

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF PURDUE UNIVERSITY]

**Steric Effects in Displacement Reactions. IX. Steric Strains in the Reactions of 2,6-Lutidine and 2,4,6-Collidine with Methyl Iodide and with Boron Trifluoride<sup>1</sup>**BY HERBERT C. BROWN, DANIEL GINTIS<sup>2</sup> AND HAROLD PODALL<sup>3,4</sup>

RECEIVED APRIL 11, 1956

Kinetic data have been obtained for the rates of reaction of methyl iodide with 2,6-lutidine and 2,4,6-collidine at several temperatures. Moreover, the heats of reaction of these bases with methanesulfonic acid and with tetrahydropyran-boron trifluoride have been determined. From the data the steric strains in 2,6-lutidine- and 2,4,6-collidine-boron trifluoride may be calculated and compared with the steric strains in the transition states for the methyl iodide reactions. The results do not follow the linear strain energy relationship which was demonstrated previously to hold for the monoalkylpyridines. The deviation is attributed to the large difference between the steric requirements of boron trifluoride in the addition compound and those of methyl iodide in the transition state. It is proposed that borane may be expected to yield an improved linear strain energy relationship which should hold for pyridine bases containing either one or two alkyl substituents in the *ortho* positions.

Study of the stabilities of molecular addition compounds has provided a fruitful tool for the investigation of steric effects.<sup>5-7</sup> A close similarity was noted in the effects of structural changes on the stability of molecular addition compounds<sup>7</sup> and on the rates of typical displacement reactions.<sup>8</sup> This similarity suggested that the study of molecular addition compounds might also provide a tool for investigating the importance of steric strains in the transition state on the rates of displacement reactions.

The rates of reaction of methyl iodide with a series of monoalkylpyridine bases<sup>9a</sup> could not be correlated with their base strengths.<sup>9b</sup> In such a comparison the 2-alkylpyridines exhibited deviations which increased in the order 2-Me < 2-Et < 2-*i*-Pr < 2-*t*-Bu, suggesting that the deviations were due to steric strains arising from the conflicting steric requirements of the 2-alkyl group and the methyl iodide molecule. The reaction rates could be correlated with the heats of reaction of boron trifluoride with these bases.<sup>9c</sup>

It was concluded that the existence of a linear relationship between the activation energy (or the log of the rate constant) for the reaction of methyl iodide with these monoalkylpyridines and their heats of reaction with boron trifluoride meant that the strain energies in the transition state and in the addition compound must be linearly related. The present investigation was undertaken to ascertain whether this linear relationship could be extended to pyridine bases containing two alkyl substituents in the *ortho* position. To this end we measured for 2,6-lutidine and 2,4,6-collidine the heats

of reaction with methanesulfonic acid, the heats of reaction with tetrahydropyran-boron trifluoride, and the rates of reaction with methyl iodide. The  $pK_a$  values for these bases have been previously reported.<sup>10</sup>

The heats of reaction of 2,6-lutidine and 2,4,6-collidine with tetrahydropyran-boron trifluoride and with methanesulfonic acid, both in nitrobenzene solution, were determined using the mercury-well calorimeter and the technique previously described.<sup>9d</sup> The results are summarized in Table I.

TABLE I

HEATS OF REACTION OF 2,6-LUTIDINE AND 2,4,6-COLLIDINE WITH BORON TRIFLUORIDE AND METHANESULFONIC ACID IN NITROBENZENE SOLUTION

Base used	Concn., <i>M</i>	THP: BF <sub>3</sub> , <sup>a</sup> <i>M</i>	CH <sub>3</sub> SO <sub>3</sub> H, <i>M</i>	Heat of reaction, -Δ <i>H</i> (kcal./mole)
2,6-Lutidine	0.179	0.284		4.75
	.171	.315		4.91
	.156	.210		4.68
	.179	.284		4.62
				4.74 ± 0.09
2,4,6-Collidine	0.200	0.249		5.64
	.200	.249		5.69
	.177	.209		5.81
	.177	.209		5.56
				5.68 ± 0.08
	0.1256		0.1012	20.72
.1256		.1012	20.73	
			20.73 ± 0.01	

<sup>a</sup> Tetrahydropyran-boron trifluoride.

The rates of reaction of 2,6-lutidine and of 2,4,6-collidine with methyl iodide in nitrobenzene were determined at three temperatures, using equal initial concentrations of the reactants. In the case of 2,6-lutidine it was noted that the methiodide was relatively insoluble and precipitated after 45% reaction at 70°. However, the precipitation did not appear to affect the kinetics, since identical rate constants were obtained both at 76% reaction and in the initial stages. The rates were relatively slow and some free iodine formation was encountered in the latter stages. In order to avoid these difficulties, the rate constants were based on kinetic data obtained in the first 30-40% of the reaction.

The reaction followed clean second-order kinetics. The results are summarized in Table II.

(10) H. C. Brown, S. Johnson and H. Podall, *ibid.*, **76**, 5556 (1954).

(1) Based upon theses submitted by Daniel Gintis and Harold Podall in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

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(5) H. C. Brown, H. Bartholomay, Jr., and M. D. Taylor, *THIS JOURNAL*, **66**, 435 (1944).

(6) H. C. Brown and G. K. Barbaras, *ibid.*, **69**, 1137 (1947).

(7) H. C. Brown and S. Sujishi, *ibid.*, **70**, 2878 (1948).

(8) H. C. Brown and N. R. Eldred, *ibid.*, **71**, 445 (1949).

(9) (a) H. C. Brown and A. Cahn, *ibid.*, **77**, 1715 (1955); (b) H. C. Brown and X. R. Mihm, *ibid.*, **77**, 1723 (1955); (c) H. C. Brown and R. R. Holmes, *ibid.*, **77**, 1727 (1955); (d) H. C. Brown and R. H. Horowitz, *ibid.*, **77**, 1730 (1955); (e) H. C. Brown and R. H. Horowitz, *ibid.*, **77**, 1733 (1955).

TABLE II  
RATE CONSTANTS FOR THE REACTION OF METHYL IODIDE  
WITH 2,6-LUTIDINE AND 2,4,6-COLLIDINE IN NITROBENZENE

Base	Rate constant, $k_2 \times 10^4$ , 1. mole <sup>-1</sup> sec. <sup>-1</sup>			$E_{act}$	Derived data log A $\Delta H^\ddagger$ $\Delta S^\ddagger$		
	40.07°	55.13°	70.28°		A	$\Delta H^\ddagger$	$\Delta S^\ddagger$
2,6-Lutidine	0.487	1.53	4.12	15.1	6.24	14.5	-32.2
2,4,6-Collidine	1.23	3.77	9.94	14.8	6.42	14.2	-31.4

### Discussion

For convenience in examining the results, the available data involving pyridine and the 2- and 2,6-alkyl derivatives are summarized in Table III.

TABLE III  
SUMMARY OF RATE AND EQUILIBRIUM DATA FOR REACTIONS  
INVOLVING THE PYRIDINE BASES

Substituent in pyridine base	Heat of reaction <sup>a</sup>		$\Delta H$	Rate data <sup>d</sup> for $k_2^{25^\circ}$ $\times 10^{-5b}$	$\text{CH}_3\text{I}$ $E_{act}^a$
	$pK_a^c$	$\text{CH}_3\text{SO}_3\text{H}^d$			
Hydrogen	5.17	17.1	32.9	34.3	13.9
4-Methyl	6.02	18.4	33.4	76.0	13.6
3-Methyl	5.68	17.8	33.2	71.2	13.6
2-Methyl	5.97	18.3	31.2	16.2	14.0
2-Ethyl	5.92 <sup>h</sup>	18.2	30.6	7.64	14.2
2-Isopropyl	5.83	18.1	29.6	2.45	14.8
2- <i>t</i> -Butyl	5.76	18.0	22.7	0.0080	17.5
2,6-Dimethyl	6.75	19.5 <sup>i</sup>	25.4 <sup>j</sup>	1.45 <sup>j,k</sup>	15.1 <sup>j</sup>
2,4,6-Trimethyl	7.59 <sup>i</sup>	20.7 <sup>j</sup>	26.4 <sup>j</sup>	3.75 <sup>j,k</sup>	14.8 <sup>j</sup>

<sup>a</sup> Kcal./mole. <sup>b</sup> L. mole<sup>-1</sup> sec.<sup>-1</sup>. <sup>c</sup> Ref. 9b. <sup>d</sup> Ref. 9c. <sup>e</sup> These data were previously reported for the reaction,  $\text{BF}_3(\text{soln.}) + \text{Py}(\text{soln.}) = \text{Py}:\text{BF}_3(\text{soln.})$ . At present the reaction  $\text{BF}_3(\text{g}) + \text{Py}(\text{soln.}) = \text{Py}:\text{BF}_3(\text{soln.})$  is known with much greater precision and it appears preferable to base the data on this reaction. See H. C. Brown and D. Gintis, *THIS JOURNAL*, **78**, 5378 (1956). <sup>f</sup> Ref. 9e. <sup>g</sup> Ref. 9a. <sup>h</sup> Unpublished work with J. Donahue; previous value, 5.97 (ref. 9b). <sup>i</sup> Ref. 10. <sup>j</sup> This study. <sup>k</sup> Calculated from data at other temperatures.

The introduction of a single methyl group in the 2-position results in an increase in the  $pK_a$  value from 5.17 to 5.97 ( $\Delta pK_a$  0.80). A second methyl group results in a further increase to 6.75 ( $\Delta pK_a$  0.78). This regular increase of 0.78-0.80 per methyl group argues against any significant steric effect in the addition of a proton to 2,6-lutidine.

Similarly, the heat of reaction of 2-picoline with methanesulfonic acid, 18.3 kcal./mole, is 1.2 kcal. greater than for pyridine, 17.1 kcal./mole. A second methyl group in 2,6-lutidine causes a rise to 19.5, an identical increment of 1.2 kcal. Consequently, here also the data correspond to the absence of any significant steric effect in 2,6-lutidine.

If we allow for the contribution of a 4-methyl group, estimated from the behavior of 4-picoline, the results with 2,4,6-collidine correspond closely with those observed for 2,6-lutidine.

The energy of activation for the reaction of 4-picoline with methyl iodide is 0.3 kcal. smaller than that for pyridine. In view of the similarity in base strengths, the activation energy for the reaction of 2-picoline with methyl iodide may be estimated to be 13.6 kcal./mole in the absence of steric effects. The observed activation energy, 14.0 kcal./mole, therefore, corresponds to steric strain in the transition state of approximately 0.4 kcal./mole.

In 2,6-lutidine and 2,4,6-collidine the estimated activation energies are 13.3 and 13.0 kcal./mole, respectively. The observed values, 15.1 and 14.8

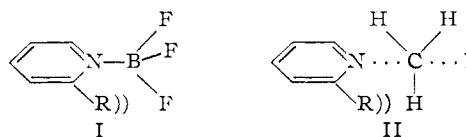
kcal./mole, points to the presence of 1.8 kcal./mole of steric strain in the transition state.

This increase in the strain from 0.4 kcal./mole for one *o*-methyl group to 1.8 kcal./mole for two such groups is consistent with the steric interpretation. With a single methyl group, the methyl iodide molecule may bend slightly in such a manner as to minimize the energy of the transition state. With a methyl group in both *ortho* positions this mechanism for the reduction of strain is no longer available to the reacting alkyl halide, resulting in an increase in strain that is considerably greater than twice the strain observed in the mono-substituted base.

The same phenomenon is observed in the reactions with boron trifluoride. Here the estimated strain is 2.2 kcal./mole in 2-picoline-boron trifluoride, and 8.5 and 8.0 kcal./mole in 2,6-lutidine-boron trifluoride and 2,4,6-collidine-boron trifluoride, respectively.

In both reactions a factor of approximately 4 is noted between the strains in the 2-methyl- and in the 2,6-dimethylpyridine bases. It is too early to state whether such a factor will be general.

It was previously noted that a linear relationship exists between the heats of reaction of boron trifluoride with pyridine and the monoalkylpyridines and the activation energies for the reaction of these bases with methyl iodide.<sup>9b</sup> Such a correlation implies a linear strain energy relationship between the strains in the boron trifluoride addition compounds (I) and the strains in the transition states for the methyl iodide reactions (II).



The data previously available for the monoalkylpyridines yield the relationship

$$(\Delta E_s^\ddagger)_{\text{MeI}} = 0.33 (\Delta E_s)_{\text{BF}_3}$$

where  $\Delta E_s$  is the strain energy accompanying reaction. This relationship was applied to calculate the strain energies in the reaction of the 2,6-dimethylpyridine derivatives examined in the present investigation. The results are summarized in Table IV.

TABLE IV  
EXPERIMENTAL AND CALCULATED STRAIN ENERGIES IN THE  
REACTIONS OF PYRIDINE BASES WITH BORON TRIFLUORIDE  
AND METHYL IODIDE

Base	Steric strains (exptl.)		Steric strains (calcd.)	
	Py + $\text{CH}_3\text{I}$	Py + $\text{BF}_3$	Py + $\text{BF}_3$	$\Delta$
2-Picoline	0.4	2.2	1.2	-1.0
2-Ethylpyridine	0.6	2.8	1.8	-1.0
2-Isopropylpyridine	1.2	3.8	3.6	-0.2
2- <i>t</i> -Butylpyridine	3.9	10.7	11.7	+1.0
2,6-Lutidine	1.8	8.5	5.4	+3.1
2,4,6-Collidine	1.8	8.0	5.4	+2.6

It is quite apparent that the strain energies calculated for the addition compounds of 2,6-lutidine and 2,4,6-collidine exhibit serious discrepancies. That is to say, the linear relationship previously

developed from data for pyridine bases with but one *ortho* substituent cannot be applied to pyridine bases with two alkyl substituents. The extent of the failure of the relationship is made clear in Fig. 1.

It was pointed out that the steric requirements of the boron trifluoride group in the addition compounds (I) must be considerably greater than those of the methyl group in the activated complex (II). On this basis the existence of a fair linear relationship involving the monoalkylpyridines is somewhat surprising and the failure of the relationship with the di-*o*-substituted pyridine bases is not entirely unexpected. It is probable that to achieve a linear relationship which will include both mono- and di-*o*-substituted pyridine bases, it will be necessary to utilize reference acids with steric requirements which are far nearer those of the methyl group than is the case with boron trifluoride. As will be discussed in the following papers of this group, we were successful in this endeavor by utilizing borane,  $BH_3$ , as such a reference acid.

### Experimental Part

**Materials.**—The purification of the commercial 2,6-lutidine and 2,4,6-collidine has been described previously.<sup>10</sup> The samples used in the present investigation exhibited purities of 99.8 and 99.0 mole %, based upon cooling curve data.<sup>11</sup> The samples were kept over calcium hydride in a sealed glass ampoule until used.

Tetrahydropyran-boron trifluoride<sup>9d</sup> and methanesulfonic acid<sup>9a</sup> were prepared and purified by the methods previously reported. Nitrobenzene (du Pont technical grade) was carefully fractionated at atmospheric pressure (b.p. 209° at 745 mm.,  $n_D^{20}$  1.5529) and stored over calcium hydride. The cooling curve indicated a purity of better than 99.8 mole %. Methyl iodide was fractionated with a column packed with glass helices: b.p. 41.5° (750 mm.),  $n_D^{20}$  1.5295. The purity was checked by analysis for iodide with silver nitrate.

**Calorimetric Measurements.**—The heats of reaction were run in the improved mercury-well calorimeters.<sup>12</sup> The experimental procedures were identical with those reported.<sup>9a,d</sup>

**Kinetic Measurements.**—Standard solutions (0.2 *M*) of the pyridine bases and of the methyl iodide in nitrobenzene were prepared. The concentrations of the pyridine solutions were checked by titration with standard acid, the iodide solution by titration with alcoholic silver nitrate.

Aliquots of these solutions (5.00 ml.) were sealed in capsules, maintained in a constant temperature bath ( $\pm 0.02^\circ$ ) for the desired time, opened and analyzed. Owing to the high volatility of methyl iodide the concentration of the standard solution tended to change slightly each time an aliquot was removed. This difficulty was overcome in the following manner. Dry nitrogen, bubbled through nitrobenzene containing methyl iodide (0.6 *M*), was used to raise the standard solution into the pipet. With this technique, no change in the concentration of the standard methyl iodide solution was observed over a period of a month.

The concentrations in the ampules were calculated using the densities of nitrobenzene at the reaction temperatures.<sup>9a</sup>

Two different techniques were used for the kinetic measurements. In one series the unreacted base was titrated with a standard solution of perchloric acid in glacial acetic

(11) The technique used for these purity determinations was developed by Dr. K. L. Nelson and is described in a paper by Dr. Nelson now in press.

(12) H. C. Brown and R. R. Holmes, *THIS JOURNAL*, **78**, 2173 (1956).

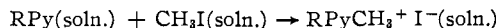
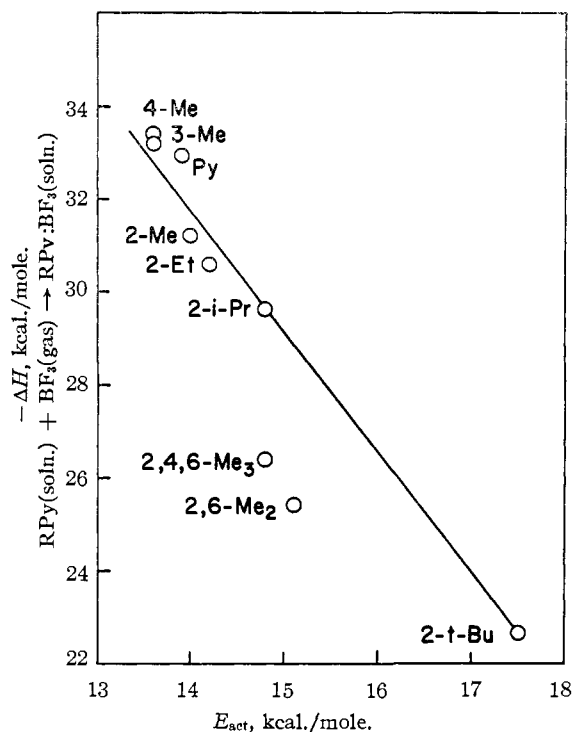


Fig. 1.—Relationship between the heats of reaction of the alkylpyridine bases with boron trifluoride and the activation energies for their reactions with methyl iodide.

acid.<sup>9a</sup> In the other the iodide ion was determined, using the Volhard procedure. Excellent agreement was realized with both methods.

Representative data for a kinetic run are summarized in Table V.

TABLE V  
REPRESENTATIVE KINETIC DATA FOR THE REACTION OF 2,6-LUTIDINE AND METHYL IODIDE AT 40.07°<sup>d</sup>

Time, hr.	Silver nitrate, ml. 0.0500 <i>M</i>	Iodide, <sup>a</sup> <i>M</i>	$\frac{1a, b}{a-x}$	$\delta^c$
0.00	0.22	0.0011	9.92	0.00
3.00	1.26	.0062	10.45	+ .02
7.00	2.38	.0118	11.10	.00
11.00	3.52	.0174	11.83	.02
15.00	4.41	.0218	12.48	− .01
20.00	5.42	.0268	13.32	− .02
31.00	7.36	.0364	15.27	+ .01

<sup>a</sup> Corrected to thermostat temperature. <sup>b</sup> Initial concentrations corrected to thermostat temperature were 0.1019 *M*. <sup>c</sup> Discrepancy between the observed values of  $1/(a-x)$  and the values obtained from the least squares line. <sup>d</sup>  $k_2 = 0.480 \times 10^{-4}$  l. mole<sup>-1</sup> sec.<sup>-1</sup> from plot of  $1/(a-x)$  vs. time.

The rate constants reported in Table III are averages of two or more determinations with average deviations of 1–2%. The energies of activation are reproducible to  $\pm 0.10$  kcal./mole.

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