[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF PURDUE UNIVERSITY]

Steric Effects in Displacement Reactions. IV. Heats of Reaction of Methanesulfonic Acid with the Monoalkylpyridines

BY HERBERT C. BROWN AND ROBERT R. HOLMES[1,2]

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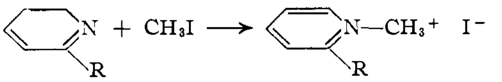
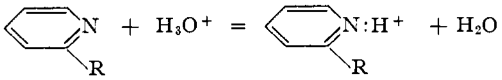
The heats of reaction of the pyridine bases with methanesulfonic acid in nitrobenzene solution were measured calorimetrically: RC_5H_4N(soln.) + CH_3SO_3H(soln.) = $RC_5H_4NH^+ {}^-O_3SCH_3$(soln.). In the case of pyridine the heat of reaction is 17.1 kcal./mole. Introduction of a methyl group in the 2- or 4-position increases the heats of reaction by about 1.2 kcal./mole. In the 3-position the increase is less, 0.7 kcal./mole. Change in the structure of the alkyl substituent (ethyl, isopropyl and *t*-butyl) has little effect in the 3- or 4-position over that observed with methyl. In the 2-position there is observed a slight decrease in the heat of reaction with increasing bulk of the 2-substituent. The heat of reaction for 2-picoline is 18.3 and for 2,6-lutidine, 19.5. Thus the first methyl group results in an increase in the heat of reaction of 1.2 kcal./mole and the second methyl group has an identical effect. It is concluded that steric effects are not important in this reaction. Plots of log k_2 and ΔE_{act} for the reaction of methyl iodide with the pyridine bases against ΔH for the reaction of these bases with methanesulfonic acid do not yield simple linear relationships including the 2-alkyl derivatives. On the other hand, a plot of ΔH for the methanesulfonic acid reaction *versus* pK_a does give an excellent linear relationship for all of the bases. It is concluded that to obtain a linear plot of this kind for two reactions (rates or equilibria) involving reactants of high steric requirements it is essential that the steric requirements of the two reactions be quite similar.

In the previous paper it was pointed out that a plot of log k_2 or E_{act} for the reaction of the alkylpyridines with methyl iodide *versus* pK_a did not yield a linear relationship.[3] In particular the 2-alkylpyridines deviated considerably from a linear plot which included pyridine and the 3- and 4-alkylpyridines. Moreover, it was observed that the deviation of the 2-alkylpyridines from the linear plot increased in the series: methyl < ethyl < isopropyl < *t*-butyl.

It was considered that these deviations are probably due to steric strains in the activated complex, steric strains which arise from the conflicting steric requirements of the 2-alkyl groups in the pyridine base with those of the methyl group of the alkyl iodide. Such steric strains are presumably largely absent in the reactions of these pyridine bases with the proton in aqueous solution.



Reaction with large steric requirements



Reaction with small steric requirements

It was apparent that solvation effects offered a possible difficulty in the interpretation of the results. The reactions with methyl iodide were carried out in nitrobenzene as solvent. The pK_a values were measured in water. It has been suggested that steric hindrance to solvation of ions with bulky *ortho* substituents can play an important role in acid–base equilibria.[4] It therefore appeared desirable to measure the base strengths of the pyridine bases in the same solvent as that used for the alkyl iodide reactions, namely, nitrobenzene.

After careful consideration of the different complications which can arise in studies of acid–base strength in non-aqueous systems,[5] it was decided to measure in nitrobenzene solution the heat of reaction of these pyridine bases with a strong acid, methanesulfonic acid.

Results

A calorimeter which had been developed for measuring the heats of reaction of the pyridine bases with boron trifluoride[6] was utilized. In this calorimeter equal volumes of solutions of the pyridine base and of the methanesulfonic acid are mixed to give the product. The latter is soluble in the reaction solvent. Consequently the heat evolved is attributed to the reaction

$$RC_5H_4N(\text{soln.}) + CH_3SO_3H(\text{soln.}) = RC_5H_4NH^+ \; {}^-O_3SCH_3(\text{soln.})$$

A study was made of the effect of the relative molar quantity of pyridine base to methanesulfonic acid on the over-all heat of reaction. With methanesulfonic acid held constant at 0.09595 *M*, the concentration of 2-picoline was varied from 0.1274 to 0.2489 *M*. Thus the ratio, *R*, of the 2-picoline present to the methanesulfonic acid present varied from 1.33 to 2.59. Yet the observed heat of reaction was sensibly constant, 18.27 ± 0.18 (Table I). Evidently there is no interaction of the excess pyridine base with the product.

TABLE I

HEAT OF REACTION OF METHANESULFONIC ACID WITH EXCESS 2-PICOLINE

Methanesulfonic acid, *M*	2-Picoline, *M*	R^a	Heat of reaction[b] $-\Delta H$, kcal./mole
0.09595	0.1274	1.33	18.19
.09595	.1593	1.66	18.08
.09595	.2489	2.59	18.54

[a] *M*(2-picoline)/*M*(methanesulfonic acid). [b] Based on methanesulfonic acid.

The concentration of the reactants was varied from 0.07272 to 0.1894 *M* (methanesulfonic acid,

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[1] Based upon a thesis submitted by Robert R. Holmes in August, 1953, in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

[2] Research Fellow at Purdue University, 1951, under a contract with the Office of Naval Research for the study of "Steric Strains in Chemical Reactions."

[3] H. C. Brown and X. R. Mihm, THIS JOURNAL, **77**, 1723 (1955).

[4] P. D. Bartlett, M. Roha and R. M. Stiles, *ibid.*, **76**, 2349 (1954).

[5] M. M. Davies and H. B. Hetzer, *J. Research Natl. Bur. Standards*, **48**, 381 (1952), and additional papers by M. M. Davies and her co-workers in the same journal; M. M. Davies, THIS JOURNAL, **71**, 3544 (1949).

[6] H. C. Brown and R. H. Horowitz, *ibid.*, **77**, 1730 (1955).

with 2-picoline in excess), but the heat of reaction was not noticeably affected. If the product were only partially ionized, variation of the concentration would have been expected to change the degree of dissociation and alter the observed heat of reaction. The data are summarized in Table II.

TABLE II

EFFECT OF CONCENTRATION ON THE HEAT OF REACTION OF METHANESULFONIC ACID WITH 2-PICOLINE

Methanesulfonic acid, M	2-Picoline, M	Heat of reaction[a] $-\Delta H$, kcal./mole
0.07272	0.09300	18.44
.1212	.1550	18.35
.1212	.1550	18.41
.1515	.1938	18.41
.1894	.2422	18.31

[a] Based on methanesulfonic acid.

Similar experiments were tried in which the 2-picoline was held in constant controlled amounts while the methanesulfonic acid was varied from a slight excess to a large excess. In this case the heat of reaction did not remain constant, but increased with increasing amounts of excess acid. This behavior is not unique with 2-picoline since a similar increase in the heat of reaction with increasing acid was observed with 2-isopropylpyridine. The data for 2-picoline are summarized in Table III.

TABLE III

HEAT OF REACTION OF 2-PICOLINE WITH EXCESS METHANESULFONIC ACID

Methanesulfonic acid, M	2-Picoline, M	R[a]	Heat of reaction[b] $-\Delta H$, kcal./mole
0.08966	0.07743	1.16	18.80
.1041	.07743	1.34	20.04
.1301	.07743	1.68	21.85
.1554	.07765	2.00	23.46
.1943	.07765	2.50	24.73
.2573	.08594	2.99	25.35
.3216	.08594	3.74	26.31
.4020	.08594	4.68	26.63

[a] M(methanesulfonic acid)/M(2-picoline). [b] Based on 2-picoline.

The increase in the heat of reaction from $R = 1$ to $R = 2$ is linear suggesting that there is a 2:1 compound formed between methanesulfonic acid and 2-picoline. Such a compound would presumably have the structure: $2\text{-}CH_3C_5H_4NH^+\ CH_3SO_3^-\text{---}HO_3SCH_3$. With additional methanesulfonic acid the increase in the heat of reaction is more gradual and apparently approaches a limiting value. Presumably this latter effect is due to solvation of the 2:1 compound by additional methanesulfonic acid.

TABLE IV

MOLAR HEATS OF REACTION OF METHANESULFONIC ACID WITH ALKYL PYRIDINES

Pyridine base RC_5H_4N, R-	Heats of reaction, $-\Delta H$ (kcal./mole) position of substituent 2-	3-	4-
Hydrogen	17.1	17.1	17.1
Methyl	18.3	17.8	18.4
Ethyl	18.2	18.1	18.3
Isopropyl	18.1	18.0	18.4
t-Butyl	18.0	18.2	18.3
2,6-Lutidine	19.5		

In view of these results, the heats of reactions were measured with the pyridine bases in slight excess. The final values for the molar heats of reaction of methanesulfonic acid with the pyridine bases in nitrobenzene are summarized in Table IV.

Discussion

The introduction of an alkyl group in the 4-position results in an increase in the heat of reaction of 1.2–1.3 kcal. Change of the structure of the alkyl group from methyl to *t*-butyl has no noticeable effect upon the increase—it is essentially constant at 1.25 ± 0.05 kcal./mole.

An alkyl group in the 3-position has a somewhat smaller effect, and there is evident a tendency toward increasing values of the heat of reaction with increasing size of the alkyl group.

These changes are quite similar to those observed in the pK_a values.[3] As before, these phenomena suggest that there are relatively small differences in the inductive and hyperconjugative properties of the four alkyl groups in this system. In the 3-position the inductive effect alone operates, so that the observed order is $t\text{-Bu} > i\text{-Pr} > \text{Et} > \text{Me} >> \text{H}$. In the 4-position the changes in inductive and hyperconjugative effects with increasing size of the alkyl group oppose and largely cancel.

A methyl group in the 2-position results in an increase in the heat of reaction of 1.2 kcal./mole. A second methyl group in 2,6-lutidine results in the identical further increase of 1.2 kcal. This observation suggests that steric hindrance to solvation cannot be significant in the 2-methyl derivatives.

With increasing size of the alkyl group there is observed a decrease in the heat of reaction from 18.3 for 2-picoline to 18.0 for 2-*t*-butylpyridine. This decrease might be the result of steric hindrance to solvation by the larger alkyl groups. However, in view of the fact that no evidence for this effect is observed in 2,6-lutidine, this explanation cannot be considered entirely satisfactory and the phenomenon should receive further consideration.

Plots of the activation energy or of the logarithm of the rate constants for the reactions of these pyridine bases with methyl iodide[7] *versus* the heats of reaction of these bases with methanesulfonic acid are shown in Figs. 1 and 2. A rough linear relationship is observed for pyridine, 3- and 4-alkylpyridines. However, the 2-alkylpyridines deviate from the linear plot with the deviation increasing with increasing steric requirements of the 2-substituent. The plots are quite similar to those involving the pK_a values of the pyridine bases.[3] Consequently it must be concluded that the failure to obtain linear plots between the rate data and the pK_a values is not a result of the vast difference in the solvents used for the respective reactions. The same phenomena are observed in plots in which the base strengths were measured in the same solvent as that used in the methyl iodide reactions.

Indeed a plot of the heat of reaction of the pyridine bases with methanesulfonic acid against the pK_a values exhibits an excellent linear relationship (Fig. 3). The existence of this linear relationship suggests either that solvent effects (including steric

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(7) H. C. Brown and A. Cahn, THIS JOURNAL, **77**, 1715 (1955).

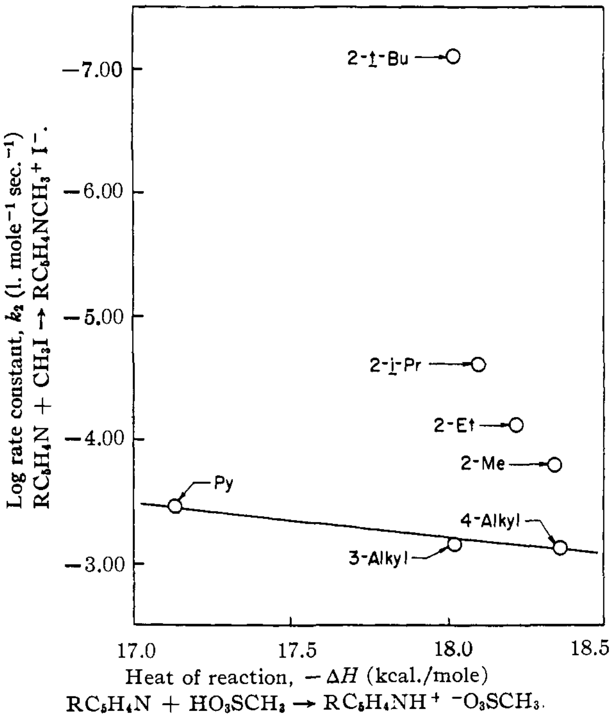

Fig. 1.—Relationship between the logarithm of the rate constants for the reactions of methyl iodide with the pyridine bases (25°) and their heats of reaction with methanesulfonic acid.

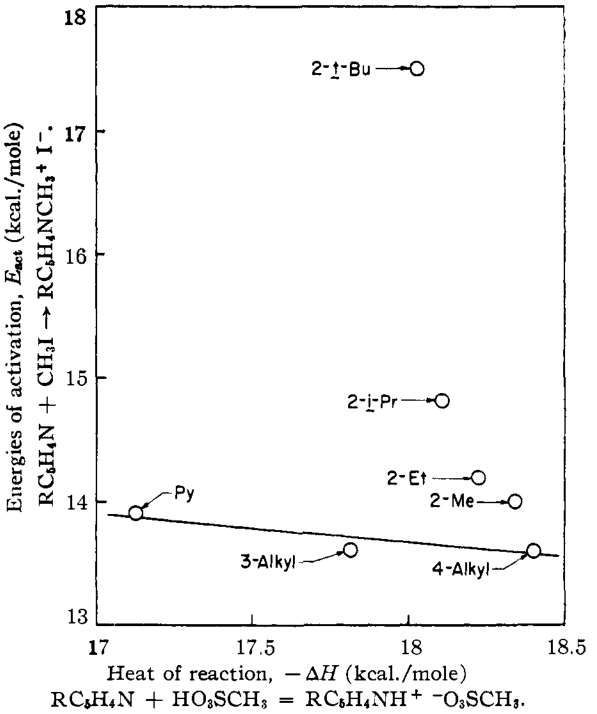

Fig. 2.—Relationship between the energies of activation for the reactions of methyl iodide with the pyridine bases and their heats of reaction with methanesulfonic acid.

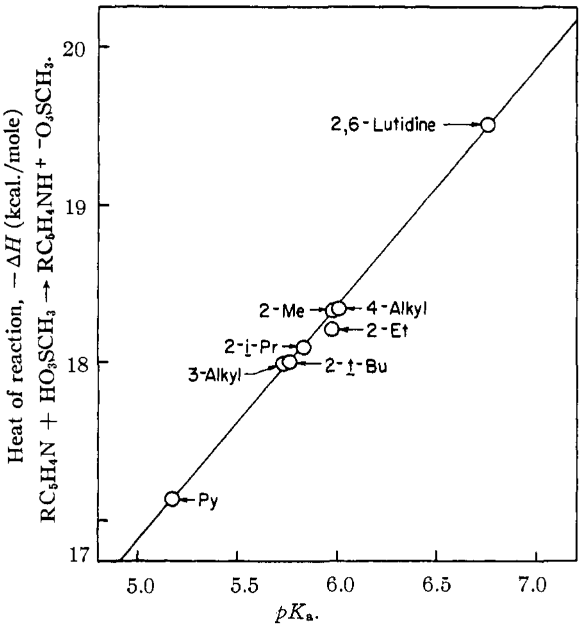

Fig. 3.—Relationship between the heat of reactions of the pyridine bases with methanesulfonic acid and their pK_a values.

hindrance to solvation) must be sufficiently small as to be considered negligible, or that these solvent effects are practically identical in the two reactions under consideration. The latter assumption appears improbable in view of the vast difference in the characteristics of the two solvents, water and nitrobenzene. It is therefore concluded that solvent effects cannot be playing a very important role in determining the relative strengths of these pyridine bases.

Failure to observe a linear relationship between the rate data and the pK_a values is due not to the difference in the solvents used in the two reactions, but to the difference in the steric requirements of these reactions. In Fig. 3 the two reactions have the same steric requirements and a simple linear relationship is obtained. According to the interpretation, a linear relationship involving the rate data could be attained by measuring the strengths of the pyridine bases by a reference acid with steric requirements similar to those of methyl iodide. Examination of this possibility is reported in a subsequent paper.[8]

Experimental Part

Materials.—The pyridine bases were materials purified or prepared as described in earlier papers in this group.[3,7] In all cases the purities were established to be 99% or better by cooling curve studies.

Methanesulfonic acid (Standard Oil Co., Indiana) was fractionally distilled in an all-glass apparatus at pressures of less than 0.5 mm. The individual fractions were sealed in ampules without exposure to moisture. The weight % impurity content by acid titration was 0.5%; by freezing point curve it was 2.2 mole %.

Nitrobenzene (du Pont technical grade) was distilled at atmospheric pressure and then dried over calcium hydride. The cooling curve indicated an impurity content of 0.16 mole %.

Technique.—Measurements of the heats of reactions were made using mercury-well calorimeters developed for the study of the reaction of amines with Lewis acids. A complete description of the apparatus and procedure is contained in the following paper.[6]

Standard solutions of pyridine compounds and methane-

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[8] H. C. Brown and R. H. Horowitz, THIS JOURNAL, **77**, 1733 (1955).

sulfonic acid in nitrobenzene were made up with the aid of hypodermic syringes. The pyridine compound or methanesulfonic acid was drawn up into the syringe. This was weighed. Approximately the amount desired was transferred to a 250-ml. volumetric flask containing 200 ml. of nitrobenzene. The syringe and remaining contents were reweighed to obtain the precise amount transferred. The solution in the volumetric flask was then diluted to volume. These solutions were then transferred to the calorimeter by means of pipets, taking great precautions to minimize exposure to moisture.

The precision attained is indicated by the observed heats of reaction of methanesulfonic acid with 2-picoline in a series of eight different measurements: 18.44, 18.41, 18.35, 18.41, 18.31, 18.19, 18.08, 18.54 kcal./mole. These lead to the mean value of 18.34 ± 0.11 kcal./mole, reported as 18.3 kcal./mole in Table IV.

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Steric Effects in Displacement Reactions. V. The Heat of Reaction of Pyridine with Boron Trifluoride. A Convenient Calorimeter for Measuring the Heat of Formation of Molecular Addition Compounds

BY HERBERT C. BROWN AND RAYMOND H. HOROWITZ[1,2]

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A simple calorimeter has been developed for determining the heat of formation of molecular addition compounds in solution with an accuracy of 1%. The calorimeter has been applied to the determination in nitrobenzene of the heat of reaction of pyridine with boron trifluoride and with a number of addition compounds of boron trifluoride:

$$C_5H_5N(\text{soln.}) + BF_3(\text{soln.}) = C_5H_5N{:}BF_3(\text{soln.}) \quad -\Delta H = 25.0 \text{ kcal./mole}$$

$$C_5H_5N(\text{soln.}) + (CH_2)_5O{:}BF_3(\text{soln.}) = C_5H_5N{:}BF_3(\text{soln.}) + (CH_2)_5O(\text{soln.}) \quad -\Delta H = 12.2 \text{ kcal./mole}$$

It is convenient that the heat of the latter reaction is essentially independent of the concentration of the reactants over the range, 0.086 − 0.17 *M*. The heat of reaction increases to 14.1 and 15.9 kcal./mole for the corresponding addition compounds of ethyl and *n*-butyl ether. The heat of reaction of pyridine with benzonitrile-boron trifluoride and anisole–boron trifluoride are very similar to the value obtained with dissolved boron trifluoride, and it is concluded that these addition compounds must exist largely dissociated in the nitrobenzene solution.

The development of techniques for the precise determination of thermodynamic data for the dissociation of molecular addition compounds in the vapor phase has been described in earlier papers.[3] These techniques have been highly satisfactory in their application to the study of molecular addition compounds which exhibit a measurable dissociation in the vapor phase over a convenient temperature range.[4]

However, there exist many addition compounds which are either too stable or too unstable to be studied by this method. A calorimetric procedure which would permit the determination of the heats of formation in solution of molecular addition compounds which cannot be handled by the vapor phase technique should be very useful. Accordingly we decided to undertake the development of a simple calorimetric procedure which would permit the determination of the heats of formation with a precision of approximately 1%.

It was proposed to utilize the calorimeter for the estimation of the strains in selective series of addition compounds of pyridine bases containing bulky 2-alkyl substituents. These strains were to be compared with the strains estimated for the reactions of these pyridine bases with alkyl halides.[5] Since the data for the latter reactions were obtained with nitrobenzene as solvent, this substance was used also for the calorimeter studies.

The addition compound formed by pyridine and boron trifluoride is a compound of such low volatility that its study by vapor phase dissociation appears to offer major difficulties.[6] Moreover, the compound is very sensitive to moisture. Consequently, a study of the heat of formation of the compound was undertaken to provide a rigorous test of the proposed procedure.

Results and Discussion

The calorimeter which was finally developed consisted of a Dewar vessel in which there was a central receptacle which dipped into a small pool of mercury, thereby providing two compartments of equal volume for the solutions of the two reactants (Fig. 1). In the outer compartment there was placed a standard solution of pyridine in nitrobenzene; in the inner compartment, a solution of boron trifluoride in nitrobenzene or, preferably, a solution of tetrahydropyran–boron trifluoride in nitrobenzene. Since the concentration of the pyridine in the solution could be established with greater accuracy, the boron trifluoride component usually was used in excess.

The calorimeter was immersed in a water-bath at 24°. As soon as the thermometer in the central chamber reached the temperature of the water-bath, the air in the double wall of the vessel was pumped out to insulate the reaction chamber. The solutions were now allowed to react by raising and lowering the central reaction chamber at a standardized rate and observing the increase in temperature.

The solubility of boron trifluoride in nitrobenzene is relatively low. Such solutions fumed badly in the

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[1] Based upon a thesis submitted by Raymond H. Horowitz in January, 1951, in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

[2] Research Fellow at Purdue University, 1948–1951, under a contract with the Office of Naval Research for the study of "Steric Strains in Chemical Reactions."

[3] H. C. Brown, M. D. Taylor and M. Gerstein, THIS JOURNAL, **66**, 431 (1944); H. C. Brown and M. Gerstein, *ibid.*, **72**, 2923 (1950).

[4] H. C. Brown, H. Bartholomay, Jr., and M. D. Taylor, *ibid.*, **66**, 435 (1944); H. C. Brown and M. D. Taylor, *ibid.*, **69**, 1332 (1947); H. C. Brown and G. K. Barbaras, *ibid.*, **69**, 1137 (1947); **75**, 6 (1953).

[5] H. C. Brown and A. Cahn, *ibid.*, **77**, 1715 (1955).

[6] P. A. van der Meulen and H. A. Heller, *ibid.*, **54**, 4404 (1932).