Steric Effects on the Proton-Transfer Equilibria of Ketones, Sulfoxides, and Phenols

Alessandro Bagno,*[a] Renato L. Boso,[a] Nicola Ferrari,[a] and Gianfranco Scorrano[a]

Keywords: Ketones / Sulfoxides / Phenols / Steric hindrance / Acidity / Basicity / NMR spectroscopy

The proton-transfer equilibrium of several bases and acids, including some sterically hindered ketones, sulfoxides, and phenols, has been investigated by means of the determination of the thermodynamics of the equilibrium, NMR ^{13}C relaxation measurements, and quantum chemical calculations. The analysis of such data yields information about the steric effects on basicity or acidity and about the underlying reasons for the anomalous behavior of species having a sterically hindered basic or acidic site. Thus, it is demonstrated that the anomalously low basicity of two sterically hindered ketones (tBu$_2$CO and PhCOtBu) is enthalpic in origin and stems from steric hindrance to the solvation of their protonated forms. No such effect is found for analogous sulfoxides, whereas phenols display a more complex behavior.

Introduction

The question whether steric hindrance around a site of ionization affects its strength is a long-standing one. In fact, the assumption that "steric hindrance of solvation" affects the order of acidities in the gas phase and in solution[1] has been used in textbooks,[2] e.g. to explain the different acidity order of alcohols and carboxylic acids in the gas phase and in solution. More generally, steric and strain effects on amine basicities have been reviewed;[3] methods are available for estimating the steric bulk of neutral and ionic groups,[4] and peculiar solvent effects on reactivity related to the steric bulk of the solvent are well documented.[5]

The idea that steric hindrance to protonation[6] or solvation is responsible for the diminished basicity of sterically hindered bases is intuitively appealing. Relevant thermodynamic data for a few such compounds are collected in Table 1.

The best known example is given by the basicity of some substituted pyridines. It has long been known that 2,6-di-*tert*-butylpyridine (2,6-DTBP) is a weaker base than its 2,4-isomer by almost 2 pK units.[7−10] The former notion, first invoked to explain the low basicity of 2,6-DTBP,[7] was rejected when gas-phase protonation equilibria (where solvation effects are obviously absent and one can isolate structural effects on the basicity) could be investigated. The unremarkable gas-phase basicity of 2,6-DTBP conclusively indicated that the access of unsolvated H^+ is not hindered.[8] The proposition that basicity may be controlled by steric hindrance to solvation was tested by comparing the thermodynamic functions of proton transfer in the gas and aqueous phase ($\Delta P°_{(g)}$, $\Delta P°_{(aq)}$), as well as of gas-phase → water transfer ($\Delta P_{aq}°$) (P = G, H, S), of 2,4-, 2,6-DTBP and their conjugate acids,[9][10] whereby a different picture emerged. It was found that the decreased solution basicity of 2,6-DTBP is not due of steric hindrance to solvation, since the expected effect for an ion whose solvation is sterically inhibited, i.e. has a less exothermic enthalpy of solvation,[1] is absent. In fact, the hydration of 2,6-DTBPH$^+$ is normal, the values of $\Delta H_{aq}°(BH^+)$ of 2,4- and 2,6-DTBPH$^+$ being −59 and −60 kcal/mol, respectively.[9] The low aqueous basicity of 2,6-DTBPH$^+$ (in terms of $\Delta G°_{(aq)}$) is entirely due to an unfavorable entropy of protonation (more positive entropy of ionization), because the rotation of the methyl groups in the ion is hindered by the solvent molecules, as confirmed by NMR relaxation measurements;[10] the same takes place in gas-phase clusters with water molecules.[11] Thus, the entropy of hydration of 2,6-

Table 1. Thermodynamic parameters for the ionization at 25°C of some sterically hindered acids and bases and their parent compounds[a]

Species	pK	$\Delta G°$	$\Delta H°$	$\Delta S°$	Ref.
pyridine	5.21	7.11	4.8	−7.7	[9]
2,4-di-*tert*-butylpyridine	6.70	9.1	9.3	0.7	[9]
2,6-di-*tert*-butylpyridine	4.95	6.8	8.5		[9]
piperidine	9.90	–	–	–	[14]
cis-2,6-di-*tert*-butylpiperidine	7.09	–	–	–	[14]
pyridine *N*-oxide	0.69	0.95	−1.79	−9.17	[20a]
2,4-dimethylpyridine *N*-oxide	1.63	2.23	−1.00	−10.83	[20a]
2,6-dimethylpyridine *N*-oxide	1.37	1.86	−1.05	−9.77	[20a]
phenol	14.36	19.6	8.9	−35.8	[12]
2,4-di-*tert*-butylphenol	16.64[b]	22.7	11.8	−36.3	[12]
	11.57	15.8	–	–	[13]
2,6-di-*tert*-butylphenol	17.20[b]	23.5	8.3	−50.7	[12]
	11.70	16.0	–	–	[13]

[a] Quoted pK is for the ionization of the protonated base (pK_{BH^+}) for pyridines and amines, and for the ionization of neutral acid (pK_a) for phenols. Gibbs energies and enthalpies in kcal/mol; entropies in cal/mol K. Solvent is water except where otherwise noted. − [b] In methanol.

[a] Centro CNR Meccanismi Reazioni Organiche, Dipartimento di Chimica Organica, Università di Padova
via Marzolo 1, 35131 Padova (Italy)
Tel. (internat.): +39 0498275660
Fax (internat.): +39 0498275239
E-mail alex@chor.unipd.it

Supporting information for this article is available on the WWW under http://www.wiley-vch.de/home/eurjoc or from the author.

  1434−193X/99/0707−1507 $ 17.50+.50/0

$DTBPH^+$ was found to be more negative than for 2,4-$DTBPH^+$ (−56 and −47 cal/mol K, respectively).[9]

More complex cases are also known. The acidity of aliphatic carboxylic acids was investigated in detail by Bartmess,[1] who concluded that the well-known acid-weakening effect of increased steric bulk of the aliphatic chain cannot be ascribed simply to steric hindrance to solvation; the net result derives from a close balance of enthalpy and entropy factors affecting both the acid and the anion.

The acid strengths of 2,4- and 2,6-di-*tert*-butylphenol differ by 0.5 and 0.1 p*K* units in MeOH[12] and in water,[13] respectively, the 2,6-isomer being less acidic. However, this small difference in p*K* (and $\Delta G^\circ_{(aq)}$) actually stems from the balance of markedly different values of $\Delta H^\circ_{(aq)}$ and $\Delta S^\circ_{(aq)}$, thus indicating a competition between two opposing factors.

Other known cases in which bulky groups close to an ionization site affect acid-base properties are given by *cis*-2,6-di-*tert*-butylpiperidine, which is less basic than piperidine by a larger amount than pyridines,[14] although the origin of this has not been investigated in detail, and some *ortho*-methylanilines, whose base strength has been interpreted as steric inhibition of resonance.[15] Therefore, in all known cases steric effects on proton transfers do not show up simply as a lower exothermicity of ionic solvation, but rather in more complex ways.

In a previous communication,[16] we reported on the basicity of ketones, including the sterically hindered di-*tert*-butyl ketone and phenyl *tert*-butyl ketone, and found large steric effects on their basicity. The protonation equilibria of weak bases are characterized by the equilibrium constant (p*K*) and a parameter (*m**) which expresses activity coefficient behavior in nonideal acid solutions, according to Equation 1.[17]

$$\log I - \log c_{H^+} = m^*X + pK \qquad (1)$$

In Equation 1, *I* (ionization ratio) is defined by $[BH^+]/[B]$ and is experimentally determined from NMR chemical shifts or UV absorbances, and *X* (excess acidity) is a measure of acid strength in concentrated, nonideal aqueous acids.[17] The parameter *m** is determined as the slope of the correlation line of Equation 1, and its value has been shown to depend primarily on the solvation energy of the protonated base.[17−19]

Previous studies on the protonation of ketones[18][19] have shown that aliphatic derivatives form a closely similar family, whose basicity undergoes only small and regular changes with alkyl substitution (e.g. the p*K* varies from −3.06 for acetone to −3.48 for pinacolone and −4.25 for diisopropyl ketone). This decrease of p*K* with increasing electron-donating power of substituents is well known and common among weak bases,[17−19] and is generally accompanied by an increase in *m**, which in turn gives a measure of the solvation requirements of the protonated base (*m** values for the above compounds are 0.35, 0.40, 0.45, respectively).[18][19] This trend is explained by recalling that better charge dispersal through electron-donating groups leads to stabilization only in poorly solvating media, while in water (the standard state) stabilization is mainly achieved through hydrogen bonding and therefore charge delocalization is actually base-weakening. The entropies of ionization of these compounds are markedly constant, so the differences in ΔG° are generally determined by the enthalpies of ionization.[19]

On the contrary, the behavior of di-*tert*-butyl ketone (tBu$_2$CO)[16][18] is quite different from its analogues, since its *m** (0.8) is much higher and p*K* (−7.2) is much lower than expected for its substitution pattern, since substituting *t*Bu for Me (Me_2CO to MeCO*t*Bu) brings only small changes in *m** and p*K*. Thus the observed changes follow the same trend seen before, but the magnitude far exceeds that expected for simple alkyl substitution. Such changes cannot be due to electronic effects, because the *m** and p*K* values are higher and lower, respectively, even than those of Ph_2CO (*m** = 0.67, p*K* = −4.71), where resonance interactions between the aromatic rings and the protonated carbonyl group indeed play a major role in delocalizing the positive charge. Also, earlier results for heavy cyclic ketones[20] indicate no major difference relative to lighter ones (although in this case the species is forced to be in a less hindered conformation). All these data suggest that the diminished basicity of tBu$_2$CO is probably due to steric effects, whose mode of action is yet to be established. Given the significance of the *m** parameter, the solvation of tBu$_2$COH$^+$ seems much lower than, for example, Me_2COH^+ or *t*BuC(OH$^+$)Me. However, *m** is a combination of activity coefficients, each representing Gibbs energies of transfer;[17] hence, although this parameter detects an anomaly in the solvation of tBu$_2$COH$^+$, by itself it does not give information on how steric effects act upon this system, because it contains both enthalpic and entropic contributions.

The structure and properties of tBu$_2$CO have been much studied, especially in comparison with other nonhindered ketones. Thus, FT-IR measurements[21] indicate that the carbonyl stretching frequency (in cm^{-1}) of tBu$_2$CO in CCl_4 (1686) is smaller than that in analogous ketones (e.g. 1716 for nBu$_2$CO), *t*BuCOMe (1709) being intermediate. The same behavior was found to hold also for PhCO*t*Bu (1678) with respect to PhCO*n*Bu (1691). This effect points to a decreased C=O bond strength in the hindered ketones, and in fact, agrees with gas-phase electron diffraction data,[22] from which a C=O distance of 1.222 Å, and a C(O)−C distance 1.544 Å were obtained (the latter is slightly longer than in Me_2CO, 1.520 Å). By the same technique it was also found that the C−C(O)−C angle in tBu$_2$CO (124.9°) increases with respect to the value in Me_2CO (116.0°), although the increase is smaller than that found for analogous hydrocarbons and amines.[22] Further evidence is provided by ^{17}O-NMR data,[23] which show a progressive shielding of the ^{17}O nucleus in the series Me_2CO (δ 571) > *t*BuCOMe (δ 563) > tBu$_2$CO (δ 555) and may also be interpreted as a slight decrease in π bond order. Finally, hydrogen bonds between tBu$_2$CO and OH donors (such as al-

cohols and phenols) are relatively weaker than those for other ketones.[24][25]

All the above data point out that the basic carbonyl group in tBu$_2$CO and PhCOtBu is indeed perturbed by the steric bulk of the nearby *tert*-butyl groups. However, no spectroscopic or structural parameter is dramatically different from those of unhindered ketones, and the overall characteristics of the ketone functionality seem preserved even in the presence of bulky substituents.

In this paper we report our full results concerning the thermodynamics of protonation of a series of weak bases (ketones and sulfoxides), some of which are sterically hindered, as well as NMR studies (for the above ketones and sulfoxides, plus some phenols) related to the dynamics of the methyl groups within the *tert*-butyl groups which give rise to the steric hindrance sought. We also included *cis*-2,6-di-*tert*-butylcyclohexanone, whose structure is more similar to the pyridines seen before.

Since the steric hindrance around pyridine *N*-oxides should be similar to that in the corresponding pyridines, available literature data on the basicity of pyridine *N*-oxides[26] were screened with the aim of detecting possible steric effects on their basicity. The closest comparison we can make (2,4- vs. 2,6-dimethylpyridine *N*-oxide; see Table 1) indicates that the latter is less basic (as in the case of pyridines), but the ΔpK is much smaller. The decrease in base strength again rests entirely with the entropies. Hence, steric hindrance in pyridine *N*-oxides seems to affect their basicity in a way similar to pyridines. Unfortunately, while the oxidation of 2,4-di-*tert*-butylpyridine easily led to its *N*-oxide, 2,6-DTBP resisted oxidation with a wide variety of oxidizing agents (see Experimental Section). Likewise, di-*tert*-butyl sulfide (initially selected for comparison with known sulfides) underwent rapid decomposition in concentrated H_2SO_4. The study of these compounds was not further pursued.

Results

Protonation Equilibria in Aqueous H_2SO_4

The protonation equilibria of di-*n*-butyl ketone (nBu$_2$CO), di-*iso*-butyl ketone (iBu$_2$CO), di-*sec*-butyl ketone (sBu$_2$CO), di-*tert*-butyl ketone (tBu$_2$CO), phenyl *tert*-butyl ketone (PhCOtBu), *cis*-2,6-di-*tert*-butylcyclohexanone (2,6-DTBC), phenyl methyl sulfoxide (PhSOMe), phenyl *tert*-butyl sulfoxide (PhSOtBu), and di-*tert*-butyl sulfoxide (tBu$_2$SO) were studied in aqueous H_2SO_4 at ca. 25, 40, 60, and 80°C. Since the behavior of 2,6-DTBC was regular, the unhindered isomer 2,4-DTBC was prepared (see Experimental Section) but not studied. The measurements were carried out by monitoring the NMR chemical shift change of a ^{1}H signal, relative to internal trimethylammonium sulfate (TMA), as a function of the acid concentration.[18] For species possessing more than one proton signal, data were collected for as many signals as convenient (the intense tBu signals are easily detected, while the other signals are complex multiplets with low intensities). Aromatic proton signals were never used, since their chemical shifts undergo complicated changes with acidity.[19] All heavy ketones are poorly soluble in water and dilute H_2SO_4. Hence, for measurements in < 60% H_2SO_4 saturated solutions were prepared by stirring the acid solution and the ketone for at least one hour and allowing the phases to separate, in order to avoid the formation of emulsions. All ketones and sulfoxides are sufficiently stable throughout the acidity and temperature range chosen, except tBu$_2$CO. The latter is known to undergo a rearrangement reaction in concentrated H_2SO_4,[18] which at 80°C becomes too fast to record a ^{1}H spectrum. Therefore, in this case measurements were carried out at five lower temperatures (25, 33, 40, 50, 60°C) in order to increase the accuracy of thermodynamic data. Raw protonation data (normalized chemical shift vs.% H_2SO_4) for nBu$_2$CO and tBu$_2$CO are plotted in Figure 1. The results at 25°C are collected in Table 2; the full data set (protonation parameters at each temperature for each proton signal) is available as Supporting Information. All pK values obtained from different signals, where applicable, were averaged to yield the reported value and the corresponding Gibbs energy of ionization, $\Delta G_{(aq)}^\circ = 2.303RT\mathrm{p}K$. The other thermodynamic parameters ($\Delta H_{(aq)}^\circ$ and $\Delta S_{(aq)}^\circ$) were determined as the slope and intercept of van't Hoff plots (pK vs. $10^3/T$).

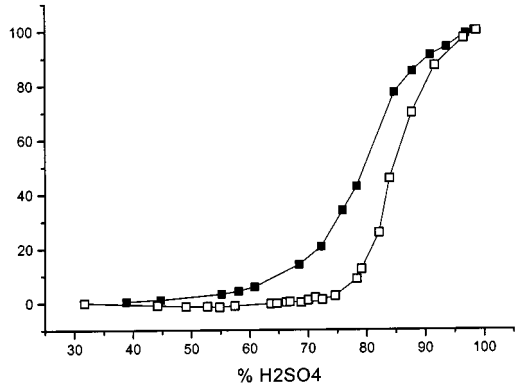

Figure 1. Plot of raw protonation data (chemical shifts normalized between 0 and 100) vs.% w/w H_2SO_4 for nBu$_2$CO (filled squares) and tBu$_2$CO (open squares)

Table 2. Protonation parameters of ionization at 25°C[a]

Base	m^*	pK
nBu$_2$CO[b]	0.44 ± 0.01	−3.89 ± 0.08
iBu$_2$CO[b]	0.44 ± 0.01	−3.97 ± 0.06
sBu$_2$CO[c]	0.47 ± 0.01	−4.30 ± 0.07
tBu$_2$CO[d,e]	0.78 ± 0.02	−6.8 ± 0.2
PhCOtBu[d]	0.72 ± 0.01	−6.25 ± 0.07
cis-2,6-DTBC[d]	0.350 ± 0.004	−3.40 ± 0.03
PhSOMe[c]	0.51 ± 0.03	−2.23 ± 0.08
PhSOtBu[d]	0.55 ± 0.02	−2.24 ± 0.06
tBu$_2$SO[d]	0.57 ± 0.02	−1.07 ± 0.03

[a] See Equation 1. – [b] α-Methylene signal. – [c] α-Methyl signal. – [d] *tert*-Butyl methyl signal. – [e] Fast decomposition at 80°C.

Thermodynamics of Ionization and Hydration in the Gas Phase and Water

Establishing the thermodynamics of the ionization equilibrium in the gas phase and in water allows one to disentangle the often complex relationship between basicity and solvation. This analysis requires the knowledge of basicity data both in the gas phase[27−29] (gas-phase basicity $GB = -\Delta G_{(g)}$, and proton affinity $PA = -\Delta H_{(g)}$) and the aqueous phase (pK, $\Delta H^{\circ}_{(aq)}$), as well as of thermodynamic parameters of the gas → water transfer (ΔH_{aq}°, ΔG_{aq}°) for the neutral bases.[30−32] Such data, when combined in a Born−Haber cycle, define the thermodynamics of hydration of the protonated base, which is the only quantity not directly accessible to experiment. Although many of the above data are available for the ketones studied, a complete analysis can be carried out only for the two isomeric ketones nBu$_2$CO and tBu$_2$CO (Table 3) together with those for Me$_2$CO and tBuCOMe. However, since some data for neutral species are not available, notably ΔH_{aq}°, ΔG_{aq}° for tBu$_2$CO, we made use of group contributions to such quantities as proposed by Cabani et al.[32] and Hine et al.,[31] which led to estimate that ΔH_{aq}° of tBu$_2$CO is less exothermic than that of nBu$_2$CO by 1.5 kcal/mol. Although the above additivity schemes are well established, and tBu$_2$CO falls within their scope, as a further proof we calculated the ΔH_{aq}° of tBu$_2$CO and nBu$_2$CO as the difference between the heat of formation in the gas phase and in water from semiempirical AM1 and AM1$_{aq}$[33] calculations, respectively. The values thus obtained indicate a less exothermic ΔH_{aq}° for tBu$_2$CO than nBu$_2$CO by 0.9 kcal/mol, in agreement with the above values (Table 3).

For a series of pyridine bases, Aue et al.[9] found a good correlation between PA and $\Delta H^{\circ}_{(aq)}$ or $\Delta G^{\circ}_{(aq)}$, except for 2,6-di-*tert*-butyl- and 2,6-diisopropylpyridine, for which the correlation with $\Delta G^{\circ}_{(aq)}$ failed, indicating that their anomalous basicity has an entropic origin. Following this approach, we built the same plots for the few ketones for which such data are available (Figure 2).

Ab initio Calculations

In order to gain further insight into the behavior of these bases, we calculated the structures of some ketones and sulfoxides, and their protonated forms. Thus, the geometry of tBu$_2$CO, nBu$_2$CO, tBu$_2$COH$^+$, 2,6-DTBCH$^+$, and tBu$_2$SOH$^+$ was optimized at the ab initio HF/6-31G(d,p) level of theory. The three latter structures are sketched in Figure 3, and relevant geometric and electronic parameters of two neutral ketones (nBu$_2$CO and tBu$_2$CO) are collected in Table 4. All geometries are detailed as PDB files in the Supporting Information.

NMR Measurements

The rotation of the methyl groups belonging to tBu groups can be probed by the NMR relaxation rate of the quaternary carbon. Since the shielding anisotropy of sp^3 carbons is normally negligible (see below), two mechanisms contribute to the observed T_1: dipole-dipole (T_1^{DD}) and spin-rotation (T_1^{SR}), and the overall relaxation rate being given by Equation (2):[34]

$$1/T_1 = 1/T_1^{DD} + 1/T_1^{SR} \quad (2)$$

The dipole-dipole relaxation rate $1/T_1^{DD}$ is independently accessible from a $^{13}C\{^1H\}$ T_1 and NOE measurement, since it is related to the NOE enhancement η through $1/T_1^{DD} = (1/T_1)(\eta/\eta_{max})$, where η_{max} is a simple function of the magnetogyric ratios (γ) of the involved nuclei; $\eta_{max} = \gamma_H/2\gamma_C = 1.988$.[34] The magnitude of T_1^{DD} depends on the number of proton nuclei located at a distance r from the observed carbon, and on the rotational correlation time τ_c ($1/T_1^{DD} \propto \tau_c/r^6$). The SR contribution can thus be extracted from the overall T_1. This relaxation pathway depends on the angular momentum of the molecule or a part thereof[34] and therefore is a suitable probe of the mobility and dynamics of methyl groups. Thus, for instance, the hindered rotation of the methyl group in 2-nitrotoluene is easily shown by the high NOE at the carbon nucleus, indicating that SR relaxation is less important than in 4-nitrotoluene.[35]

With this approach, Hopkins[9][10] provided further proof (as well as a physical explanation) of the entropic origin of the low aqueous basicity of 2,6-DTBP, because the quaternary carbon in 2,6-DTBPH$^+$ has a maximum NOE. This proves the restricted rotation of the *tert*-butyl groups caused by the strong hydration of the NH$^+$ group, and accounts for the low entropy of the ion.

In the case of weak acids or bases, there is the additional complication that the neutral and ionized (protonated or deprotonated) form must be generated in media with different viscosity. Thus, for example, in MeOH/water the SR and DD mechanisms provide ca. 50% each to the overall relaxation rate of the methine carbons of ketones, whereas in concentrated H_2SO_4 T_1's are much shorter and the relaxation is fully dipolar (as shown by the almost maximum NOE enhancements). This is simply due to its much higher viscosity, which implies long correlation times. Since, loosely speaking, $1/T_1^{SR} \propto 1/\tau_c$,[34] in highly viscous media the SR contribution is effectively switched off regardless of any change in the dynamics of the *tert*-butyl group. A better medium for studying the protonated form is triflic acid (CF_3SO_3H), which is stronger than H_2SO_4 and has a much lower viscosity in pure form. Hence, further experiments were carried out for tBu$_2$CO, PhCOtBu, and tBuCOMe in 73% aq. nPrOH and CF_3SO_3 H, which have a similar viscosity (ca. 3 cP).[36][37] T_1 and NOE data are collected in Table 5 for the quaternary carbons only; complete data for all carbon nuclei are available as Supporting Information.

A control experiment to check for the occurrence of CSA (shielding anisotropy) relaxation was run on tBuCOMe by comparing the T_1 of all ^{13}C nuclei at $B_0 = 4.7$ and 9.4 T (since, other things being equal, $1/T_1^{CSA} \propto B_0^2$).[34] As the T_1's at both fields are essentially equal, in our systems CSA is not operating even on the carbonyl carbon, which often

Table 3. Thermodynamic parameters of ionization of ketones and sulfoxides in the gas phase and water, and of gas → water transfer at 25°C[a]

Base	$\Delta G^\circ_{(aq)}$	$\Delta H^\circ_{(aq)}$	$\Delta S^\circ_{(aq)}$	*GB*	*PA*	ΔG_{aq}°	ΔH_{aq}°	ΔS_{aq}°	ΔG_{aq}°	ΔH_{aq}°	ΔS_{aq}°
	ionization in water[b]			gas-phase ionization[c]		g → w transfer of B[d]			g → w transfer of BH^+[e]		
Me_2CO[f]	−4.18 ± 0.04	0.2 ± 0.3	14 ± 1	188.9	196.7	−1.9	−9.7	−26	−66	−80	−47
MeCO*t*Bu	−4.74 ± 0.05	−0.5 ± 0.5	14 ± 1	194.5	202.3	−1.2[h]	−11.9	−36			
nBu_2CO	−5.3 ± 0.1	−2.6 ± 0.7	9 ± 3	196.3	204.1	−0.8	−16.0	−51	−57	−77	−67
iBu_2CO	−5.3 ± 0.1	−1.7 ± 0.4	12 ± 2			−0.5	−14.2	−46			
secBu_2CO	−5.9 ± 0.1	−1.8 ± 0.7	14 ± 2			−0.7	−10.8	−34			
tBu_2CO	−9.3 ± 0.2	−6.5 ± 3.4	9 ± 11	198.5	206.3	−0.5[h,i]	−14.5[h,i]	−47	−50	−69	−64
cis-2,6-DTBC	−4.64 ± 0.04	−0.6 ± 0.4	13 ± 1								
PhCO*t*Bu	−8.5 ± 0.1	−6.2 ± 0.8	8 ± 3								
Ph_2CO[f]	−6.4 ± 0.1	−3.3 ± 1.2	10 ± 4	203.1	210.9	−3.8	−18.6	−50			
Me_2SO[g]	−2.10 ± 0.01	−2.3 ± 0.2	−0.7 ± 0.6	203.5	211.3	−8.2	−17.2	−30			
tBu_2SO	−1.46 ± 0.04	−3.4 ± 0.2	−6.4 ± 0.7								
PhSOMe	−3.04 ± 0.11	−2.3 ± 0.8	2 ± 3								
PhSO*t*Bu	−3.06 ± 0.08	−2.6 ± 0.5	2 ± 2								

[a] Gibbs energies and enthalpies in kcal/mol; entropies in cal/mol K. – [b] All data from this work except where otherwise noted. – [c] Ref.[28]. – [d] Ref.[32], except where otherwise noted. – [e] Calculated through a Born−Haber cycle relative to the protonation equilibrium of NH_3, and converted into absolute values with $\Delta G_{aq}^\circ(NH_3) = -2.409$, $\Delta H_{aq}^\circ(NH_3) = -8.243$ kcal/mol[30] and $\Delta G_{aq}^\circ(NH_4^+) = -77$, $\Delta H_{aq}^\circ(NH_4^+) = -84$ kcal/mol.[29] – [f] Data for ionization in water from ref.[19]. – [g] Data for ionization in water from ref.[51]. – [h] Calculated from group contributions.[31][32] – [i] Confirmed by $AM1_{aq}$ calculations (see text).

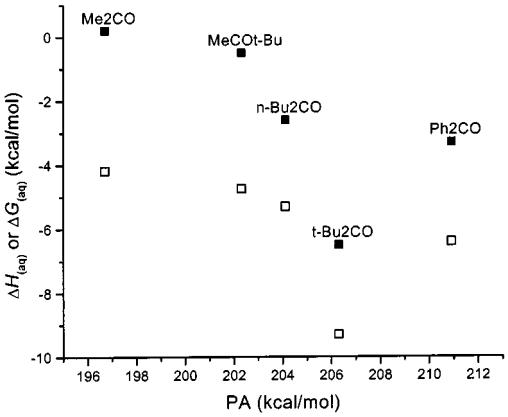

Figure 2. Correlation between *PA* and $\Delta H^\circ_{(aq)}$ (filled squares) or $\Delta G^\circ_{(aq)}$ (open squares) for ketones

Table 4. Calculated parameters for *n*Bu_2CO and *t*Bu_2CO[a]

Species	*r*(C=O)	*r*(C(O)−C)	>C−C(O)−C	CO bond order	q_C[b]	q_O[b]
nBu_2CO	1.193	1.519	116.2	1.855	0.71	−0.64
tBu_2CO	1.196	1.554	125.3	1.825	0.71	−0.64

[a] Distances in Å, angles in degrees at the HF/6-31G(d,p) level. – [b] Atomic charges calculated with the Natural Bond Orbital (NBO) method.[52]

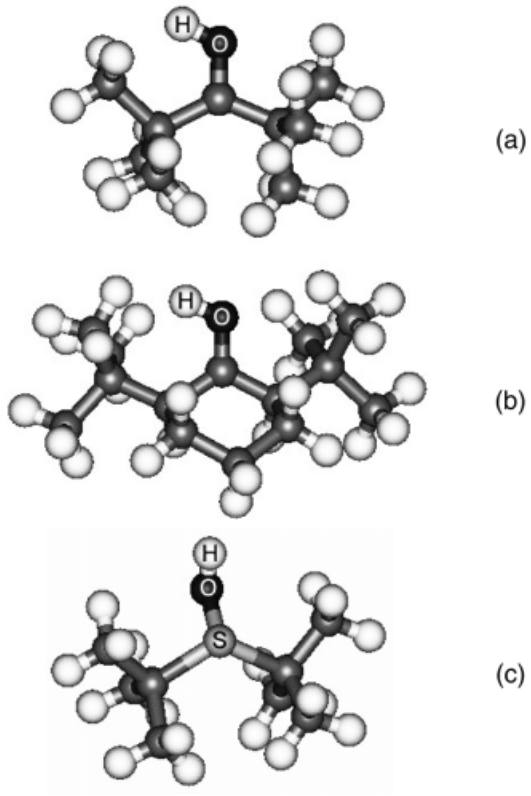

Figure 3. Structures of tBu_2COH^+ (a), protonated 2,6-di-*tert*-butylcyclohexanone (b), and tBu_2SOH^+ (c) calculated at the HF/6-31G(d,p) ab initio level. The average distance between the acidic and the closest *tert*-butyl hydrogen atoms are (a) 2.0, (b) 2.3, (c) 3.3 Å

relaxes through this mechanism owing to the large shielding anisotropy of sp^2 carbons.

The pK_a's of 2,4- and 2,6-di-*tert*-butylphenol (2,4- and 2,6-DTBPH) in methanol are 16.64 and 17.20, respectively, which correspond to −0.28 and 0.28 introducing the autoprotolysis constant of the solvent (16.916).[38] The extent of ionization of these weak acids was calculated using the excess basicity function previously determined for MeONa in MeOH.[39] The values of m^* can be estimated from the data by Rochester,[40] who reported that the slope of log *I* vs. the H_- basicity function (determined from aromatic amine indicators, for which m^* is ca. 1.0[39]) were 0.76 and 0.86, respectively. Introducing these values in the excess basicity Equation (3)

$$\log I - \log[MeO^-] + \log a_{MeOH} = m^*X - pK \quad (3)$$

Table 5. ^{13}C chemical shifts, T_1's and NOE enhancements of the quaternary carbon of ketones[a] and phenols[b] in neutral and ionized form

Species	δ (ppm)	T_1 (s)	η
MeCO*t*Bu			
73% *n*PrOH	44.3	50.9	1.3
CF_3SO_3H	47.2	18.9	1.5
***t*Bu$_2$CO**			
73% *n*PrOH	45.7	46.2	1.5
CF_3SO_3H	49.0	15.4	1.6
PhCO*t*Bu			
73% *n*PrOH	44.0	43.9	1.8
CF_3SO_3H	46.1	15.0	1.5
2,4-*t*Bu$_2$C$_6$H$_3$OH[c]			
MeOH	35.0, 34.2	18.9, 35.4	2.0, 1.6
3.7 M MeONa	34.8, 33.6	3.3, 7.7	1.4, 1.0
2,6-*t*Bu$_2$C$_6$H$_3$OH			
MeOH	34.7	28.5	1.7
3.7 M MeONa	34.9	4.2	1.4

[a] The T_1 of other unprotonated (carbonyl, phenyl *ipso*) and protonated (methyl, phenyl) carbons is 20−40 s and 2−10 s, respectively, and decrease by a factor of 2−4 in CF_3SO_3H. − [b] The T_1 of other unprotonated (phenyl *ipso*) and protonated (methyl, phenyl) carbons is 20−30 s and 2−3 s, respectively, and decrease by a factor of ca. 10 in MeONa. − [c] Data for the 2- and 4-position, respectively.

one can calculate log I and $\%[A^-] = 100I/(1 + I)$ at a given concentration of sodium methoxide. The values of $[MeO^-]$ necessary in order to attain > 99.9% deprotonation are therefore 3.5 M (2,4-DTBPH) and 4.0 M (2,6-DTBPH). ^{13}C T_1 and NOEs have been determined in MeOH and 3.7 M MeONa (Table 5). The viscosity of these solutions is higher than that of methanol; however, we were unable to find model (i.e. aqueous or hydrophilic) media with a lower viscosity and known base strength. In the basic medium, 2,6-DTBPH formed a deep red solution, while 2,4-DTBPH only turned pale yellow. In both cases, some minor new ^{13}C peaks appeared in the aromatic region, whose intensity with respect to the main ones remained constant over the experimental time, and no new methyl or quaternary signals. The NOE′s are rather low (1.0−1.4; Table 5). This would point to a large intervention of spin-rotation relaxation and hence to a high rotational freedom of the methyl groups; however, it is doubtful that spin-rotation relaxation is operating at high viscosities. Owing to the difficulties in studying the process under other conditions of medium or temperature, we will not discuss such data in detail.

Discussion

Ketones

We will firstly comment on the structure and bonding of two similarly substituted ketones (*n*Bu$_2$CO and *t*Bu$_2$CO) which mainly differ in the steric hindrance around the carbonyl group (Table 4). The main structural changes occurring for the sterically hindered ketone are a very slight lengthening (by 0.003 Å) of the C=O bond, a more noticeable lengthening (by 0.035 Å) of the C(O)−C bond, and a widening of the C−C(O)−C angle by 9°, in excellent agreement with gas-phase electron diffraction data.[22] A slight decrease in the C=O bond order is also apparent, which also agrees with the observed trends in IR[21] and NMR[23] spectra. Hence, although bulky substituents do induce geometry changes in the CO group, such changes are not so large as to imply a different bonding nature in *t*Bu$_2$CO. Most notably, NBO charges at the carbonyl carbon and oxygen atoms (Table 4) are identical for both ketones, strongly suggesting that the above geometry changes do not entail any significant variation in their base strengths, which, in fact, agrees with gas-phase basicity data (see below). In conclusion, none of the structural and electronic data is consistent with the idea that *t*Bu$_2$CO is a ketone of an unusual type, so any observed peculiarity must be due to steric effects occurring in solution.

The different protonation behavior of *n*Bu$_2$CO (or the other dibutyl ketones) and *t*Bu$_2$CO is immediately highlighted by Figure 1. It is apparent, even without any assumption about the quantitative treatment of the equilibrium, that the two protonation curves have inflexion points located at different acidity and different slopes; a similar pair of curves can be built for PhCOMe and PhCO*t*Bu. The quantitative analysis according to the excess acidity treatment (Equation 1) affords the values of pK and of the solvation parameter m*. The hindered ketones *t*Bu$_2$CO and PhCO*t*Bu have higher m* and more negative pK values than similarly substituted but unhindered ones. This holds throughout the entire series of isomeric dibutyl ketones investigated, as well as, of course, for lighter ones. The abrupt onset of the anomalies, and the comparison with Ph$_2$CO, indicates a steric rather than an electronic effect, which is slightly lower for PhCO*t*Bu, consistent with a smaller size of the phenyl group.[3]

The enthalpies of ionization ($\Delta H°_{(aq)}$) of *t*Bu$_2$CO and PhCO*t*Bu are more negative than those for the corresponding nonhindered dibutyl ketones, the entropies ($\Delta S°_{(aq)}$) being essentially constant within the experimental error for the whole series of ketones reported in Table 3. We remark that the higher uncertainty in pK and $\Delta H°_{(aq)}$ for *t*Bu$_2$CO stems from the long extrapolation to the standard state necessary for this very weak base. Furthermore, its fast decomposition prevented us from obtaining any data above 60 °C, which affects the accuracy of the van′t Hoff plot too, despite its excellent correlation coefficient ($r^2 = 0.999$); the typical accuracy of the data is better shown by the data of PhCO*t*Bu.

Therefore, the lower standard-state basicity ($\Delta G°_{(aq)}$) of *t*Bu$_2$CO and PhCO*t*Bu is due to the enthalpy term, with no recognizable entropy effect. No such effect is borne out by the gas-phase data, which show that, if anything, *t*Bu$_2$CO is a *stronger* base than *n*Bu$_2$CO both in enthalpy and free-energy terms. Moreover, the correlation of *PA* with both $\Delta H°_{(aq)}$ and $\Delta G°_{(aq)}$ (Figure 2) fails for *t*Bu$_2$CO, again indicating that the effect involved is not entirely entropic. The enthalpy of hydration ($\Delta H_{aq}°$) of *t*Bu$_2$COH$^+$ is less exothermic than that of *n*Bu$_2$COH$^+$ by 8 kcal/mol, which is the effect expected for steric hindrance of solvation,[1] whereas the values of $\Delta S_{aq}°(BH^+)$ are again very similar.

Rather unexpectedly, the thermodynamics of ionization of *cis*-2,6-DTBC, whose structure matches more closely that of 2,6-DTBP, was also found to be regular. Thus, its enthalpy (−0.6 kcal/mol) and entropy (13 cal/mol K) of ionization in water fit with the analogous data for unhindered ketones.

Consistent evidence is provided by NMR measurements. The NOE of quaternary carbons of ketones undergoes small and erratic changes on going from the neutral to the protonated form, and in no case does it reach the maximum value. This demonstrates that the spin-rotation pathway is a major contributor to the relaxation of quaternary carbons in both forms, and therefore that the rotation of methyl groups is essentially not hindered in $PhC(OH^+)tBu$ and tBu_2COH^+. The overall behavior, as probed by the thermodynamics of ionization and molecular dynamics, is precisely the opposite to that of pyridines.

These results indicate steric hindrance of the solvation of $PhC(OH^+)tBu$ and tBu_2COH^+. This is somewhat unexpected, considering that the main solvation site of tBu_2COH^+, i.e. $C{=}O{-}H^+$, is not located in a cavity like that in 2,6-$DTBPH^+$. An explanation consistent with the data lies in the stereoelectronic requirements of carbonyl protonation. In fact, the only stable conformation of the $C{=}O{-}H^+$ group (as obtained theoretically; Figure 3a) is essentially coplanar with the quaternary *tert*-butyl carbons, and features a C−O−H angle (115.4°) that points the added hydrogen directly into the space occupied by the methyl groups (the average distance being ca. 2.0 Å), whose rotation causes them to have a large hydrodynamic volume resulting in a steric bulk higher than apparent. Owing to their stronger solvation,[17,27,29] the energy of oxonium ions will be more sensitive than that similar ammonium ions.

The normal behavior of *cis*-2,6-DTBC shows that such effects are very subtle, and seem to depend on minute changes in interatomic distances. Since *cis*-2,6-DTBC is expected to have both *t*Bu groups in equatorial positions,[41] even though the general geometric features of *cis*-2,6-$DTBCH^+$ are similar to those of 2,6-$DTBPH^+$, steric effects are absent. This result seems to be due to the distances between the added hydrogen and the methyl hydrogens, which on the average are slightly longer (2.3 Å) than those in tBu_2COH^+.

Sulfoxides

Unlike ketones, the basicity of sulfoxides is weakly affected by substituents, including *t*Bu groups; in fact the protonation parameters for PhSOMe and PhSO*t*Bu are the same. tBu_2SO is slightly more basic than Me_2SO owing to a favorable entropy contribution, which overwhelms an unfavorable enthalpy term. However, this comparison is unwarranted, since the hydration of Me_2SO is known to be anomalous[19][42] and their substitution pattern is different.[27] This trend is opposite to that of ketones, for which alkyl substitution always brings a decrease in the aqueous basicity (lower p*K*) and solvation (higher *m**).[19]

This lack of sensitivity to steric hindrance is consistent with the structure of protonated sulfoxides. Quite at variance with ketones, the added hydrogen does not lie within a C−S−O plane, but perpendicular to the C−S−C plane (see Figure 3c) in a *trans* conformation. This arrangement, found also in an unhindered species like Me_2SOH^+,[42] places the hydrogen much farther from the methyl groups. As a consequence, also owing to the longer bond lengths than in ketones, the solvent can presumably approach it without affecting the dynamics of nearby groups.

Phenols

2,6-Di-*tert*-butylphenol is slightly less acidic than its 2,4 isomer ($\Delta pK = -0.56$ in MeOH, −0.13 in water). As noted above, this small difference stems from the cancellation of two counteracting factors. In fact, the enthalpy of ionization of 2,6-DTBPH (8.3 kcal/mol) is quite similar to that of phenol (8.9 kcal/mol) and points to an acid-strengthening effect, since the analogous term for 2,4-DTBPH (11.8 kcal/mol) is more endothermic (acid-weakening). Hence, the slightly lower acid strength of 2,6-DTBPH derives from an unfavorable entropy of ionization, which is markedly more negative (−51 cal/mol K) than that for phenol and 2,4-DTBPH (ca. −36 cal/mol K). In this case steric hindrance seems to affect both the enthalpy and entropy terms, implying a situation between that of pyridines (entropy-controlled) and of ketones (enthalpy-controlled). However, before proceeding any further one should bear in mind that, unlike the previous cases, the protonated form (which gives rise to steric effects) is neutral rather than ionic, and should suffer from weaker solvation effects than the anionic deprotonated form (since the solvation of charged species is normally stronger than that of neutrals). The large entropies of ionization of phenols are obviously connected to the high degree of solvent ordering connected with the formation of the anion. Hence, the larger entropy decrease occurring on the deprotonation of 2,6-DTBPH can be tentatively dissected into an intrinsic component (amounting to ca. −36 cal/mol K) due to deprotonation itself, and −15 cal/mol K presumably due to steric effects. We note that the solvation of the two phenoxide anions is significantly different, since the slopes reported by Rochester for log *I* vs. H_- are akin to *m** values and indicate that the 2,6-di-*tert*-butylphenoxide anion is less solvated than the 2,4-isomer.

In the neutral species, the quaternary carbons in the 2-*t*Bu groups of both 2,4- and 2,6-DTBPH have almost maximal NOEs (Table 5), which implies that their rotation is hindered. This is consistent with the interference of the O−H hydrogen with the motion of nearby *t*Bu hydrogen atoms. An additional contribution to steric hindrance might stem from solvation, since an O−H···OHMe hydrogen bond (HB) can form. In fact, the NOE for 2,6-DTBPH is somewhat lower, suggesting a higher degree of freedom, which is probably related to its very poor HB donor capability.[43] Hence, the presence of the OH hydrogen is only partly responsible for the observed hindered rotation, since

the effect is larger in 2,4-DTBPH which is much *less* hindered (from a molecular viewpoint) than 2,6-DTBPH. Solvation is again confirmed to play a major role in the observed effect.

As noted previously the data in MeONa are more difficult to interpret, owing to the larger viscosity of the solution, and also because proton abstraction should by itself remove most steric hindrance and give rise to a charged and more strongly solvated species. The picture that can be tentatively drawn from these results implies that the methyl groups have a larger rotational freedom in the anions, irrespective of their stronger solvation. Hence, although the whole situation is dictated by a complex balance of opposing factors, we suggest that the less negative entropy of ionization of 2,4-DTBPH is due to the unfreezing of the motions of the methyl groups in the 2-position, an effect which is only partly present in 2,6-DTBPH owing to its poor HB donor capability mentioned above.

Summary and Conclusions

Steric hindrance affects the energetics of proton transfer. However, available data consistently point out that such effects only show up in solution. Hence, no reasonable degree of steric hindrance attainable by having bulky groups in the vicinity of the basic site can block the access of a "free", unsolvated proton, and no steric hindrance to protonation can be invoked to explain such effects. Indeed, it is only through the presence of a solvent that noticeable, and sometimes large, effects can be measured. This recognition leads directly to the concept that "steric hindrance to solvation" is the responsible factor. However, if we assume that any such effect must entail a less exothermic solvation of the protonated form,[1] it is by no means general. A powerful technique (other than thermodynamic measurements) to obtain information on how steric effects act upon a given system is the NMR determination of the dynamics of rotation of the groups supposedly connected with the steric effect. Thus, the basicity of hindered pyridines was shown to be controlled by entropic effects that, although connected with (and, indeed, due to) solvation, do not conform to the above prescription. A more complicated example is provided by phenols, which display a mix of enthalpy and entropy factors, partly connected with the different nature of the equilibrium involved ($AH \rightarrow A^- + H^+$ rather than $BH^+ \rightarrow B + H^+$). In contrast, ketones provide an example where steric effects indeed show up in enthalpic terms, bearing out a considerable degree of steric hindrance to the solvation of the protonated base. The latter effect is largely due to the peculiar (bent) geometry of the protonated carbonyl group, as confirmed by the lack of any steric effect on the protonation of similar sulfoxides, owing to the very different structure of the protonated sulfinyl group. On the other hand, the different behavior displayed by tBu$_2$CO and *cis*-2,6-DTBC indicates that this effect is also very sensitive to the distance between the interacting atoms.

Experimental Section

Materials: All chemicals are commercially available, except for the following: PhSOtBu and tBu$_2$SO were prepared by oxidation of the corresponding sulfides with acidic H_2O_2/EtOH;[44] PhStBu was prepared by literature methods.[45]

tBu$_2$CO is commercially available with a low purity (90%); the impurities could not be satisfactorily separated even with a high-resolution distilling apparatus. Therefore it was prepared by oxidation of the alcohol and purified by column chromatography.

cis-2,4- and 2,6-di-*tert*-butylcyclohexanone were synthesized by hydrogenation of 2,4- and 2,6-di-*tert*-butylphenol, respectively.[46] The reaction of 2,6-di-*tert*-butylphenol gave both *cis* and *trans* ketones, which were separated by column chromatography. The 2,4-isomer led to a mixture containing starting material and cyclohexanol, but only the *cis* ketone. The crude reaction mixture was purified by oxidation with bichromate. The products were identified by NMR.[47]

2,4- and 2,6-Di-*tert*-butylpyridine *N*-Oxide: 2,4-Di-*tert*-butylpyridine *N*-oxide was prepared by oxidation of 2,4-DTBP with *m*-chloroperbenzoic acid (mCPBA);[48] 2,4-di-*tert*-butylpyridine was prepared in turn by homolytic alkylation of 4-*tert*-butylpyridine with pivalic acid and $Ag^+/S_2O_8^{2-}$.[49] – ^{1}H NMR ($CDCl_3$): δ = 1.31 [s, 9 H, C(CH_3)$_3$]; 1.54 [s, 9 H, C(CH_3)$_3$]; 7.10 [dd, 1 H, H-5: J_{56} = 6.8 Hz, J_{35} = 2.8 Hz]; 7.30 [d, 1 H, H-3]; 8.15 [d, 1 H, H-6]. – MS (70 eV); *m*/*z* (%): 207 (17) [M^+], 191 (11) [$M^+ - O$], 192 (28) [$M^+ - CH_3$], 165 (100), 160 (42), 150 (30) [$M^+ - C(CH_3)_3$]. – $C_{13}H_{21}NO$ (207): calcd. C 75.31, H 10.27, N 6.76; found C 74.23, H 10.21, N 6.47.

2,6-DTBP did not react with any of the following oxidants: mCPBA in CH_2Cl_2 at 40°C; magnesium monoperphthalate in AcOH at 85°C; CH_3CO_3H (prepared from 35% or 70% H_2O_2) at 80°C; CF_3CO_3H (70% H_2O_2, at 50°C); 70% H_2O_2 at room temperature; dioxirane at room temperature; Mn^{III} meso-tetramesitylporphyrin with mCPBA, Bu_4NHSO_5, or NaClO. Fenton's reagent led to various ring-oxidized products. Homolytic alkylation of pyridine *N*-oxide with pivalic acid (see above) yielded only 2- and 4-*tert*-butylpyridine and their *N*-oxides.

NMR Measurements: Protonation ^{1}H measurements were carried out with a Bruker AC 200 spectrometer (4.7 T, 200 MHz). ^{13}C Measurements were carried out at 100 MHz on a Bruker AM 400 spectrometer operating at 9.4 T, except the control experiment for CSA relaxation (AC 200). The samples were generally degassed by three freeze-pump-thaw cycles directly in a screw-cap NMR tube. However, the samples in 98% H_2SO_4 tend to form emulsions during the degassing procedure. To avoid this, these samples, as well as those in MeONa, were degassed by bubbling argon or nitrogen at room temperature through a PTFE tube. Owing to the higher solubilities and shorter T_1's in these media, measuring times were much shorter than in water, thus avoiding any substantial extent of side reactions. T_1's were determined by inversion-recovery or saturation-recovery, by running 10–16 measurements with $0.01 < \tau_D < 300$ s. In order to determine peak intensities accurately, 128 K data points were collected. NOE's were determined by nonselective proton irradiation during 2–4 times T_1.

Calculations: All calculations were carried out with Spartan v. 4-5[50] running on an IBM RS/6000 workstation.

[1] B. Wilson, R. Georgiadis, J. E. Bartmess, *J. Am. Chem. Soc.* **1991**, *113*, 1762 and references cited therein.
[2] [2a] T. H. Lowry, K. S. Richardson, *Mechanism and Theory in Organic Chemistry*, 3rd edn., Harper and Row, New York, **1987**.

– [2b] J. March, *Advanced Organic Chemistry*, 3rd edn., Wiley, New York, **1985**.
[3] R. W. Alder, *Chem. Rev.* **1989**, *89*, 1215.
[4] C. L. Perrin, M. A. Fabian, K. B. Armstrong, *J. Org. Chem.* **1994**, *59*, 5246.
[5] For a recent example see: M. Oki, H. Ikeda, H. Miyake, H. Mishima, S. Toyota, *Bull. Chem. Soc. Jpn.* **1998**, *71*, 915.
[6] IUPAC recommends using "hydron", and related terms, rather than "proton" if no distinction between protium and deuterium is to be made. In the present work, this would not be appropriate for NMR relaxation measurements, which strictly require ^1H rather than ^2H in order to apply the concepts presented later in the paper. Moreover, all quantities necessary for the study of acid-base equilibria and thermodynamics are accurately known only for aqueous H_2SO_4 rather than D_2SO_4. Hence, we will always use the term "proton", etc.
[7] H. C. Brown, B. Kanner, *J. Am. Chem. Soc.* **1966**, *88*, 986.
[8] E. M. Arnett, B. Chawla, *J. Am. Chem. Soc.* **1979**, *101*, 7141 and corrections (*J. Am. Chem. Soc.* **1981**, *103*, 7036).
[9] H. P. Hopkins, D. V. Jahagirdar, P. S. Moulik, D. H. Aue, H. M. Webb, W. R. Davidson, M. D. Pedley, *J. Am. Chem. Soc.* **1984**, *106*, 4341.
[10] [10a] H. P. Hopkins, S. Z. Ali, *J. Phys. Chem.* **1980**, *84*, 203. – [10b] H. P. Hopkins, S. Z. Ali, *J. Phys. Chem.* **1980**, *84*, 2814.
[11] M. Meot-Ner (Mautner), L. W. Sieck, *J. Am. Chem. Soc.* **1983**, *105*, 2956.
[12] [12a] C. H. Rochester, B. Rossall, *Trans. Faraday Soc.* **1969**, *65*, 1004. – [12b] P. D. Bolton, C. H. Rochester, B. Rossall, *Trans. Faraday Soc.* **1970**, *66*, 1348.
[13] T. N. Pliev, *Proc. Acad. Sci. USSR, Chem. Sect. (Engl. Transl.)* **1969**, *184*, 123.
[14] [14a] J. C. Day, *J. Org. Chem.* **1978**, *43*, 3646. – [14b] J. C. Day, *J. Am. Chem. Soc.* **1981**, *103*, 7355.
[15] S. Böhm, M. Decouzon, O. Exner, J.-F. Gal, P.-C. Maria, *J. Org. Chem.* **1994**, *59*, 8127.
[16] A. Bagno, R. L. Boso, N. Ferrari, G. Scorrano, *J. Chem. Soc. Chem. Commun.* **1995**, 2053.
[17] A. Bagno, G. Scorrano, R. A. More O'Ferrall, *Rev. Chem. Interm.* **1987**, *7*, 313.
[18] A. Bagno, V. Lucchini, G. Scorrano, *Bull. Soc. Chim. France* **1987**, 563.
[19] A. Bagno, V. Lucchini, G. Scorrano, *J. Phys. Chem.* **1991**, 95, 345.
[20] R. A. McClelland, W. F. Reynolds, *Can. J. Chem.* **1976**, *54*, 718.
[21] R. A. Nyquist, C. L. Putzig, L. Yurga, *Appl. Spectrosc.* **1989**, *43*, 983.
[22] S. Liedle, H. Oberhammer, N. L. Allinger, *J. Mol. Struct.* **1994**, *317*, 69.
[23] H. Dahn, P. Péchy, H. J. Bestmann, *J. Chem. Soc. Perkin Trans. 2* **1993**, 1497.
[24] R. A. Nyquist, *Appl. Spectrosc.* **1990**, *44*, 433.
[25] A. Massat, A. Cossé-Barbi, J. P. Doucet, *J. Mol. Struct.* **1989**, *212*, 13.
[26] [26a] C. Klofutar, S. Paljk, D. Kremser, *Spectrochim. Acta* **1973**, *29A*, 139. – [26b] M. J. Cook, N. L. Dassanayake, C. D. Johnson, A. R. Katritzky, T. W. Toone, *J. Chem. Soc. Perkin Trans. 2* **1974**, 1069.
[27] R. W. Taft, J. F. Wolf, J. L. Beauchamp, G. Scorrano, E. M. Arnett, *J. Am. Chem. Soc.* **1978**, *100*, 1240.
[28] S. G. Lias, J. F. Liebman, R. D. Levin, *J. Phys. Chem. Ref. Data* **1984**, *13*, 695 and updates.
[29] R. W. Taft, *Prog. Phys. Org. Chem.* **1983**, *14*, 247.
[30] F. M. Jones, E. M. Arnett, *Prog. Phys. Org. Chem.* **1974**, *11*, 263.
[31] J. Hine, P. K. Mookerjee, *J. Org. Chem.* **1975**, *40*, 292.
[32] S. Cabani, P. Gianni, V. Mollica, L. Lepori, *J. Solution Chem.* **1981**, *10*, 563.
[33] R. W. Dixon, J. M. Leonard, W. J. Hehre, *Israel J. Chem.* **1993**, *33*, 427.
[34] [34a] J. H. Noggle, R. E. Schirmer, *The Nuclear Overhauser Effect*, Academic Press, New York, **1971**. – [34b] D. Neuhaus, M. Williamson, *The Nuclear Overhauser Effect in Structural and Conformational Analysis*, VCH, New York, **1989**.
[35] W. J. Chazin, L. D. Colebrook, *Magn. Reson. Chem.* **1985**, *23*, 597.
[36] R. D. Howells, J. D. McCown, *Chem. Rev.* **1977**, *77*, 69.
[37] *International Critical Tables*, vol. 23, McGraw-Hill, New York, **1930**.
[38] J.-C. Hallé, F. Terrier, R. Gaboriaud, *Bull. Soc. Chim. Fr.* **1973**, 37.
[39] A. Bagno, G. Scorrano, F. Terrier, *J. Chem. Soc. Perkin Trans. 2* **1990**, 1017.
[40] C. H. Rochester, *J. Chem. Soc.* **1965**, 676.
[41] B. Rickborn, *J. Am. Chem. Soc.* **1962**, *84*, 2414.
[42] A. Bagno, G. Scorrano, *J. Phys. Chem.* **1996**, *100*, 1536.
[43] A. Bagno, J. Kevelam, G. Scorrano, unpublished results.
[44] M. Bonchio, M. A. De Conciliis, F. Di Furia, F. P. Ballistreri, G. A. Tomaselli, R. M. Toscano, *J. Org. Chem.* **1995**, *60*, 4475 and references cited therein.
[45] V. N. Ipatieff, H. Pines, B. S. Friedmann, *J. Am. Chem. Soc.* **1938**, *60*, 2731.
[46] N. L. Allinger, H. M. Blatter, L. A. Freiberg, F. M. Karkowski, *J. Am. Chem. Soc.* **1966**, *88*, 2999.
[47] K. L. Servis, D. J. Bowler, *J. Am. Chem. Soc.* **1975**, *97*, 80.
[48] R. L. Augustine, *Oxidation*, Marcel Dekker, New York, **1969**, vol. 1.
[49] F. Minisci, R. Bernardi, F. Bertini, R. Galli, M. Perchinummo, *Tetrahedron* **1971**, *27*, 3575.
[50] Wavefunction Inc., Irvine, CA.
[51] G. Perdoncin, G. Scorrano, *J. Am. Chem. Soc.* **1977**, *99*, 6983.
[52] A. E. Reed, L. A. Curtiss, F. Weinhold, *Chem. Rev.* **1988**, *88*, 899.

Received February 23, 1999
[O99105]