Solvent effects on ^{15}N NMR chemical shifts of 2,6-di-*tert*-butylpyridine. Absence of hydrogen bonding with the nitrogen atom

Dan Fărcaşiu,* Marta Lezcano and Alina Vinslava

Department of Chemical and Petroleum Engineering, University of Pittsburgh, 1249 Benedum Hall, Pittsburgh, PA 15261, USA. E-mail: dfarca@vms.cis.pitt.edu

Comparison of the ^{15}N chemical shifts of 2,6-di-*tert*-butylpyridine (DTBP) and pyridine (Py) in a series of solvents demonstrates the inability of the nitrogen atom in DTBP to participate in hydrogen bonds. Both bases are fully hydronated in trifluoromethanesulfonic acid (TFMSA) and trifluoroacetic acid (TFA) solutions, but the chemical shift values for Py differ in the two media, indicating hydrogen bonding between the N–H group of the pyridinium ion and the trifluoroacetate anion in the ion pair, which is absent in hydronated DTBP.

Introduction

2,6-Di-*tert*-butylpyridine (DTBP) was found to be an unusual compound in the seminal work of Brown and Kanner, which showed DTBP to be a much weaker base than all the lower 2,6-dialkylpyridine homologs.[1] Also, reaction with one equivalent of hydrogen chloride neutralized only half of the DTBP, forming [DTBPH]$^{+}$·[ClHCl]$^{-}$, whereas pyridine (Py) formed salts with both the chloride and the hydrogen dichloride anions. The behavior of DTBP was rationalized as due to steric hindrance, which prevents the hydronated† DTBP from forming a hydrogen bond with the anion.[1]

The much reduced basicity of DTBP was confirmed for carbon tetrachloride[3a] and dimethylsulfoxide (DMSO) solutions.[3b] Steric hindrance to hydration of the cation was also considered responsible for the change in basicity of DTBP from the gas phase (high) to water solution (very low).[4]

Contradictory information exists, however, about the interactions of DTBP with various types of acids. Thus, a complete analysis of the thermodynamics of protonation in the gas phase and in water solution led to the conclusion that both the cation and the free base are hydrogen-bonded at nitrogen in water.[5] The reduced basicity was ascribed to a decrease in entropy because of an increased barrier to *tert*-butyl group rotation.[5] From an IR spectroscopic investigation, it was concluded that 4-fluorophenol hydrogen-bonds with the π-electron system of DTBP, rather than with the nitrogen atom,[6] whereas from another study it was concluded that, in spite of the steric hindrance, DTBP interacts not only with Brønsted acid sites, but even with Lewis acid sites on the surface of boron phosphate.[7]

All the previous studies were based on the examination of changes in the spectra of the hydrogen-bond donors. Previous studies in our laboratory have shown, however, that the hydrogen-bond donor ability of solvents and solid surfaces can be assessed from the NMR chemical shift of carbon atoms in some hydrogen-bond acceptors, such as unsaturated ketones.[8] We decided to evaluate the strength of hydrogen

bonds involving DTBP by looking at the atom in the acceptor directly involved in the hydrogen bond, the nitrogen atom. Literature reports indicate that the ^{15}N NMR chemical shifts of pyridine (Py) and 3,5-dimethylpyridine exhibit sizable variations with the solvent, particularly in hydrogen-bond donor solvents.[9] We have, therefore, conducted a comparative NMR study of Py and DTBP in various solvents and we report our results here.

Experimental

Material

Py, DTBP, and the solvents used in the study were reagent grade commercial materials. The solvents were used as purchased, Py was taken from freshly opened containers, and DTBP was stored over calcium hydride.

NMR spectra

The ^{1}H NMR spectra were recorded at 300.13 MHz and the ^{15}N NMR spectra at 30.41 MHz, on a Bruker DMX300 instrument. The solutions (1.54 M or 0.06–0.08 M) were prepared by weighing the bases and solvents in 8 mm NMR tubes. The dilute solutions were prepared from isotope-enriched (99%) base. The mixtures with phenol as solvent were prepared under nitrogen, then placed in an oil bath at 40 °C until the phenol melted and a homogeneous solution resulted. The mixtures then remained liquid at 20 °C. The sample of pyridine in trifluoromethanesulfonic acid (TFMSA) was prepared by freezing pyridine in the NMR tube in liquid nitrogen, adding less than the total calculated amount of TFMSA, then bringing to room temperature and adding the exact weight of acid required. The spectra were run in a 10 mm/8 mm coaxial tube setting.[10] For the ^{15}N spectra, the outer tube contained a 4 : 1 mixture of Py (chemical shift standard) and DMSO-d$_6$ (lock solvent). An inverse gated decoupling pulse sequence was applied and a number of 4000 scans per spectrum were typically acquired. The proton chemical shifts were measured from internal TMS for the non-acidic solvents, but TMS could not be used for the solutions in acids. Dichloroethane was used as the secondary internal

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† The name "hydron" has been recommended for the cation of hydrogen in natural isotopic distribution, to be distinguished from the isotopically pure proton, deuteron and triton.[2]

Table 1 Relative ^{15}N chemical shifts, δ_{rel}, for DTBP and Py in various solvents

No.	Solvent	δ_{rel}	
		DTBP[a]	Py
1	Hexane	0.00;[a] 0.00[b]	0.00
2	CH_2Cl_2	−0.68[a]	−7.0;[a,c] −7.6[d]
3	MeOH	−0.91;[a] −1.36[e]	−21.05;[a] −23.4[d]
4	MeOH–H_2O	−1.41[f]	(−26.6)[d,g]
5	PhMe	−1.17;[a] −1.43[h]	−4.00[a]
6	PhOH	−2.55[a]	−33.83[a]
7	CF_3COOH	−128.08[a]	−125.33;[a] −124.8[i]
8	CF_3SO_3H	−128.06[a]	−128.31[a]
9	FSO_3H	—	−129.2[i]

[a] This work, concentration 1.54 M. [b] This work, concentration 0.063 M. The signal in the dilute solution was shifted to lower frequency (upfield) by 0.04 ppm from the value in the 1.54 M solution. [c] Signal partially overlapped with the standard (4 : 1 mixture of Py and DMSO). [d] Literature values, at infinite dilution, with the solution in cyclohexane ($\delta − 57.7$ from neat $MeNO_2$) taken as standard.[9a,12] [e] This work, concentration 0.077 M. [f] This work, concentration 0.076 M, ratio H_2O : DTBP 10 : 1. [g] Pure water as solvent. [h] Measurement repeated at the same time with the dilute DTBP solution (new chemical shift standard mixture). [i] Literature value, 0.5 M solution, recalculated from the same cyclohexane solution standard.[9a,12a]

reference in those experiments. Its chemical shift was determined as 3.72 ± 0.09 ppm in hexane, dichloromethane, and methanol. Thus, the values measured from an external reference (TMS in $CDCl_3$)[11] are corrected as indicated in Table 2. The signal for the N–H$^+$ proton of $[PyH]^+ \cdot [TFMSA]^-$ in TFA[11] can likewise be corrected to 13.59 ppm.

Results and discussion

Assessments of the hydrogen-bond acceptor ability of DTBP have, so far, been indirect. Thus, steric hindrance of hydrogen-bonding was offered as an explanation for the observed low acidity.[1,3b] Thermodynamic analyses of reactions with acids have been interpreted for[5] and against[3] the existence of hydrogen bonds to the nitrogen of DTBP. From infrared measurements, some authors concluded that the nitrogen atom of DTBP does not accept hydrogen bonds from methanol and 4-fluorophenol,[6] but other authors concluded that it can interact with much more sterically demanding Lewis sites on a solid surface.[7]

The ^{15}N chemical shift of Py was found to vary only by a few ppm upon transfer from the gas phase to a dilute cyclohexane solution and from that to a polar solvent, such as DMSO.[9a,12] A large change was observed, however, upon transfer to hydrogen-bond donor solvents, like methanol, water, and trifluoroethanol, proving the sensitivity of this parameter to the formation of hydrogen bonds involving the nitrogen atom.[9a,12b,13] The other base, DTBP, was previously studied only as a neat liquid.[14] We compared, therefore, the ^{15}N resonances for Py and DTBP dissolved, mostly at a concentration of 1.54 M, in some selected solvents indicated in Table 1. Because DTBP is not soluble in trifluoroethanol, phenol was used as a strong hydrogen-bond donor. Phenol should also have lower steric requirements than trifluoroethanol because the phenyl ring can orient itself such as to slide between the two tertiary butyl groups. The results are expressed as chemical shifts, δ, increasing with the increase in frequency, rather than nuclear shieldings, increasing with the increase in field (decrease in frequency), as recommended for nitrogen NMR.[9a,12a] Our approach is that preferred for other nuclei commonly studied by NMR spectroscopy. Each spectrum was referenced to the signal of Py in a 4 : 1 (v : v) mixture with DMSO in the outer (coaxial) tube[10] and the chemical shift was recalculated relative to the solution in hexane (δ_{rel}).

Our measurements revealed large upfield shifts (lower frequency) of the ^{15}N resonance of Py in methanol and especially in phenol. The high hydrogen-bond donor ability of the latter and its effects on the generation of carbocations[15a–c] and the strength of dissolved acids[15d] has been reported previously.[15e] Some hydrogen-bonding of Py probably occurs even with dichloromethane (Table 1, entry 2). The behavior of DTBP is entirely different. The variation of its chemical shifts with the solvent, also shown in Table 1, is quite small and thus shows that there is no interaction involving the nitrogen

Table 2 Proton NMR spectra of DTBP and Py in various solvents[a]

No.	Solvent	DTBP			Py		
		CMe_3	β-H	γ-H	α-H	β-H	γ-H
1	Hexane[b]	1.34(s)	7.00(d) J 7.7	7.38(t) J 7.7	8.53(br, d)[c]	7.14(dd) J 7.7; 5.5	7.53(tt) J 7.7; 1.8
2	Hexane[b,d]	e	7.00(d) J 7.7	7.37(t) J 7.8	—	—	—
3	CH_2Cl_2[b]	1.34(s)	7.08(d) J 7.7	7.48(t) J 7.7	8.57(br, dd) J 5.9; ∼ 1.8	7.25(dd) J 7.7; 5.9	7.65(tt) J 7.7; 1.7
4	MeOH[b]	1.33(s)	7.10(d) J 8.1	7.50(t) J 8.1	8.54(dd) J 6.2; 1.8	7.41(dd) J 7.7 5.9	7.83(tt) J 7.7; 1.8
5	MeOH–H_2O[b,f]	1.32(s)	7.12(d) J 7.7	7.53 J 7.8	—	—	—
6	PhOMe[b]	1.35(s)	6.97(d) J 7.7	7.32(t) J 7.9	8.52(dd) J 5.9; 1.8	6.96(dd) J 7.7; 5.9	7.32(tt) J 7.5; 1.7
7	PhOH[b]	1.37(s)	7.03(d) J ∼ 8	7.41(t) J 7.9	8.36(dd) J ∼ 6.2; ∼1.8	7.05[g]	7.43(tt) J 7.7; ∼1.7
8	CF_3COOH[h]	1.59(s)[i]	7.93(dd)[j] J 8.1; 1.8	8.48(t) J 8.1	8.85(br)[c,k]	8.16(dd) J 8.1; 6.1	8.74(t) J 8.1
9	CF_3SO_3H[h]	1.59(s)[l]	7.98(dd)[j] J 8.1; 1.8	8.55(t) J 8.1	8.72[m,n]	8.14(br, t) J ∼ 6.6	8.70[m]

[a] 1.54 M solutions, unless otherwise stated; chemical shifts (δ) in ppm from the internal reference indicated in each case, coupling constants (J) in Hertz. When slightly different values were read for the same coupling constant, J, for the two coupled atoms, the measured values, rather than the average, was entered. [b] TMS as internal reference. [c] Coupling constants could not be reliably measured. [d] Concentration 0.063 M. [e] The signal was obscured by the solvent peak. [f] Concentration 0.076 M, ratio H_2O : DTBP 10 : 1. [g] Partially overlapped with the solvent peak. [h] 1,2-Dichloroethane as internal reference, δ 3.72 (see Experimental). [i] δ(N–H) 11.17 (br, s). [j] The smaller splitting results from coupling with the proton at N. [k] δ(N–H) 13.96 (br, t, $|J|$ (^{14}N–H) 62.5 Hz). [l] δ(N–H) 11.28 (br, s). [m] The two signals are incompletely separated. [n] δ(N–H) 12.70 (t, $|J|$ (^{14}N–H) 68.3 Hz). The significance of the line shapes of the N–H signals is discussed in ref. 11.

atom. If DTBP was forming hydrogen bonds, but its low basicity was the result of *tert*-butyl group rotation freezing in the hydrogen bonded complex,[5] the ^{15}N chemical shift would reflect the interaction.

The effect of concentration on chemical shifts of Py was ascertained from the comparison of our data at 1.54 M with literature data extrapolated to infinite dilution.[9a,12] For DTBP, we examined 0.06–0.08 M solutions in hexane and methanol. As shown in Table 1, no significant variation of chemical shifts with concentration was found for any of these solvents.

Analysis of the thermodynamics of protonation of DTBP in the gas phase and in solution, which concluded that hydrogen-bonding of a molecule of solvent at nitrogen occurs, employed water as the hydrogen-bond donor. As indicated above for phenol, the steric hindrance to hydrogen-bonding comes mostly from the interaction of the R group in ROH with the tertiary butyl groups. It was important to examine the case where R is hydrogen. We recorded, therefore, the ^{15}N spectrum of DTBP at high dilution in methanol (0.076 M), in the presence of a ten-molar excess of water. The chemical shift, also listed in Table 1, was essentially the same as in anhydrous methanol.

It can be seen that DTBP does not interact at nitrogen with strong hydrogen-bond donors like methanol, water, and phenol. The hydrogen bond energy in all these cases would not be strong enough to induce the required angular deformation of the *tert*-butyl substituents.

The ^{15}N NMR spectra of Py and DTBP were also recorded in two acids of very different strength: trifluoroacetic (TFA), $H_o - 3.0$,[16] and $99+\%$ trifluoromethanesulfonic acid (TFMSA), $H_o \leqslant -13$.[17] The equality of chemical shifts indicated that DTBP was hydronated in both acids. There was, however, a difference in the chemical shifts of Py in the two solutions (Table 1, entries 6 and 7). As a comparison of TFA with the even weaker trichloroacetic acid (TCA) had indicated that the pyridinium ion, PyH$^+$, had been fully formed with both TFA and TCA,[9a,13] we conclude that the variation of the nitrogen chemical shift in PyH$^+$ reflects the hydrogen-bonding with the anion in the ion pairs which are formed in the weaker acid. Like its parent, DTBP, sterically hindered DTBPH$^+$ seems unable to form hydrogen bonds involving the N–H group, at least with the trifluoroacetate anion.

The proton NMR spectra of Py and DTBP in the same solvents were also recorded (Table 2), but they are much less informative. The only significant solvent dependence is shown by the γ protons of pyridine (total range, 0.51 ppm, compared with 0.18 ppm for the corresponding proton in DTBP). As stated in the footnotes under Table 2, the line shapes of the N–H signals are different for DTBPH$^+$ (a broad singlet) and PyH$^+$ (triplet) on account of the faster longitudinal relaxation of ^{14}N in the former.[18] Significant differences between the relaxation times ($T_1 = 1/R_1$) for the carbon atoms in the β and γ positions (4.71 and 4.75 sec for PyH$^+$, 0.55 and 0.79 sec for DTBPH$^+$) were observed as well. Therefore, the difference in longitudinal relaxation rates originates in a different rate of tumbling in solution, rather than a difference in the electrical field gradient.[11]

Acknowledgements

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