁺ group hinder the rotation of the methyl groups, thus decreasing its entropy.^{4–6} The hallmark of steric hindrance to solvation (a less exothermic enthalpy of hydration of the hindered species)¹ is absent; in fact, the enthalpies of hydration ($\Delta H_{\text{aq}}^\circ$) of 2,4- and 2,6-DTBP⁺ are negligibly different.⁵ Likewise, the acid-weakening effect of increased steric bulk of the aliphatic chain of carboxylic acids results from a balance of enthalpic and entropic effects affecting both the acid and the anion.¹ We show herein that the basicity of sterically hindered ketones has totally different characteristics.

The protonation equilibria of weak bases are characterized by the equilibrium constant (p*K*) and a parameter (m^*) related to the solvation energy of the protonated base.¹¹ Typical values for dialkyl ketones are $m^* = 0.4$, p*K* = -4 ;^{12,13} however, the parameters of di-*tert*-butyl ketone ($m^* = 0.8$, p*K* = -7.2) are quite different.¹² Although the changes follow an established trend,^{11–13} their extent is much larger than expected for increased alkyl substitution. This can hardly be ascribed to electronic effects, because even the values for Ph₂COH⁺ ($m^* = 0.67$, p*K* = -4.71), where the positive charge is largely delocalized, do not reach that range. These data suggest that the diminished basicity of Bu₂CO is due to steric effects, whose mode of action has to be established. Given the significance of

m^* ,¹¹ the solvation of Bu₂COH⁺ seems lower than that of normal dialkyl ketones. However, m^* is a combination of activity coefficients (containing enthalpic and entropic contributions), so this parameter in itself does not give information on how steric effects act upon the system.

Thus, we determined the protonation constants of di-*tert*-butyl ketone, diisobutyl ketone, di-*sec*-butyl ketone, di-*tert*-butyl ketone and phenyl *tert*-butyl ketone in aqueous H₂SO₄ at various temperatures (25–80 °C),^{†12,13} thereby obtaining enthalpies and entropies of ionization (ΔH_i° , ΔS_i°). For Bu₂CO and Bu^sCO, a complete thermodynamic analysis of the gas phase → water transfer was also made combining the above data with gas-phase proton affinities. Thus, values of $\Delta G_{\text{aq}}^\circ$, $\Delta H_{\text{aq}}^\circ$ and $\Delta S_{\text{aq}}^\circ$ of the protonated ketones were also obtained (Table 1).

The values of ΔH_i° for Bu₂CO and PhCOBu^t are more negative than for the other di-*tert*-butyl ketones, which lie in their normal ranges, whereas the values of ΔS_i° are normal (within their lower accuracy) for all. Therefore, their lower standard-state basicity (ΔG_i°) is only of enthalpic origin. The abrupt onset of the anomalies indicates a steric effect, which is slightly lower for PhCOBu^t, consistently with a lower size of the phenyl group.⁶ The energetics of the gas phase → water transfer show that $\Delta H_{\text{aq}}^\circ$ of Bu₂COH⁺ is less exothermic than that of Bu₂COH⁺ by 8 kcal mol⁻¹ (1 cal = 4.184 J), which is the effect expected for steric hindrance to solvation.¹ Again, the values of $\Delta S_{\text{aq}}^\circ$ (BH⁺) are very similar.

Consistent evidence is provided by NMR measurements. The longitudinal NMR relaxation rate ($1/T_1$) of ¹³C is given by dipole–dipole (DD) and spin–rotation (SR) contributions.^{‡20} The DD and SR mechanisms depend on the presence of proton nuclei near the ¹³C nucleus, and on the angular momentum of the molecule or a part thereof, respectively. Therefore, the relative weight of DD and SR relaxation for the quaternary carbon in CMe₃ provides information on the mobility of methyl groups in a given system; the DD contribution can be obtained through a T_1 and NOE (η) measurement, from $1/T_1^{\text{DD}} = (1/T_1)(\eta/\eta_{\text{max}})$ and $\eta_{\text{max}} = \gamma_{\text{H}}/2\gamma_{\text{C}} = 1.988$.²⁰ We carried out these measurements on Bu₂CO, PhCOBu^t and pinacolone.§

Table 1 Thermodynamics of ionization and hydration of aliphatic ketones at 25 °C^a

Ketone	Ionization in water					Gas-phase ionization ^d		Gas → water transfer (B)			Gas → water transfer (BH ⁺) ^e		
	m^*	p <i>K</i>	ΔG_i°	ΔH_i°	ΔS_i°	GB	PA	ΔG°	ΔH°	ΔS°	ΔG°	ΔH°	ΔS°
Me ₂ CO ^b	0.35 ± 0.01	-3.06 ± 0.03	-4.18 ± 0.04	0.2 ± 0.3	14 ± 1	188.9	196.7	-1.9 ^c	-9.7 ^c	-26	-66	-80	-47
Bu ⁿ ₂ CO	0.44 ± 0.01	-3.89 ± 0.08	-5.3 ± 0.1	-2.6 ± 0.7	9 ± 3	196.3	204.1	-0.8 ^c	-16.0 ^c	-51	-57	-77	-67
Bu ^s ₂ CO	0.47 ± 0.01	-4.30 ± 0.07	-5.9 ± 0.1	-1.8 ± 0.7	14 ± 2								
Bu ^t ₂ CO	0.41 ± 0.01	-3.86 ± 0.05	-5.3 ± 0.1	-1.7 ± 0.4	12 ± 2								
Bu ₂ CO ^c	0.78 ± 0.02	-6.8 ± 0.2	-9.3 ± 0.2	-6.5 ± 3.4	9 ± 11	198.5	206.3	-0.5 ^f	-14.5 ^f	-47	-50	-69	-64
PhCOBu ^t	0.72 ± 0.01	-6.25 ± 0.07	-8.5 ± 0.1	-6.2 ± 0.8	8 ± 3								

^a Energies in kcal mol⁻¹; entropies in cal mol⁻¹ K⁻¹; 1 cal = 4.184 J. ^b Data for ionization in water from ref. 13. ^c The higher uncertainty in p*K* and ΔH_i° stems from the long extrapolation to the standard state necessary for this very weak base. Furthermore, owing to its fast decomposition we could not obtain p*K* values above 60 °C, which affects the accuracy of the van't Hoff plot too, despite the excellent correlation ($r^2 = 0.999$). The attainable accuracy is better shown by the data of PhCOBu^t. ^d Gas-phase basicities (GB) and proton affinities (PA) from ref. 14. ^e Ref. 15. ^f Calculated from group contributions^{15,16} and confirmed by AM1_{aq}¹⁷ calculations. The heat of formation of Bu₂CO in water was less exothermic than that of Bu₂CO by 0.9 kcal mol⁻¹. ^g Calculated through a Born–Haber cycle with NH₃ and converted to absolute values with $\Delta G_{\text{aq}}^\circ$ (NH₃) = -2.409 , $\Delta H_{\text{aq}}^\circ$ (NH₃) = -8.243 kcal mol⁻¹ (ref. 18) and $\Delta G_{\text{aq}}^\circ$ (NH₄⁺) = -77 , $\Delta H_{\text{aq}}^\circ$ (NH₄⁺) = -84 kcal mol⁻¹ (ref. 19).

The NOEs of quaternary carbons in the neutral forms ($\eta = 1.3, 1.5$ and 1.8 respectively) are similar to those for the protonated forms ($\eta = 1.4, 1.6$ and 1.5 respectively) and do not reach the maximum value, which suggests that SR relaxation is important for both B and BH^+ , and the rotation of the methyl groups is affected to the same extent for both. The overall behaviour is precisely opposite to that of pyridines.

In conclusion, the results indicate steric hindrance to the solvation of the protonated ketones; this is somewhat unexpected, considering that the main solvation site of Bu_2COH^+ is not located in a cavity like in 2,6-DTBPH⁺.⁴ An explanation consistent with the data is that the $\text{C}=\text{O}-\text{H}^+$ angle (*ca.* 120°) is such that the acidic proton points directly into the space occupied by the methyl groups, whose rotation causes them to have a large hydrodynamic volume, resulting in a steric bulk higher than apparent. The energy of oxonium ions will be more affected than similar ammonium ions, owing to their stronger solvation.^{13,19}

Received, 18th July 1995; Com. 5/04741B

Footnotes

† NMR measurements and data processing have been carried out as described elsewhere.¹³

‡ Chemical shift anisotropy relaxation is generally not important for sp^3 carbons;²⁰ this was verified comparing T_1 values for pinacolone at 4.7 and 9.4 T.

§ At 9.4 T with a Bruker AM 400 spectrometer (128 K data points, spectral window 30 kHz, $\pi/2$ pulse 9.5 μs). The spectra of B and BH^+ were obtained with degassed samples in 73% $\text{PrOH}-\text{H}_2\text{O}$ and $\text{CF}_3\text{SO}_3\text{H}$, respectively, which have approximately the same viscosity (*ca.* 3 cP). T_1 values were measured by saturation-recovery; NOE values by non-selective irradiation during $4T_1$.²¹

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