2,6-Di-t-BUTYLPYRIDINE - AN UNUSUAL BASE*

Bernard Kanner
Union Carbide Corporation, Tarrytown Technical Center, Tarrytown, New York, 10591, U.S.A.

ABSTRACT

2-6,Di-t-butylpyridine has been investigated because of its extraordinary combination of properties. As the result of steric crowding at the nitrogen atom, it does not coordinate with Lewis acids or undergo quaternization under ordinary conditions. However, it is readily sulfonated by sulfur trioxide and is a selective catalyst with basic but not nucleophilic properties.

CONTENTS

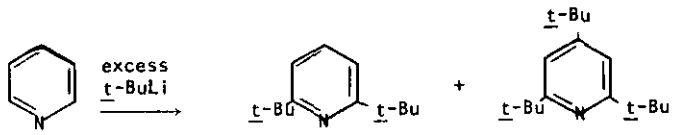
A. INTRODUCTION

The initial investigation of 2,6-di-t-butylpyridine (2,6-DTBP) reported a novel compound whose chemical behavior was dramatically modified by unusual steric crowding at the nitrogen atom.[1,2] This was evidenced by decreased base strength, a striking ability to distinguish between Lewis and protonic acids and an enhanced reactivity in electrophilic substitutions. Since this report, the useful properties of 2,6-di-t-butylpyridine and its 2,4,6-homolog (2,4,6-TTBP) which behaves similarly, have been elaborated in a variety of subsequent investigations.

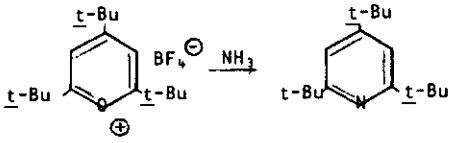
B. SYNTHESIS

2,6-DTBP is readily prepared[1] by the stoichiometric reaction of 2-t-butylpyridine with t-butyllithium at -78°. When pyridine is reacted with large excesses of t-butyllithium, the 2,4,6-homolog is also obtained in substantial yield.[3,4]

* The author is pleased to dedicate this paper to Professor H. C. Brown on the occasion of his 70th birthday.



2,4,6-TTBPY has also been prepared in excellent yield by the reaction of alcoholic ammonia with the corresponding tri-t-butyl substituted pyrylium boron tetrafluoride salt.[5]



C. BASE STRENGTH

The base dissociation constants for pyridine, the 2-alkylpyridines and 2,6-dialkylpyridines show a regular increase in strength with increasing substitution (Table I). However, for 2,t-butylpyridine and 2,6-di-t-butylpyridine, *following the usual increase for the first group*, there is a sharp decrease for the second t-butyl group (Figure 1).

FIGURE 1

Effect of Increasing the Steric Requirements of an Alkyl Group on the Base Strength of 2-Substituted Pyridines

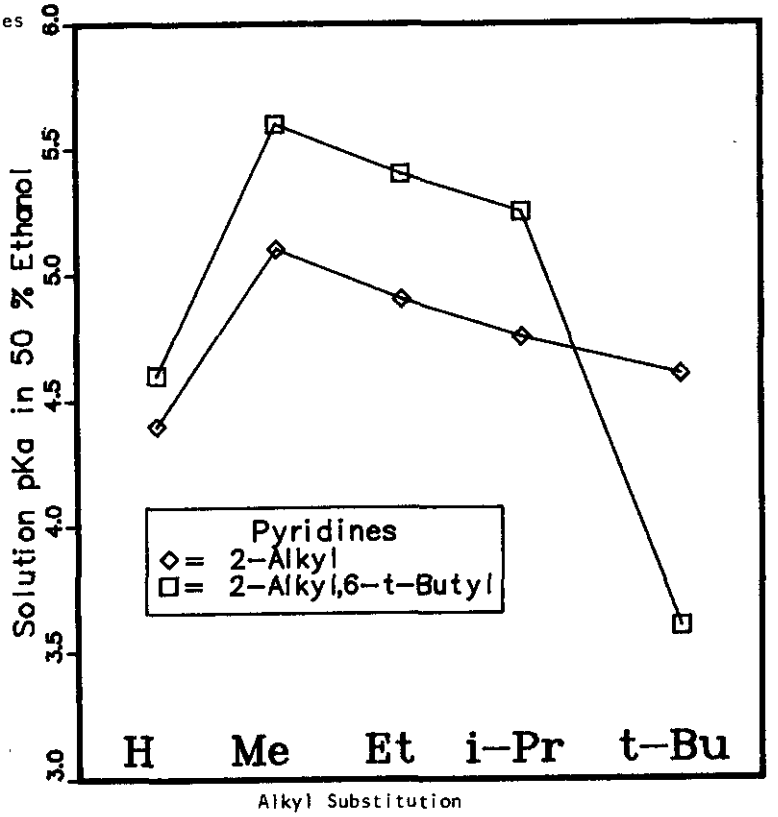


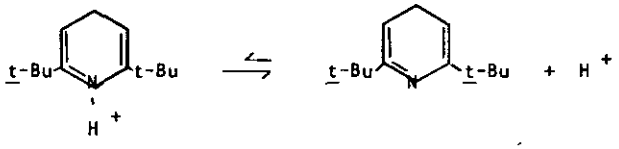
TABLE I

Dissociation Constants of Pyridine Bases in 50% Ethanol-Water

Pyridine	pK_a*	Pyridine	pK_a*
Pyridine	4.38	2,6-Lutidine	5.77
2-Picoline	5.05	2-Methyl-6-t-butyl-	5.52
2-Ethyl-	4.93	2-Ethyl-6-t-butyl-	5.36
2-Isopropyl-	4.82	2-Isopropyl-6-t-butyl	5.13
2-t-Butyl-	4.68	2,6-Di-t-butyl-	3.58
		2,6-Disopropyl-	5.34

* The measurements were made at room temperature (27 ± 2°).

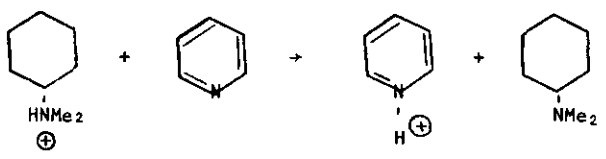
The discrepancy between the observed value and the expected value is 1.4 pK_a units. The pronounced decrease in base strength was ascribed to a possible combination of steric crowding of the nitrogen-hydrogen bond and steric interference with a solvating water molecule which is hydrogen bonded to the protonated base.[2]



The relative importance of these two possible contributing factors has now been extensively examined by a number of investigators whose results lead to a common conclusion. As the result of these investigations, it is clear that steric inhibition of solvation is responsible for the decreased base strength of 2,6-DTBP.

McDaniel and Ozcan tackled this question by examining the effects of solvents on the basicity of hindered pyridines.[6] Their objective was to distinguish between steric inhibition of solvation and steric hindrance towards a proton as the primary reason for the lower than expected basicity of 2,6-DTBP. They determined pK_a values in methanol, ethanol, and isopropanol for pyridine, 2-t-butylpyridine and 2,6-DTBP. If the deviation in base strength of 1.4 pK_a units observed for 2,6-DTBP were due primarily to steric hindrance toward the proton, variations in the solvent system would not affect the size of the deviation. However, their experimental results showed that the deviation does vary with solvent choice, supporting the conclusion that steric inhibiton of solvation is responsible for the decrease in base strength.

Menger, et al, have measured entropies of activation for nitrogen to nitrogen proton transfer.[7] They determined $\Delta S^{\ddagger}$ for proton transfer from an aliphatic amine salt to a series of substituted pyridines in chloroform. Both the rate constants and the entropy of activation correlated directly with the basicity of the pyridine compound. Interestingly, no steric effect was noted for proton transfer for 2,6-DTBP. This was attributed to a late transition state for proton transfer.



Solvation effects on acid-base equilibrium constants have been measured by Wolf, et al, using pulsed ion cyclotron reconance spectroscopy.[8] By comparing equilibrium constants in the gas phase (Kg) with the corresponding equilibrium constants determined in aqeuous solution (Kaq) they obtained a measure of the solvation effects of water on the proton transfer equilibrium. Extremely large medium effects of water were noted on proton transfer ($Kg/Kaq \sim 10^{25}$) with carbon base precursors of aryl carbocations. These ions are poorly solvated because of the extensive delocalization of the cationic charge. Pyridinium ions, in general, show much smaller solvation effects because of a highly localized cationic charge. However, 2,6-DTBP demonstrates the same very large solvent effect as seen for aryl carbocations confirming once more that steric hindrance towards solvation was present.

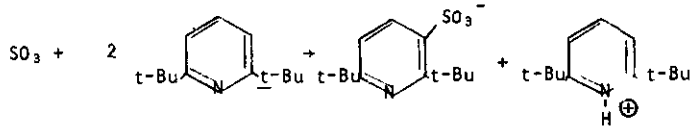
Gas- and solution-phase basicities of substitued pyridine were also compared by Aue, Liotta, Hopkins, et al.[9] Their results suggested that the 2,6-di-t-butylpyridinium ion is less well solvated than its 2,6-dimethyl homolog. The deviation was estimated at about 3.5 K cal/mol. Condon has calculated the steric hindrance to hydration by 2,6-DTBP decreases its base strength by ca. 2.2 pK units.[10]

Knözinger has examined the hydrogen bonding properties of substitued pyridines on silica.[11] Although the other 2,6-dialkylpyridines exhibited normal hydrogen bonding, including 2,6-diisopropylpyridine, hydrogen bonding to the hydroxyl groups on the surface of silica was absent for 2,6-DTBP. Steric hindrance has been noted as a factor in hydrogen bonding interactions between phenol and substituted pyridines.[12]

Steric crowding at the nitrogen atom in 2,6-DTBP has also had a striking effect on its chemical properties as well as will be noted in the sections that follow.

D. SULFONATION

The unusual sluggishness of pyridine towards electrophilic substitution has been attributed to the powerful electron-withdrawing effect of the positively charged quaternary nitrogen formed during the reactions. The aprotic sulfonation of 2,6-DTBP offered the opportunity to explore the true reactivity of the free pyridine base. Because of unusual steric hindrance to coordination, 2,6-DTBP reacted readily, under mild conditions, with sulfur trioxide in liquid sulfur dioxide to give the sulfonic acid. The product was tentatively identified as the 4-sulfonic acid because of steric hindrance at the 3-position.[1]



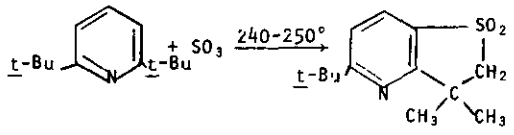
Although the structure could not be established by pK_a measurements,[13,14] it was firmly established by synthesis,[15,18,19] NMR,[16] and reactivity considerations.[17] A comparison of sulfonic acid yield under the same reaction conditions (Table II) indicated that the reactivity of the free 2,6-DTBP base is comparable to nitrobenzene.[2]

TABLE II

Sulfonation of 2,6-Di-t-butylpyridine and Representative Model Compounds by Sulfur Trioxide in Liquid Sulfur Dioxide

		Reaction Product Yield, %	
Compound	Time, hr	Addition	Substitution
Benzene	4	0	100
Nitrobenzene	4	0	70
Pyridine	1	100	0
2,6-Lutidine	4	100	0
2,6-Di-t-butyl-pyridine	4	0	37
	20	0	45

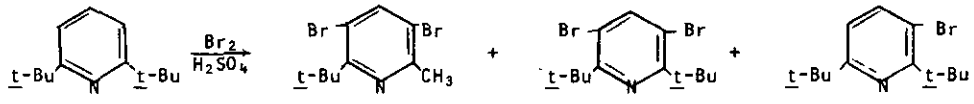
Interestingly, when the reaction with sulfur trioxide is carried out at the high temperatures typically needed for the sulfonation of pyridine, an unusual and new reaction was observed in addition to sulfonation:[20]



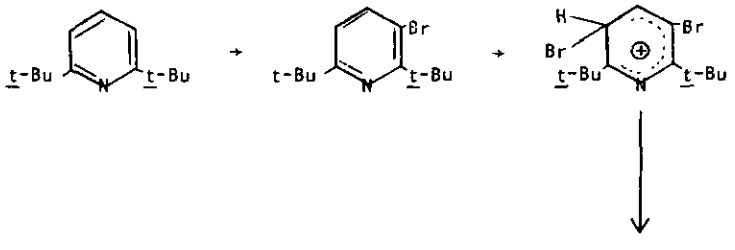
The structure of the substituted dihydrothiophene derivative was supported by IR and NMR data.

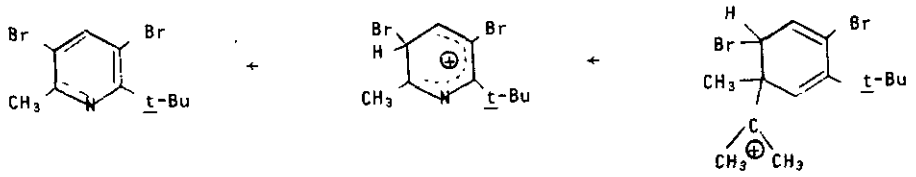
E. BROMINATION

Bromination of t-butylpyridine in fuming sulfuric acid results in partial conversion of t-butyl groups into methyl groups in addition to the normal bromination.[21] The bromination of 2,6-di-t-butylpyridine gave the following:



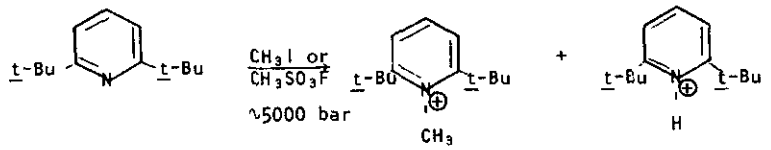
The conversion of a t-butyl group to a methyl group had also been observed in the nitration of 2,4,6-tri-t-butylnitrobenzene. The products observed for the bromination of t-butylpyridines were interpreted to arise in the same manner:





F. QUATERNIZATION

Menshutkin reactions of 2,6-DTBP are not observed under ordinary conditions.[2] In order to promote the reaction with methyl iodide, pressures of at least 4000 bar are required.[22,23] Under these conditions, the N-methylpyridinium iodide and hydrogen iodide salts were reported as the main products in a 2 to 8 ratio.[23] Both 2,6-DTBP and 2,4,6-TTBP also react with methyl fluorosulphonate under similar conditions of high pressure to give mixtures of the N-methyl and protonated compounds. In this instance, however, the N-methyl compounds were the principal products.[23]

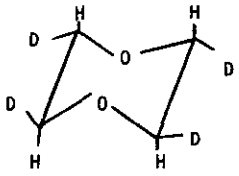


Other reports, however, indicate that only the protonated base is obtained under conditions of high pressure with either methyl iodide or the fluorosulphonate.[24,25,26] Thus, Weber and coworkers reported that the reactions of 2,4,6-TTBP with FSO_3CH_3 even under 10,000 atm gave only the N-proton compound (1 to 99%).[26] However, they successfully synthesized the N-methyl compound by refluxing 2,4,6-TTBP with FSO_3CH_3 at 180° for 48 hours in p-chlorotoluene. They have investigated the crystal structure of the iodide and perchlorate and showed that the pyridinium ring deformed slightly. However, the compounds do not show unusual thermal stability.

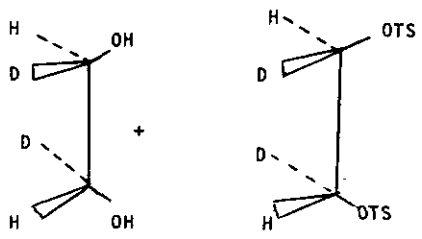
The reactions of 2,6-di-t-butylpyridine derivatives with FSO_3CH_3 have been recently re-examined by Okamoto and Hou who found that the reactions gave N-methyl products in high yield under 4500 atm at 80°C.[27] The formation of N-proton compounds was accounted for by the reactions of the pyridine compounds with fluorosulfonic acid produced by the hydrolysis of FSO_3CH_3. They found that the pyridinium iodide compounds were decomposed at about 125°C which agreed with Weber's observation on the thermal stability of the iodide compounds.

G. CATALYSIS

The ability of 2,6-DTBP to act as a base with virtually no nucleophilic properties is illustrated in a report by Jensen and Neese.[28] The geometric isomer, trans-2,3-trans-5,6-dioxane-d_4 needed for an investigation, could not be satisfactorily synthesized by condensing ethylene glycol



with ethylene glycol di-tosylate. Acid catalysis gave a mixture of self condensation and co-condensation. Using quinoline as an added base yielded only a tar. When the condensation was carried out with two equivalents of 2,6-DTBP, deuterated dioxane was obtained as a 65% yield of two stereoisomers.



Deutsch and Cheung sought to study the reactions of metal ions in buffered aqueous solution uncomplicated by coordination of the Lewis base buffers with the metals.[29] In their search for water soluble noncoordinating buffers, they synthesized a broad variety of quaternary salt derivatives of hindered pyridine bases including 2,6-DTBP. The salts prepared included chlorides, bromides, nitrates and perchlorates.

As part of a general study of base catalyzed trapping of sulphenes, King and Kang reported that 2,6-di-t-butylpyridine behaved as a base rather than a nucleophilic catalyst.[30]

H. MISCELLANEOUS

The ability of 2,6-DTBP to distinguish between protonic and Lewis acids combined with basic but relatively non-nucleophilic properties has led to suggestions of practical utility as well.[31,32] An interesting example involves the commercial recovery of olefins by complexation with salts such as $CuAlCl_4$, $CuBF_4$, and $CuPF_6$.[32] These salts in aromatic hydrocarbon solution dissociate partly into Lewis Acids. The resulting Lewis Acids can combine with small amounts of HCl to catalyze alkylation of the aromatics by the olefins:

$$CuAlCl_4 \rightleftharpoons CuCl + AlCl_3 \xrightarrow{HCl} HAlCl_4 \xrightarrow[\text{aromatic}]{\text{olefin}} \text{alkylated aromatics}$$

It was sought to prevent the undesired alkylation by scavenging traces of HCl with pyridine. However, this resulted in formation of an insoluble pyridine-Lewis Acid complex. The desired effect was obtained with 2,6-DTBP which absorbed HCl without complexing the Lewis Acid and thereby effectively inhibited alkylation.

Spectral studies have been carried out to measure fundamental chemical properties of 2,6-DTBP and 2,4-6-TTBP. Natural-abundance N^{15} NMR has been employed to obtain the ^{15}N chemical

shifts for substituted pyridine compounds.[33] It was observed that t-butyl substitution at the ortho position resulted in upfield shifts characteristic of γ gauche interactions. Heilbronner et al have measured the ionization potentials of 2,4,6-tri-t-butylpyridine using high-resolution photoelectron spectroscopy.[34 35]

Griller, Dimroth, Fyles, and Ingold have determined that steric factors have a dominant role in the stability of carbon-centered free radicals in solution.[36] Using electron paramagnetic resonance spectroscopy, they have demonstrated that azacyclohexadienyl radicals derived from 2,6-DTBP and 2,4,6-TTBP were exceptionally persistent. Infrared and ultraviolet spectra of alkylpyridines, including 2,6-DTBP were shown to correlate primarily with the positions of the alkyl groups on the pyridine ring and did not depend on whether the group was Me, Et, iPr or t-Bu.[37]

Finally, it may be noted that the odor of 2,6-DTBP is not that typical of pyridine compounds. It is pleasant and aromatic, unlike other pyridines, including the closely related 2-isopropyl-6-t-butylpyridine. Our perception of odors is apparently also influenced by steric factors.

REFERENCES

1. H. C. Brown and B. Kanner, J. Amer. Chem. Soc., 1953, 75, 3865.
2. H. C. Brown and B. Kanner, J. Amer. Chem. Soc., 1966, 88, 986.
3. F. V. Scalzi and N. F. Golob, J. Org. Chem., 1971, 36, 2541.
4. R. F. Francis, J. T. Weisener, and J. M. Paul, Chem. Comm., 1971, 1420.
5. K. Dimroth and W. Mach, Angew. Chem. Internat. Edit., 1968, 7, 460.
6. D. H. McDaniel and M. Ozcan, J. Org. Chem., 1968, 33, 1922.
7. F. M. Menger, T. D. Singh, and F. L. Bayer, J. Amer. Chem. Soc., 1976, 98, 5011.
8. J. F. Wolf, P. G. Harch, and R. W. Taft, J. Amer. Chem. Soc., 1975, 97, 2904.
9. D. H. Aue, H. M. Webb, M. T. Bowers, C. L. Liotta, C. J. Alexander, and H. P. Hopkins, Jr., J. Amer. Chem. Soc., 1976, 98, 854.
10. F. E. Condon, J. Amer. Chem. Soc., 1965, 87, 4494.
11. H. Knőzinger, Surface Science, 1974, 41, 339.
12. A. Halleux, Bull. Soc. Chim. Belges., 1959, 68, 381.
13. R. F. Evans and W. Kynaston, J. Chem. Soc., 1962, 1005.
14. R. F. Evans and H. C. Brown, J. Org. Chem., 1962, 27, 3127.
15. H. C. van der Plas and H. J. den Hertog, Tetrahedron Letters, 1960, 13.
16. N. Muller and W. J. Wallace, J. Org. Chem., 1959, 24, 1151.
17. H. C. van der Plas and H. J. den Hertog, Chem. Weekblad, 1957, 53, 560.
18. H. C. van der Plas, Thesis, Amsterdam, 1960.
19. H. C. van der Plas and H. J. den Hertog, Rec. Trav. Chim., 1962, 81, 841.
20. H. C. van der Plas and T. H. Crawford, J. Org. Chem., 1961, 26, 2611.
21. L. van der Does, A. van Veldhuizen, and H. J. den Hertog, Rec. Trav. Chim., 1974, 93, 61.
22. Y. Okamoto and Y. Shimagawa, Tetrahedron Letters, 1966, 3, 317.
23. Okamoto and K. I. Lee, J. Amer. Chem. Soc., 1975, 97, 4015.
24. W. J. LeNoble and Y. Ogo, Tetrahedron, 1970, 26, 4119.
25. W. J. LeNoble and T. Asano, J. Amer. Chem. Soc., 1975, 97, 1778.
26. H. Weber, J. Part, M. Liedigk, and H. Wunderlich, Chem. Ber., 1981, 114, 1145.
27. Y. Okamoto, Personal Communication.

28. F. R. Jensen and R. A. Neese, J. Org. Chem., 1972, 37, 3037.
29. E. Deutsch and N. K. V. Cheung, J. Org. Chem., 1973, 38, 1123.
30. J. F. King and Y. I. Kang, J.C.S. Chem. Comm., 1975, 52.
31. H. C. Brown and B. Kanner, U.S. 2,780,626, 1957.
32. H. H. Horowitz, H. W. Ruhle, U.S. 3,758,607, 1973.
33. A. J. DiGiola, G. T. Furst, L. Psota, and R. L. Lichter, J. Phys. Chem., 1978, 82, 1644.
34. E. Heilbronner, V. Hornung, F. H. Pinkerton, and S. F. Thames, Helv. Chim. Acta, 1972, 55, 289.
35. H. Oehling, W. Schafer and A. Schweig, Angew. Chem., 1971, 10, 656.
36. D. Griller, K. Dimroth, T. M. Fyles, and K. U. Ingold, J. Amer. Chem. Soc., 1975, 97, 5526.
37. H. E. Podall, Anal. Chem., 1957, 29, 1423.

Received, 9th November, 1981