crystals (5.2% conversion of 58% based on recovered acetamidoferrocene). Ferrocene isolated after chromatography of the crude acetylation products weighed 0.784 g. (74.5% recovery); acetamidoferrocene similarly recovered weighed 1.256 g. (91.2% recovery).

Acknowledgment.—D. W. Hall is grateful to the Division of General Medical Sciences of the Public Health Service for a predoctoral research fellowship (GPM-12, 877-C1).

Base Strengths of Alkylpyridines Using Triethylaluminum as the Reference Acid. A Study in F Strain

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The heats of reaction of a series of alkylpyridines with triethylaluminum have been measured. The order of the relative base strengths observed suggests steric factors were operative in qualitatively the manner predicted on the basis of the F strain concept of Brown and coworkers. The magnitude of these effects, however, was considerably smaller than observed previously with trimethylboron as the reference acid. The source of these differences together with some anomalous results obtained are discussed and suggested reaction schemes presented.

Brown and co-workers in a series of investigations have shown that the relative base strengths of alkylpyridines depend on the structure of the reference acid.[3–5] The basicity towards proton increases with alkyl group substitutions on the pyridine ring, as one would predict from simple inductive effects. On the other hand, as the "steric requirements" of the reference acid (Lewis acid) increase, the order of the observed relative base strengths of the alkylpyridines is different than for protonic acids. The basicity of the alkylpyridines depends on the size and position of the alkyl groups. One of the most dramatic examples cited is that of 2,6-lutidine (2,6-dimethylpyridine). Although a strong base for protonic acid ($-\Delta H = 19.5$ kcal./mole for CH_3SO_3H), a very low heat of reaction was observed with trimethylboron.[3,4]

This result has been interpreted by Brown and coworkers to be due to the steric repulsion of the alkyl groups of the reference acid and the alkyl groups surrounding the nitrogen atom of the pyridine ring. This type of contribution of steric factors to chemical reactivity has been called F strain.[3] Due in large measure to the work of Brown and co-workers, an excellent fund of data is now available on the influence of steric strain in the reactions of hindered nitrogen bases with alkylboron compounds. In contrast, very little is known of the contribution of steric factors to the reactivity of hindered nitrogen bases with other structurally related organometallic compounds, in particular with trialkylaluminum.

In this present study, we have measured the heats of reaction of various alkylpyridines with triethylaluminum. One objective of this work has been to compare the importance of F strain in the chemical reactivity of alkylpyridines as the central atom of the reference acid was changed from boron to aluminum.

Experimental

Materials.—Normal decane was chosen as the solvent for these reactions because of its low vapor pressure at room temperature. A practical grade of normal decane was rapidly stirred with concentrated sulfuric acid (3 l. of decane/1 l. of concentrated sulfuric acid) for several days at room temperature. The ultraviolet spectrum of the decane was scanned to detect residual unsaturation (250–290 mμ). When no ultraviolet absorption was detected, the decane layer was separated, washed twice with dilute potassium hydroxide followed by three washings with distilled water. The n-decane was then dried with anhydrous calcium sulfate and finally stored over calcium hydride. The decane was purged with nitrogen and stored in a nitrogen atmosphere.[5b] The middle third (b.p. 115.2°, lit. b.p. 115.3°, n^{20}_{D} 1.5090, lit. b.p. 1.5092) was collected and stored over calcium hydride. The 2,6-dimethylpyridine (99% pure from Matheson, Coleman and Bell) was distilled from potassium hydroxide through a 12-in. Vigreux column under a reduced nitrogen pressure. The middle third (n^{20}_{D} 1.4967) was collected and stored over calcium hydride. The 2-methyl-6-ethylpyridine, 2-methyl-6-n-propylpyridine, and 2-methyl-6-isobutylpyridine were obtained as pure research samples from Reilly Tar and Chemical Company. Before use, they were stored over calcium hydride. The triethylaluminum was obtained from the Ethyl Corporation. According to their analysis, this sample was 97.5% by weight triethylaluminum (minimum), the remainder being primarily butylaluminum compounds. All handling of the triethylaluminum was carried out under a protective blanket of dry nitrogen. All of the equipment used in preparing the triethylaluminum solutions in n-decane was rigorously dried.

Colorimetric Procedure.—The calorimeter and technique used for measuring the heats of reaction was similar to that described by Brown and Horowitz.[6] Because of a slight difference in the geometry of the mixing chamber, we used 100 g. of mercury to provide the seal between the storage chambers. Thirty milliliters each of the 0.1 M solutions of the reagents were used in these experiments. All of these measurements were made at 27.4 ± 0.02°.

Even after completion of the reaction, care was taken to avoid oxidation of the triethylaluminum. After completion of the run, the solution and mercury were drawn out under vacuum. The calorimeter was then rinsed with cyclohexane, disassembled, washed, and dried.

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[2] From the thesis of S. Liebman submitted in partial fulfillment of the requirements for the degree of Master of Science, College of Arts and Sciences, American University, 1960.

[3] H. C. Brown, *Rec. Chem. Progr.*, **14**, No. 2 (1953).

[4] H. C. Brown and X. R. Miehm, *J. Am. Chem. Soc.*, **77**, 1723 (1955).

[5] (a) H. C. Brown and D. Gintis, *ibid.*, **78**, 5378 (1958). (b) NOTE ADDED IN PROOF.—Pyridine (Fisher reagent grade) was distilled from potassium hydroxide in a nitrogen atmosphere through a 24-in. column packed with glass beads.

[6] H. C. Brown and R. H. Horowitz, *J. Am. Chem. Soc.*, **77**, 1730 (1955).

As Brown and Horowitz described, the heating and cooling curve for the chemical reaction was reproduced electrically as closely as possible. The electrical energy input was determined by measuring the drop in potential across the heating element and across a standard 0.1-ohm resistor (on loan from the National Bureau of Standards) connected in series. The heating element consisted of a 12-in. Manganin wire threaded on a Teflon rod. Strips of 12-gage copper wire strapped to the sides of the heating element reduced current loss. The power supply consisted of a 12-v. storage battery connected to a variable resistor to attenuate the current flow. Voltage changes in the bridge circuit were measured on a standard potentiometer.

The heat capacity of the total system was determined for several temperature changes, corresponding to those observed chemically.

TABLE I

HEAT CAPACITY OF CALORIMETER SYSTEM[a]

ΔT Temp., °C[b]	Voltage drop across heating element	Voltage drop across standard resistor	Watts consumed	Time, sec.	Joules consumed	Cp, cal./°C.
1.60	1.3680	0.2507	3.430	110.6	379.4	56.6
1.18	1.3681	0.2508	3.431	80.4	275.9	55.9
0.94	1.3605	0.2471	3.362	66.5	223.6	56.8
0.74	1.3615	0.2470	3.363	51.1	171.8	55.5
						Av. = 56.2 ± 0.5

[a] Containing 100 g. of Hg, 30 ml. each of 0.1 N Et_3Al and pyridine. [b] ΔT on dilution for Et_3Al was found to be 0.04°. This may have been due to trace impurities in the decane.

The observed heats of reaction were calculated from the expression $-\Delta H$ (cal./mole) = 33.33 (ΔT_{cor}) Cp/N, where ΔT is the corrected temperature rise observed, Cp is the heat capacity of the system, N is the molarity of the base solution, and the factor 33.33 arises from the use of 30 ml. of solution.

For the most part, the temperature–time curves for the reaction of pyridine and its derivatives with triethylaluminum were typical of rapid reactions which go to completion. Estimation of the temperature rise was made by standard procedures.[7]

Results

Pitzer and Gutowsky[8] have measured the molal freezing point depression of triethylaluminum in benzene. Their data indicated that triethylaluminum was largely dimeric at low temperatures (*ca.* 90%). In the earlier studies of Laubengayer and Gilliam,[9] triethylaluminum was found to be 12% associated even at 150°. Unfortunately, partial decomposition of the triethylaluminum at these high temperatures precluded the precise determination of the heat of dissociation. Further, no equilibrium data are available for triethylaluminum at lower temperatures.

In this present work, the triethylaluminum was clearly dimeric to a large degree. Lacking a value for the heat of dissociation of the triethylaluminum, the data are presented simply in terms of the observed heats of reaction under a variety or conditions. These results are shown in Table II.

TABLE II

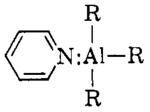
HEATS OF REACTION OF $(Et_3Al)_2$ WITH ALKYLPYRIDINES

Base[a]		ΔT_{cor}, °C.			$-\Delta H$, kcal./mole[b]	
R_3Al, moles/liter:	0.1	0.2	0.3	0.1	0.2	0.3
Pyridine	1.13	1.63	1.65	21.2	30.5	30.9
2,6-Dimethylpyridine	0.96	1.22	...	18.0	22.9	..
2-Methyl-6-ethylpyridine	0.73	0.98	...	13.7	18.4	..
2-Methyl-6-*n*-propylpyridine	0.73	0.98	...	13.7	18.4	..
2-Methyl-6-isobutylpyridine	0.73	0.98	...	13.7	18.4	..

[a] 0.1 molar in decane; ΔT did not change as base concentration was increased over concentration of R_3Al. [b] Based on concentration of base.

Discussion

A. F Strain in 1 : 1 Molecular Addition Compounds.—The heats of reaction with excess base were identical to those observed with equimolar concentrations of base and acid (Table II). This was the expected result for the formation of a 1:1 molecular addition compound of the following type.

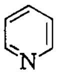
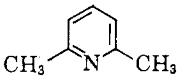


The observed heat of reaction with equimolar amounts of pyridine and triethylaluminum is in fair agreement with that obtained by Bonitz[10] ($-\Delta H$ = 19.4 kcal.).

The observed heats of reaction indicate that *alkyl substituents on the pyridine ring influence the stability of the triethylaluminum–alkylpyridine molecular addition compounds in qualitatively the manner predicted on the basis of the F strain concept of Brown and co-workers.* The contribution of "F strain" to the reactivity of alkylpyridines, however, is substantially less with triethylaluminum than with trimethylboron. Thus, the reader will note in Table III, there was observed a difference of only 3 kcal./mole between the heat of reaction of triethylaluminum with pyridine and 2,6-dimethylpyridine. This is contrasted to the results with trimethylboron; although it formed a stable addition compound with pyridine (15.3 kcal./mole), it showed almost no reaction with 2,6-dimethylpyridine.[3] Since the triethylaluminum molecule is considerably larger than the trimethylboron molecule, this result may seem puzzling. It has been observed, for example, that F strain is considerably greater in the reactions of tri-*t*-butylboron compared to trimethylboron.[11] One might, therefore, have expected the larger triethylaluminum molecule to experience the greater "steric hindrance" to reaction.

TABLE III

RELATIVE STRENGTHS OF PYRIDINE BASES

		
$-\Delta H$,[a] BMe_3[3,4]	15.3	0
$-\Delta H$,[a,b] $AlEt_3$	21.2[b]	18[b]

[a] Kcal./mole. [b] $-\Delta H$ on a comparative basis should be increased by ΔH of dissociation of dimeric $(R_3Al)_2$.

A consideration of the molecular models of addition compounds of triethylaluminum and trimethylboron with 2,6-dimethylpyridine suggests a plausible explanation. Skeletal models of the addition compounds have been drawn using observed and calculated interatomic distances, and are shown in Fig. 1. For the purpose of discussion, the most stable conformation of the 2,6-dimethylpyridine–triethylaluminum addition compound

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[7] R. Livingston, "Physico Chemical Experiments," Macmillan Co., New York, N. Y., 1948, p. 124.

[8] K. S. Pitzer and H. S. Gutowsky, *J. Am. Chem. Soc.*, **68**, 2204 (1946).

[9] A. W. Laubengayer and W. F. Gilliam, *ibid.*, **63**, 478 (1941).

[10] E. Bonitz, *Ber.*, **88**, 742 (1955).

[11] H. C. Brown, *J. Am. Chem. Soc.*, **67**, 1452 (1945).

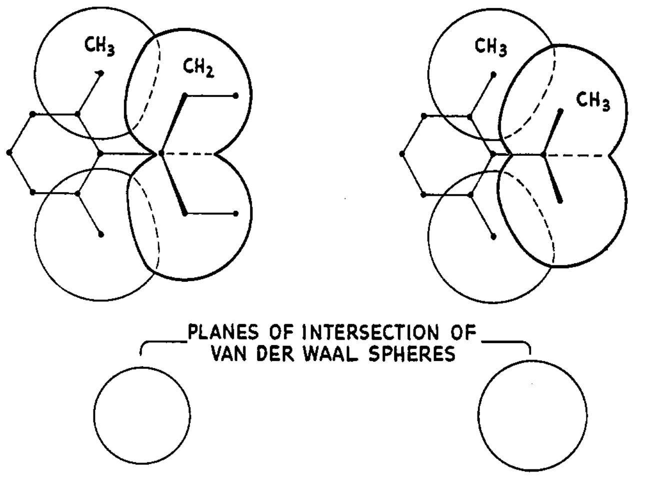


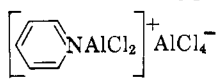
Fig. 1.[12]—F strain in 1:1 molecular addition compounds of 2,6-lutidine with triethylaluminum and trimethylboron. Scale: 1 cm. = 2.5 Å

has been chosen in which the ethyl groups on the aluminum atom are folded back away from the reaction center, and in which two of the ethyl groups lie equidistant above the plane of the alkylpyridine ring. Nonbonded alkyl group interaction has been indicated by constructing Van der Waal spheres, using the value of 2.0 Å. for the Van der Waal radii of methyl and methylene groups.[12e]

A relative measure of the steric strain in the two structures may be obtained by comparing the depth of penetration of the Van der Waal spheres. The greater steric strain in trimethylboron-2,6-dimethylpyridine model is apparent.[13] *Owing to the larger tetrahedral covalent radius of aluminum compared to boron (43% larger), the aluminum nitrogen bond may be established at a distance which does not require so severe an interpenetration of the alkyl groups surrounding the reaction center.* On this basis, F strain should generally be of less consequence in the reactions of hindered nitrogen bases with alkylaluminum compounds than with the corresponding alkylboron compounds.

Changing one of the substituents on the pyridine ring from methyl to ethyl caused a further drop in the heat of reaction with triethylaluminum (Table II); the heat of reaction, nevertheless, was still substantial (13.7 kcal./mole). It is interesting to note that further changes in the structure of one of the substituents from ethyl, to *n*-propyl, to isobutyl, did not affect materially the stability of the addition compounds formed with triethylaluminum. From the heats of reaction with unsubstituted pyridine, it is also apparent that triethylaluminum is a much stronger acid than trimethylboron.

B. Reactions with Excess Triethylaluminum.—As the concentration of triethylaluminum was increased, the heat of reaction increased. Above 2:1 moles of acid per mole of base, the heat of reaction remained constant (col. 2 and 3, Table II). Apparently, in excess triethylaluminum a structure is involved which contains two molecules of triethylaluminum and one molecule of base. Brown has suggested that in excess triethylaluminum perhaps only half of the bridged dimer structure is opened.[14] From the data obtained with pyridine in excess triethylaluminum, we estimate that the dissociation energy of dimeric triethylaluminum is in excess of 10 kcal./mole. The same order of basicity is observed with excess triethylaluminum, but surprisingly, the effect of ring substitution on the base strength of alkylpyridine appears greater for a 2:1 mole ratio of triethylaluminum to base. The difference in the heat of reaction of pyridine and 2,6-dimethylpyridine with equimolar amounts of triethylaluminum is about 3.2 kcal. While in excess triethylaluminum, the difference is 7.6 kcal. Apparently, whatever structure is involved in excess triethylaluminum, it is more sensitive to alkyl substituents on the pyridine ring.

The possibility of ionic structures of the type  analogous to the  suggested by Bax, *et al.*,[15] to explain the partial conduction of benzene solutions of pyridine and aluminum chloride were also considered. But this does not appear likely since conductometric titrations of pyridine in benzene solution with triethylaluminum showed a rise in conduction up to a 1:1 molar ratio of each. Further addition of triethylaluminum did not alter the conduction significantly (the maximum conduction of 0.2 molar solution in benzene was 2×10^{-7} ohm^{-1} cm.$^{-1}$).[16] Bonitz also did not find evidence for a stable 2:1 R_3Al-pyridine reaction product based on his conductivity studies.[10,17] Ultraviolet[15] and infrared[18] spectral studies of the pyridine–triethylaluminum system have also failed to demonstrate the existence of a stable species containing two molecules of triethylaluminum.

The nature of the reaction product formed in excess triethylaluminum and responsible for the high heat of reaction observed remains uncertain. The data at present, however, are most consistent with the suggestion that in excess triethylaluminum only half of the bridged dimer structure of the triethylaluminum is opened up by the base to produce an un-ionized intermediate structure.

Acknowledgment.—The authors acknowledge the cooperation of the Research Division of W. R. Grace

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(12) The following premises were used in constructing Fig. 1: (a) Boron and aluminum would use sp^3 hybridized orbitals in bonding in these compounds. (b) The tetrahedral covalent radii for boron and aluminum were taken as 0.88 and 1.26, respectively (L. Pauling, "Nature of the Chemical Bond," Cornell University Press, Ithaca, N. Y., p. 179). (c) The bond lengths were calculated on the basis of simple additivity of covalent radii. (d) The radius of the nitrogen atom used in calculating the N-Al and N-B interatomic distance was taken as 0.65 Å. (intermediate between a single and double bond in character); These bonds were further shortened by 0.02 Å. each because of the formal charge placed on the nitrogen (L. Pauling, *ibid.*, p. 169). (e) The Van der Waal radii (nonbonded radii) of methyl and methylene groups used was 2.0 Å. (L. Pauling, *ibid.*, p. 190). (f) For simplicity, the pyridine ring was assumed identical in shape to the benzene ring; hydrogen atoms are not shown in the skeletal models; alkyl groups below the plane of the pyridine ring are not shown.

(13) The penetration of the Van der Waal spheres in the model of the triethylaluminum-2,6-dimethylpyridine compound in Fig. 1 is about the same as that obtained for nonbonded methyl–methyl interaction in a model of durene.

(14) H. C. Brown, personal communication.

(15) C. M. Bax, A. R. Katritzky, and L. E. Sutton, *Proc. Chem. Soc.* (London), 5 (1958).

(16) D. F. Hoeg, unpublished results.

(17) The origin of the partial conduction of R_3Al-pyridine systems has been the subject of some speculation. Bonitz has suggested that heterolysis of the aluminum–carbon bond is the ion-forming reaction. It has also been suggested that alkyl group migration to the ring may occur, but we have found no evidence of this. Only unsubstituted pyridine was isolated from the hydrolyzed reaction product of pyridine and triethylaluminum at 120° for 2 hr.

(18) J. Woodbrey and R. Chadha, private communication.

and Company in providing the facilities for this research. They also acknowledge helpful discussions of this work with Drs. F. X. Werber, A. D. Ketley, and R. H. Horowitz and the valuable assistance of Mr. G. Fulmer in solving several problems in the electrical circuitry. They also express their appreciation to Professors M. L. Bender and H. C. Brown for several valuable suggestions.

Lethargic Reactions. I. The Preparation of Hindered Oximes

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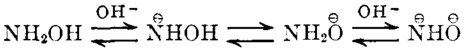
The combination of prolonged reaction times (one to six months at room temperature) and a strongly basic catalyst (potassium *tert*-amylate in *tert*-amyl alcohol) permitted the preparation of hindered oximes in nearly quantitative yields. The high yields are surprising in view of the fact that up to a few years ago the ketoximes were considered to be incapable of direct synthesis from the hindered ketones. Among the hindered ketoximes synthesized was 2,3,4,6-tetramethylacetophenone oxime, the preparation of which was claimed by Claus in 1887 and disputed by Meyer in 1896. Resolution of this dispute is attempted. Any reaction which necessitates prolonged reaction times and which cannot be forced by increasing the temperature is defined as a "lethargic reaction." The term is coined to draw attention to the potentialities of these conditions.

The oximation of hindered ketones, previously believed to be incapable of oximation,[2] was accomplished when it was discovered that a very slow reaction occurred at room temperature.[3] The reaction was so slow that several months' standing was necessary to bring about detectable oximation. At best the yields were low, and it was obvious that a more powerul reagent was needed to increase the yields to a range satisfactory for synthetic use.

The anion of hydroxylamine seemed to be the reagent of choice which possibly could react through the dianion if the medium were alkaline enough.



$$\mathrm{NH_2OH} \underset{}{\overset{\mathrm{OH^-}}{\rightleftharpoons}} \overset{\ominus}{\mathrm{N}}\mathrm{HOH} \rightleftharpoons \mathrm{NH_2}\overset{\ominus}{\mathrm{O}} \overset{\mathrm{OH^-}}{\rightleftharpoons} \overset{\ominus}{\mathrm{N}}\mathrm{H}\overset{\ominus}{\mathrm{O}}$$

I II III IV

Combining the long reaction time with a strongly basic medium (potassium *tert*-amylate in *tert*-amyl alcohol), it was found that the oximation of hindered ketones could be brought about in almost quantitative yields as shown in Table I.

TABLE I

Acetophenone (or ketone)	Time, days	Crude yield of oxime, %
2,4,6-Trimethyl-	32	98
	10	53
2,3,4,6-Tetramethyl-	180	90
	10	30
Pentamethyl-	420	81
2,6-Dimethyl-4-*tert*-butyl-	180	95
Benzoylmesitylene	450	16

From the results of Table I, there can be no doubt that the combination of prolonged standing at room temperature and of the use of a strongly basic medium has succeeded in elevating the yields of hindered ketone oximes to satisfactory values. Two other methods of making hindered oximes are available: oximation at very high pressures[4] and oximation of the corresponding imino ketone,[5] but the lethargic method is recommended because of its simplicity and general applicability.

Attempts to oximate the hindered ketones in the strongly basic medium at reflux temperatures of *tert*-amyl alcohol gave appreciable amounts of ketoxime (*ca.* 50%), but the yields could not be raised beyond this figure. The relatively low yields were attributed to the incursion of a competing side reaction at the elevated temperatures, namely the decomposition of hydroxylamine to ammonia, water, and other products.[6]

The attacking species was surmised to be II (and III)[7] rather than IV (see Experimental). IV possibly could be made in a more basic medium, but no attempt was made at this time to prepare IV.

Conditions were now at hand to settle a bitter controversy that began in 1887. Claus[8] claimed that he had made the oxime of 2,3,4,6-tetramethylacetophenone and used this fact and others to criticize the steric hindrance theory of Meyer. In the words of Claus the more precisely and carefully one attempted to abide by Meyer's rule, the more the rule had to be explained and expanded. In a crushing paper Meyer[9] countered with the statement that he had attempted to duplicate Claus' work on the oxime of the above compound, that one of his colleagues had attempted to do so and that neither could repeat a single result. In Meyer's words, the results were "ganz unverstandlich." Meyer's statement seemed to have settled the matter and cast a stigma on Claus' work, for we read later in the obituary of Claus[10] that experimental errors are to be found in the work of Claus but "who among us does not err."

The question remains some sixty years later: Did Claus make the oxime of 2,3,4,6-tetramethylacetophenone or did he not? Obviously, the new conditions permitted an easy synthesis of the oxime, and compari-

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[1] M.S. thesis, "Oximes of 2,4,6-Tri- and 2,3,4,6-Tetramethylacetophenones," Vanderbilt University, 1959.

[2] R. G. Kadesch, *J. Am. Chem. Soc.*, **66**, 1207 (1944).

[3] Frances Greer and D. E. Pearson, *ibid.*, **77**, 6649 (1955).

[4] W. H. Jones, E. W. Tristram, and W. F. Benning, *ibid.*, **81**, 2151 (1959).

[5] C. R. Hauser and D. S. Hoffenberg, *ibid.*, **77**, 4885 (1955).

[6] For comments on instability: J. S. Fritz, S. S. Yamamura, and E. C. Bradford, *Anal. Chem.*, **31**, 260 (1959).

[7] This intermediate in alkaline solution has been proposed by E. Barrett and A. Lapworth, *J. Chem. Soc.*, 85 (1908).

[8] A. Claus and C. Foecking, *Ber.*, **20**, 3097 (1887).

[9] V. Meyer, *Ber.*, **29**, 830 (1896).

[10] G. N. Vis, *J. prakt. Chem.*, [2] **62**, 127 (1900).