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Electronic Effects on the Menschutkin Reaction. A Complete Kinetic and Thermodynamic Dissection of Alkyl Transfer to 3- and 4-Substituted Pyridines

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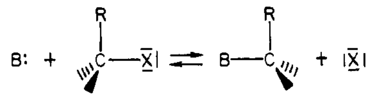
Abstract: The relationship between kinetic and thermodynamic parameters is explored for quaternization of a series of pyridines (mostly 3- and 4-substituted) with several methylating and ethylating reagents in several solvents. The reaction with methyl iodide in acetonitrile is reversible at temperatures in the neighborhood of 100 °C so that the effect of substituents on free energy, enthalpy, and entropy for activation of the forward and reverse reactions and for the overall quaternization can be determined. A variety of experimental techniques was used to obtain rates over a range of 10^{13} and to determine enthalpies and entropies of reaction. The results are self-consistent and agree generally with isolated published values for similar systems. The relationship between thermodynamic and activation parameters is examined, and a gross disparity is found between free energy and enthalpy behavior compared with that of the entropies. A consistent picture of the quaternization reaction emerges, based on many studies using a variety of mechanistic probes. The transition state is "early" as far as bond formation to the base is concerned but "late" in terms of bond rupture between the transferring alkyl group and the leaving group with solvent reorganization nearly complete. Quaternization of the 3- and 4-substituted pyridines does not follow the reactivity-selectivity principle, but that of 2-substituted pyridines does. The current practice of assigning detailed bimolecular structures to transition states for substitution, addition, or elimination reactions by application of the Hammond postulate is criticized in view of its inability to handle the dominating role of solvation dynamics and because of the considerable difference in potential energy content (and therefore structure) between the transition states and the reactants or products.

Introduction

Nucleophilic displacement reactions are of great practical importance in organic and biochemistry and have played a central role in the development of mechanistic theory. However, despite the thousands of experimental and interpretive studies of displacement reactions, there are relatively few which have examined a single, simple reaction by a wide enough range of methods to provide reasonable grounds to test the consistency of mechanistic speculations about them. This paper attempts to examine one such prototype reaction, the Menschutkin quaternization, in this way.

Thanks to the generalized Lewis theory of acids and bases, it is only a short conceptual step to consider the S_N2 reaction as the concerted transfer of a carbocation (acid) from one base to another (eq 1) in a manner entirely analogous to that of proton transfer between acids, bases, and their conjugates. With the hope of relating the kinetics and thermodynamics of alkyl transfer in the same manner as the Brønsted equation treats protolysis, a number of authors[1-11] have tried to compare nucleophilicities with the proper thermodynamic property, "carbon basicity".[12] However, there are relatively few reliable reports of both rates and equilibria for alkyl transfer which could be used for such a rigorous analysis. An obstacle to obtaining such data lies in the relatively high activation barriers for most S_N2 reactions. This makes it difficult to find experimental conditions for running them reversibly to get equilibrium constants for alkyl exchange that are equivalent to K_a's for comparing acidities. Of the few successful attempts, those of Lewis and Kukes[13] and Matsui and Tokura[14] are the most complete and most relevant to the present report.



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This study is part of a series of investigations of substituent effects on the kinetics and thermodynamics for processes that generate positive charge on the pyridine nucleus,[15,16] a system which offers great control of steric and electronic factors at a clearly defined basic (nucleophilic) center. Previous reports[16] compared rates and heats of alkylation for a series of 3- and 4-substituted pyridines. This report extends that work to include a complete analysis of standard free energies, enthalpies, and entropies for the overall reaction with methyl iodide and the corresponding kinetic parameters both for the forward and reverse (demethylation) reaction. Ever since the classic studies of Brown and his students, the use of 2- and 6-alkyl-substituted pyridines has had a fruitful history in the elucidation of steric effects.[17] We shall see below that their structure–reactivity patterns are clearly differentiated from those of the 3- or 4-substituted compounds.

No other organic chemical reaction has been studied by more physical methods over a longer period of time than the quaternization of tertiary amines by alkyl halides. Menschutkin's original (1890) study[18] of the reaction of triethylamine with ethyl iodide in 22 solvents is probably the first systemic physical–organic

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(11) Wong, C.-P.; Jackman, L. M.; Portman, R. G. *Tetrahedron Lett.* **1974**, 921.

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(17) (a) Brown, H. C.; Gintis, D.; Domash, L. *J. Am. Chem. Soc.* **1956**, *78*, 5387. (b) Brown, H. C.; et al. *Ibid.* **1955**, *77*, 1715, 1723, 1727, 1730. (c) Deady, L. W.; Finlayson, W. L.; Korytsky, O. L. *Aust. J. Chem.* **1979**, *32*, 1735. These authors describe steric effects on reversible quaternization with methyl iodide.

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0002-7863/80/1502-5892$01.00/0

investigation of the effect of solvent variation on reaction rates.[19] The subsequent history of increasingly sophisticated approaches to understanding this displacement reaction has been discussed recently by Abraham,[20] whose papers provide an entrée to the extensive literature on this subject. The quaternization of tertiary amines by alkylating agents is usually clean and, since it involves the conversion of neutral reactants into ionic products, is an attractive proving ground for electrostatic theories of reaction mechanism. The rate of the forward reaction is easily measured by many techniques for probing the response of activation parameters to changes in solvent, pressure, isotopic substitution, and variation of the alkylating agent. However, there have been relatively few studies of the effect of changing electronic factors in the amine.

It was realized quite early that, under suitable conditions, the Menschutkin reaction might be reversible, and there have been several attempts to determine reaction thermodynamics as well as kinetic parameters.[21–29] However, most of the older studies did not have adequate analytical means for determining equilibrium constants at reasonably high dilution. Many of the reported equilibrium constants were actually inferred indirectly from curvature of rate plots to which ion-pairing corrections and experimental errors probably also contributed. Of these, the results of Essex and Gelorimini,[21] from which Glasstone, Laidler and Eyring[30] deduced a product-like transition state, is a case in point. Kreevoy[31] subsequently proposed that their conclusion was wrong and suggested that ion pairing was responsible for an erroneous interpretation.

In view of the demonstrated ambiguities of estimating reverse rates and equilibrium constants we wished to approach the problem of measurement directly. Reliable kinetics and thermodynamic parameters for alkyl transfer to the variously substituted pyridines in this series required the combination of a variety of experimental techniques to measure the forward and reverse reactions over the enormous range of rates involved—13 powers of 10. In addition to obtaining activation parameters from temperature coefficients of these rates, the enthalpies and entropies of reaction can be obtained by combining activation parameters for forward and reverse reactions or by the equivalent methods of taking temperature coefficients of equilibrium constants. Fortunately, a completely independent route to enthalpies of reaction is available through solution calorimetry. In several cases we have been able to get direct calorimetric checks for the self-consistency of our kinetic and thermodynamic results. In other cases, calorimetric enthalpies of reaction have been invaluable for the calculation of equilibrium constants at temperatures where they could not be measured. Because of these strategies, it has been possible to obtain experimental results of reasonably high precision under conditions which remove many of the doubts associated with earlier studies.

Relations between kinetics and thermodynamics have had a long history in chemistry and have played an important part in the development of transition-state theory. The Brønsted catalysis equations,[32] the Hammond postulate,[33] and the Thornton rules[34] attempt to explain (or perhaps predict) transition-state behavior for simple reactions in terms of perturbation of the overall energetics.[35] Recently, Marcus has had considerable success in relating the rates of electron-transfer and proton-transfer reactions to the overall change in Gibbs free energy.[36] An extension of the Marcus equations to methyl transfer has just been published by Albery and Kreevoy,[37,38] but the necessary data to test it against our results are not presently available.

Several previous studies of the Menschutkin reaction have attempted to estimate the degree of charging in the transition state by the response of the reaction to variation of solvent or pressure. The conclusions from the present case involving variation of substitution on the amine contribute to a generally consistent picture of the energetics of this prototype substitution reaction.

Because of the good agreement which is obtained from so many viewpoints toward this reaction, we shall comment finally on the failure of our kinetic results to fit the structure–rate pattern known as the reactivity–selectivity principle.

Experimental Section

Materials. All solvents, alkylating agents, and pyridines were commercially available with the exception of 4-methoxypyridine which was produced from 4-methoxypyridine *N*-oxide by treatment with phosphorus trichloride in chloroform.[39] Compounds were purified carefully and their purities authenticated by standard procedures including melting point, boiling point, and NMR, IR, and UV spectroscopy. The pyridinium iodide salts were checked for iodide content by Volhard titration, all of which agreed with the calculated values by better than 0.1%.[40] The moisture content of solvents was kept below 100 ppm and was monitored by Karl Fischer titration, using a Photovolt Aquatest II titrator.

Three dipolar aprotic solvents were used. Nitrobenzene, the medium for the initial alkylation studies,[16b] was replaced for safety reasons with 2-nitropropane when the former solvent produced allergic reactions in several workers. Although 2-nitropropane reacts with pyridines under some conditions,[41] no evidence of instability was observed under the conditions of this study. Thus, no changes in conductance or ^{1}H NMR spectra were observed for samples of pyridines that were kept at reaction conditions for protracted periods in the absence of alkylating agents. Also, no major discrepancies were found between kinetic or thermodynamic properties in this solvent compared with those in nitrobenzene or other related media.

High-temperature equilibrations of the pyridinium iodide with the pyridine and methyl iodide (see below) were accomplished in acetonitrile to avoid UV absorption from 2-nitropropane which would interfere with high-pressure liquid chromatographic analysis of the reaction mixture.

Kinetics. The enormous range of rates (13 powers of 10) covered by the forward and reverse reactions necessitated the use of three different kinetic techniques.

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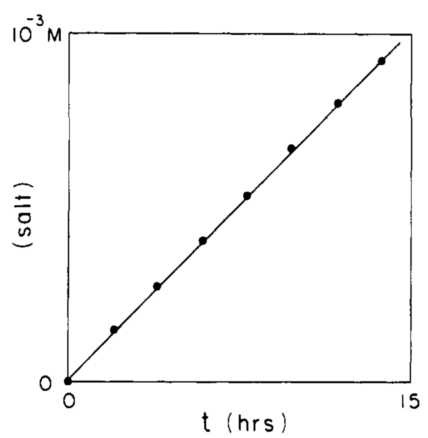

Figure 1. Pseudo-zeroth-order rate plot for the reaction of pyridine with ethyl iodide or methyl iodide in 2-nitropropane: slope = 6.69 × 10^{-4}; coefficient of linear correlation = 0.999; d[salt]/dt = k[3-chloropyridine][EtI], 2% completion after 15 h.

(1) The fastest reactions with methyl and ethyl fluorosulfonates were easily followed by the calorimetric method of Eatough, Christensen, and Izatt.[42] This technique has the added benefit of providing the heat of reaction as well as the rate constant.[43] The calorimetric kinetic procedure was checked occasionally by measuring the rate constant for the base-catalyzed hydrolysis of ethyl acetate,[42] 1.37 × 10^{-1} M^{-1} s^{-1}; that obtained in our laboratory was 1.34 ± 0.07 × 10^{-1} M^{-1} s^{-1}.

(2) The slower second-order rate constants for the reaction of pyridine with ethyl iodide in 2-nitropropane and methyl iodide in 2-nitropropane and acetonitrile were measured by using a conductance technique.[44] A Leeds and Northrup Model 4866-60 conductance bridge, which operates with an alternating current of 60 Hz, was used with a listed precision of about ±1%. The conductance cell consisted of two parallel glass contact tubes filled with mercury and sealed to enclose the leads of the platinum electrodes. The electrodes and the glass tubes were enclosed in a cylindrical solution vessel of 2.9-cm diameter and 9-cm length.

With this bridge and cell, the resistance of the solutions of the *N*-alkylpyridinium iodide salts was determined at nine concentrations in acetonitrile or 2-nitropropane covering a range of concentrations from 0.0015 to 0.00010 M. The second-order rate constant was then measured as follows. A 40-mL sample of an alkyl iodide solution of known concentration (0.100 M) in 2-nitropropane (or acetonitrile) was pipetted into a 50-mL round-bottom flask which was stoppered and placed in a constant-temperature bath. A pyridine solution (10 mL) of known concentration (0.500 M) was pipetted into another 50-mL Erlenmeyer flask fitted with a male standard taper 24/40 joint. This was also stoppered and placed in the constant temperature bath. After equilibrating for 1 h, the two flasks were joined and the solutions mixed together. A 30-mL portion of this solution was then pipetted into the conductance cell which was then immersed in the constant-temperature bath. When the resistance of the cell was equal to that of the lowest concentration of the standard salt solution determined previously, a timer was activated. The time was then recorded when the cell's resistance equalled that of each of the remaining resistances of the known salt concentrations. The second-order rate constants were calculated by plotting the change in concentration of the salt against time (Figure 1). Since the rates of alkylation using ethyl or methyl iodide were extremely slow (10^{-5} M^{-1} s^{-1}), pseudo-zeroth-order kinetic conditions were employed so that k_2 was obtained by dividing the slope of this plot by the concentrations of the pyridine and alkylating agent.

(3) The second-order rate constants for the demethylation of *N*-methylpyridinium iodide salts were determined by analysis of aliquots for pyridine and pyridinium salt content, using high-performance liquid chromatography. A sample of the reaction solution

$$XC_5H_4N^+Me + I^- \rightleftarrows XC_5H_4N + MeI \qquad (2)$$

which included *N*-methylpyridinium iodide, pyridine, methyl iodide, nitrobenzene, and acetonitrile was injected into the high-performance liquid chromatograph which separated all four UV absorbing species. By adapting an electronic Hewlett-Packard Model 33805 integrator to the Du Pont Model 830 high-performance liquid chromatograph, it was possible to quantify the concentrations of the reaction mixture by comparing their integrated areas with that of a standard chromatogram which was made in the following manner.

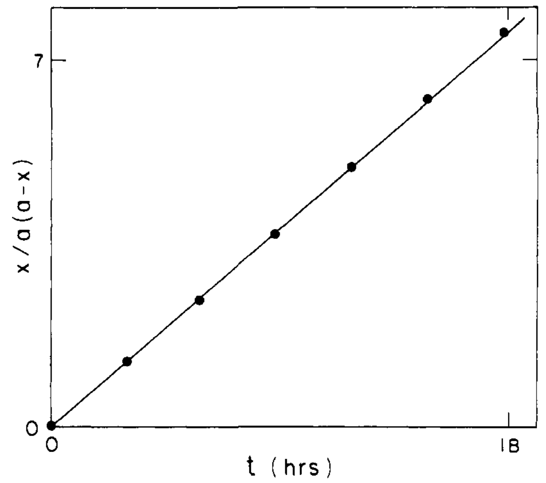

Figure 2. Second-order rate constant for the demethylation of *N*-methyl-3,5-dichloropyridinium iodide in acetonitrile: slope = 0.389; linear correlation coefficient = 0.999; a = pyridinium iodide concentration; x = methyl iodide concentration.

A known concentration of *N*-methylpyridinium iodide solution (0.0500 M) was prepared by diluting a weighed amount of the salt into a 250-mL flask with acetonitrile which contained ~5 × 10^{-4} M nitrobenzene as an internal standard. A methyl iodide solution and a pyridine solution of exactly twice this salt concentration were then prepared by diluting weighed samples of these compounds with the same stock solution of acetonitrile containing nitrobenzene. Nine solutions containing *N*-methylpyridinium iodide, pyridine, methyl iodide, and nitrobenzene were made, covering a concentration range of 1–7 × 10^{-3} M for the pyridine and methyl iodide, by pipetting exactly equal amounts of the stock solutions of the pyridine and methyl iodide into one 50-mL flask and diluting this solution to 50 mL with the *N*-methylpyridinium iodide salt solution. This process produced a series of solutions of precisely known concentrations of the salt, pyridine, and methyl iodide for standardization of the high-performance LC analysis.

Since the rate of methylation of pyridine with methyl iodide is extremely slow, as is the rate of demethylation of the *N*-methylpyridinium iodide, the standard solutions remained constant at room temperature while the necessary high-performance LC conditions that would separate the four compounds in the acetonitrile solution were being established. These separations required either an ETH reverse phase column or SCX strong cation-exchange column where water is used as the mobile phase. Separations were often poor with partially overlapping peaks. However, by using the programmed integrator to correct for tailing and by preparing stock solutions to simulate chromatographs from the rate runs, it was possible to reproduce analyses to ±2% on the average.

Second-order rates for the demethylation of *N*-methyl-3,5-dichloropyridinium iodide were then obtained by sealing in several ampules 0.5 mL of the original stock solution of this salt and placing these ampules in a thermostated bath at high temperature. After an accurately measured period of time, an ampule was removed and a sample of the solution was injected into the high-performance liquid chromatograph. The time period was chosen such that the resulting chromatogram resembled one of the standards. The concentration of the 3,5-dichloropyridine was then calculated by a series of extrapolations, using plots of the pyridine concentration vs. the relative pyridine/nitrobenzene integrated area and correcting for the volume of expansion of the acetonitrile to the reaction temperature.

The second-order rate constant was calculated by using the integrated second-order rate equation for reactants at equal concentration:

$$x/[a(a-x)] = k_2t \qquad (3)$$

where x equals the concentration of the pyridine and a equals the concentration of the salt. A computer program was used to calculate the rate constants. Figure 2 shows a graph of $x/a(a-x)$ plotted against time for the demethylation of *N*-methyl-3,5-dichloropyridinium iodide.

Results

This section reports the kinetic and calorimetric measurements used to calculate the thermodynamic parameters of reaction and

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Table I. Enthalpies of Reaction of Methyl and Ethyl Fluorosulfonate with Various Substituted Pyridines in Three Solvents at 25 °C

substituent on pyridine	$MeSO_3F$, ΔH in kcal/mol			$EtSO_3F$, 2-nitropropane	$MeSO_3F/EtSO_3F$ rate ratio
	sulfolane[a] (ϵ 42)	nitrobenzene (ϵ 34.8)	2-nitropropane (ϵ 25.5)		
4-MeO	−38.57 ± 0.35	−38.16 ± 0.29			
4-*tert*-butyl		−38.19 ± 0.49			
4-ethyl		−37.31 ± 0.49			
4-Me	−37.49 ± 0.26	−38.45 ± 0.50			
3-Me			−36.26 ± 0.39	−33.78 ± 0.28	2.45
3,5-diMe		−37.48 ± 0.26			
2,4,6-triMe	−35.33 ± 0.26	−36.20 ± 0.46			
H	−36.17 ± 0.46	−36.70 ± 0.12	−35.10 ± 0.48	−32.87 ± 0.21	2.23
3-Cl	−32.22 ± 0.24	−32.71 ± 0.36	−30.91 ± 0.44	−27.80 ± 0.33	3.11
4-CN	−31.56 ± 0.46	−31.79 ± 1.10	−30.30 ± 0.38	−26.27 ± 0.64	4.03
3-Br	−31.26 ± 0.26		−29.74 ± 0.12	−27.81 ± 0.14	1.93
3F			−31.79 ± 0.06	−28.71 ± 0.48	3.08
3,5-diCl	−28.58 ± 0.57	−28.59 ± 0.70	−27.61 ± 0.33	−25.76 ± 1.20	1.85
2-Cl	−25.63 ± 0.72	−31.60 ± 0.93			
2-F	−23.96 ± 0.32				

[a] These values were measured by Petro.[16b]

Table II. Second-Order Rate Constants for the Alkylation of Pyridines in 2-Nitropropane at 25 °C[a]

pyridine	$k_2(MeSO_3F)$	$k_2(EtSO_3F)$	$k_2(MeI) \times 10^3$	$k_2(EtI) \times 10^6$ [b]
3-Me	8.84 ± 0.46	0.326 ± 0.008	0.239 ± 0.005	14.3
H	5.36 ± 0.02	0.192 ± 0.006	0.163 ± 0.001	8.24
3-F	0.582 ± 0.006	0.02832 ± 0.008		
3-Cl	0.514 ± 0.008	0.0278 ± 0.0004	0.0126 ± 0.002	0.700
3-Br	0.515 ± 0.013	0.0289 ± 0.0004	0.0138 ± 0.002	0.742
4-CN	0.204 ± 0.005	0.0148 ± 0.0003	$0.00593 \pm 4 \times 10^{-5}$	0.348
3,5-diCl	0.0546 ± 0.0016	$0.00571 \pm 6 \times 10^{-5}$	$0.00117 \pm 2 \times 10^{-5}$	0.0780

[a] $M^{-1}\ s^{-1}$ [b] EtI values were calculated using the Eyring equation to extrapolate from rates at higher temperatures; see Table V.

Table III. Rate Constants for the Treatment of $MeSO_3F$ (4.38×10^{-3} M) with Various Concentrations of 3,5-Dichloropyridine in 2-Nitropropane at 25.00 ± 0.05 °C

concn of 3,5-dichloropyridine, M	rate constant $\times 10^2$ $M^{-1}\ s^{-1}$
0.203	5.27
0.184	5.37
0.163	5.37
0.135	5.53
0.135	5.58
0.108	5.68
0.081	5.54
av	5.46 ± 0.16

Table IV. Rate Constants for the Treatment of 3-Methylpyridine (0.118 M) with Various Concentrations of Ethyl Iodide in 2-Nitropropane

ethyl iodide concn, M	rate constant $\times 10^5$ $M^{-1}\ s^{-1}$
0.100	1.36
0.082	1.34
0.075	1.34
0.025	1.22
av	1.32 ± 0.06

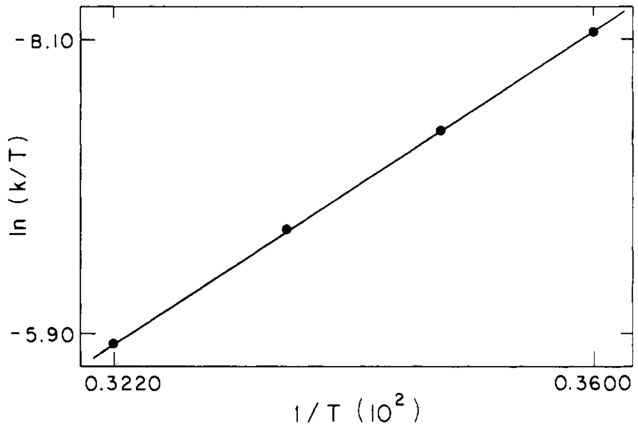

Figure 3. Eyring plot for the alkylation of 3-methylpyridine with ethyl iodide in 2-nitropropane: slope = 8.16; linear correlation coefficient = 0.996.

activation for the alkylation of various pyridines with $MeSO_3F$, $EtSO_3F$, MeI and EtI and the precautionary steps taken to insure the authenticity of these experiments.

All thermodynamic terms are related to a standard state which can be extrapolated from an infinitely dilute solution. The activity coefficients of the reactants and products are therefore taken as unity. The pyridinium salts are taken to be completely dissociated since the reported dissociation constants for similar quaternary ammonium iodide salts in solvents of the type used here are at least 100,[45,46] so that the degree of association to ion pairs would be <1% at the concentrations used. Consistent with this, no curvature was observed in rate plots or in calibration plots of conductance vs. concentration such as would be produced by ion-pairing equilibria. Furthermore, the relationship between the free energies and entropies of reaction, which was derived by a variety of kinetic and thermodynamic methods, was consistent with the electrostatic behavior of separated ions (see below).

$\Delta H°$ of Reaction. The $\Delta H°$ of reaction for the alkylation of the various pyridines with $MeSO_3F$ and $EtSO_3F$ in several solvents are presented in Table I. These values were determined by using a simple solution calorimeter,[16] and the errors were estimated from the standard deviation of six measurements. The calorimeter was checked periodically by measuring the heat of solution of ethanol into water.

Rates of Alkylation. The second-order rate constants for the alkylation of pyridines with $MeSO_3F$, $EtSO_3F$, MeI, and EtI are shown in Table II. The rates of alkylation using $MeSO_3F$ and $EtSO_3F$ were determined by using a calorimetric procedure (see Experimental Section). A check of the rate equation by this technique was made by varying the initial concentration of the

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(45) Janz, G. J.; Tomkins, R. P. T. "Nonaqueous Electrolytes Handbook"; Academic Press: New York, 1972; Vol. I.

(46) Mackay, R. A.; Poziomek, E. J. *J. Am. Chem. Soc.* **1970**, *92*, 2432. For an interesting example of variation of $\Delta S^{\ddagger}$ as a function of type of ion pair, see also Menger, F. M.; Singh, T. G.; Bayer, F. L. *Ibid.* **1976**, *98*, 5011.

Table V. Rate Constants for the Treatment of Ethyl Iodide with Substituted Pyridines in 2-Nitropropane at Various Temperatures

pyridine	temp, °C	rate constant, M^{-1} s^{-1} × 10^6
3-Me	4.64	2.11 ± 0.05
	14.00	5.27 ± 0.11
	25.00	10.32 ± 0.06
	37.38	42.50 ± 0.04
H	4.64	1.17 ± 0.06
	14.00	2.84 ± 0.02
	25.00	7.51 ± 0.48
	37.38	26.20 ± 0.03
3-Cl	33.85	1.66 ± 0.01
	43.45	3.41 ± 0.14
	54.70	9.00 ± 0.20
	66.62	22.50 ± 0.15
3-Br	36.10	2.11 ± 0.08
	43.45	3.64 ± 0.03
	54.70	8.09 ± 0.07
	66.62	23.70 ± 0.06
4-CN	33.70	7.24 ± 0.04
	44.65	1.93 ± 0.02
	53.50	5.07 ± 0.03
	66.62	9.99 ± 0.30
3,5-diCl	60.00	1.65 ± 0.05
	76.20	6.04 ± 0.02
	95.54	22.90 ± 0.20

Table VI. Activation Parameters for the Reaction of Several Pyridines with Ethyl Iodide in 2-Nitropropane at 25 °C

pyridine	$\Delta G^{\ddagger}$, kcal/mol	$\Delta H^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$, gibbs/mol
3-Me	24.08 ± 0.37	15.01 ± 0.32	−30.41 ± 0.60
H	24.42 ± 0.35	15.62 ± 0.30	−20.50 ± 0.61
3-Cl	25.81 ± 0.37	16.00 ± 0.33	−32.91 ± 0.53
3-Br	25.80 ± 0.35	16.01 ± 0.31	−32.82 ± 0.51
4-CN	26.37 ± 0.38	16.32 ± 0.31	−33.71 ± 0.71
3,5-diCl	27.22 ± 0.59	17.31 ± 0.52	−33.23 ± 0.92

pyridine for the reaction of 3,5-dichloropyridine with $MeSO_3F$ in 2-nitropropane at 25.0 °C. These results are given in Table III and show no significant change in the second-order rate constant with variation in the pyridine's initial concentration.

The second-order rate constants of alkylation using MeI and EtI were determined by conductance. The rate equation was checked for the reaction of 3-methylpyridine by variation of the initial ethyl iodide concentration over a fourfold range (see Table IV).

All conductance rate measurements were made at 25.0 °C except for EtI whose rates at 25 °C were too slow to measure. These second-order rate constants were extrapolated to 25 °C from the Eyring equation as shown in Figure 3. Each plot was made from four rate constants determined at four different temperatures. Table V contains EtI rate constants and the temperature at which they were measured. Table VI contains the derived activation parameters calculated from the Eyring equation:

$$\log k_f/T = \frac{-\Delta H^{*}}{2.303RT} + \log \frac{k}{h} + \frac{\Delta S^{*}}{2.303R} \tag{4}$$

Thermodynamic Parameters. The thermodynamic parameters $\Delta G°$, $\Delta H°$, and $\Delta S°$ of reaction were calculated for the reactions of 3-bromopyridine and 3,5-dichloropyridine with MeI in acetonitrile by combining the activation parameters of the forward reaction with those for the reverse (Table VII). The activation parameters (Tables VIII–X) for the forward and reverse reactions were calculated from the temperature coefficients of rates by the Eyring equation, where each rate constant for the forward reaction was determined by conductance and for the reverse reaction by high-performance LC. Acetonitrile, which does not absorb light in the ultraviolet region, was used as a solvent instead of 2-nitropropane, since the high-performance liquid chromatograph employed an ultraviolet spectrophotometer as a detector. The rates of alkylation of the pyridines increased about threefold compared with their rates in 2-nitropropane, but their relative values did not change.

Table VII. Rate Constants at Various Temperatures Used for Calculating the Activation Parameters for the Forward and Reverse Methylations of 3,5-Dichloropyridine and 3-Bromopyridine in Acetonitrile

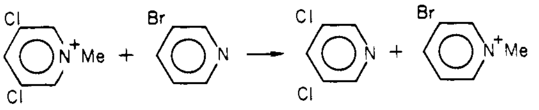
pyridine	reaction	temp, °C	rate constant, M^{-1} s^{-1}
3,5-diCl	forward	0.98	(0.508 ± 0.002) × 10^{-6}
		10.85	(0.136 ± 0.004) × 10^{-5}
		20.7	(0.327 ± 0.004) × 10^{-5}
		30.22	(0.752 ± 0.003) × 10^{-5}
	reverse	65.45	(0.290 ± 0.003) × 10^{-4}
		74.51	(0.126 ± 0.005) × 10^{-3}
		85.95	(0.450 ± 0.002) × 10^{-3}
		95.10	(0.119 ± 0.003) × 10^{-2}
3-Br	forward	0.73	(0.511 ± 0.004) × 10^{-5}
		10.80	(0.135 ± 0.006) × 10^{-4}
		20.80	(0.312 ± 0.001) × 10^{-4}
		30.72	(0.700 ± 0.005) × 10^{-4}
	reverse	84.30	(0.108 ± 0.002) × 10^{-4}
		95.11	(0.445 ± 0.005) × 10^{-4}
		106.11	(0.133 ± 0.002) × 10^{-3}
		115.64	(0.470 ± 0.007) × 10^{-3}

Tests for Internal Consistency. The equilibrium constant calculated for the reaction of 3,5-dichloropyridine with MeI from its forward and reverse activation parameters at 85 °C was checked by conductance. The resistance of an *N*-methyl-3,5-dichloropyridinium iodide salt solution which had been equilibrated in a constant temperature bath at 85 °C for 3 and 4 weeks agreed within 10% with the resistance of the original salt solution which had been diluted to twice its volume. At 85 °C (see Table VIII), the calculated $\Delta G°$ for the above reaction is zero (i.e., $T = \Delta H°/\Delta S°$); so the concentration of the pyridinium salt should decrease to one half its original value when it reaches equilibrium.

A completely independent check on the thermodynamic properties derived from the activation parameters was achieved through calorimetry. The $\delta\Delta H°$ values of reactions calculated from the activation parameters for the forward and reverse reaction for methylation of 3-bromo- and 3,5-dichloropyridine with MeI are shown to be self-consistent by combining reactions 6 and 7, whose heats have been measured calorimetrically in acetonitrile, to obtain reaction 5. Since this reaction can also be obtained by combining reactions 8 and 9, whose heats of reaction have been calculated from activation parameters, the difference in heats determined for 6 and 7 should be the same as that for 8 and 9:

$$\Delta H_5 = \Delta H_7 - \Delta H_6 = 2.45 \pm 0.58 \text{ kcal/mol} \tag{10}$$

$$\Delta H_5 = \Delta H_9 - \Delta H_8 = 2.61 \pm 0.63 \text{ kcal/mol} \tag{11}$$



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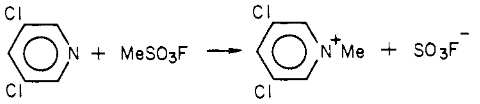

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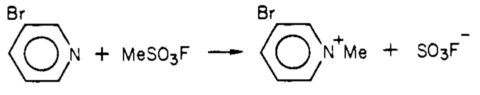

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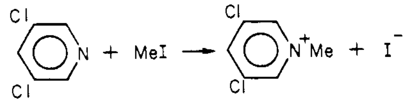

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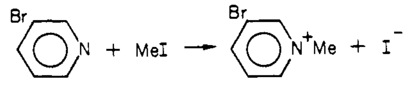

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(47) The well-known iodide exchange reaction of Hughes et al.[48] employed 2-octyl iodide. The very recent methyl exchange between substituted pyridines[29] was shown to proceed through intermediate CH_3I formation.

Table VIII. Rates and Free Energies of Activation and Reaction of Alkylations of Several Pyridines with Methyl Iodide in Acetonitrile at 25 °C

pyridine	k_f	k_r	K	$\Delta G^{\ddagger}{}_f$	$\Delta G^{\ddagger}{}_r$	$\Delta G°$, kcal/mol	α_{Me}[a]	T_0,[b] °C
H	3.59×10^{-4}	6.43×10^{-13}	5.58×10^{8}	22.15 ± 0.32	34.08 ± 0.62	−11.93 ± 0.69	0.25	335
3-Br	4.55×10^{-5}	1.19×10^{-9}	3.75×10^{4}	23.39 ± 0.17	29.63 ± 0.15	−6.24 ± 0.23	0.27	182
3-Cl	4.17×10^{-5}	1.93×10^{-9}	2.16×10^{4}	23.45 ± 0.23	30.14 ± 0.30	−5.10 ± 0.38	0.27	183
4-CN	1.50×10^{-5}	2.79×10^{-9}	5.48×10^{3}	24.03 ± 0.31	29.13 ± 0.23	−5.10 ± 0.38	0.28	149
3,5-diCl	4.94×10^{-6}	5.06×10^{-8}	9.86×10^{1}	24.69 ± 0.32	27.41 ± 0.56	−2.72 ± 0.64	0.29	85
2-Cl	4.15×10^{-6}	4.21×10^{-8}	9.85×10^{1}	25.04 ± 0.43	27.76 ± 0.41	−2.72 ± 0.59	0.29	106

[a] Extended Brønsted coefficient for methyl transfer, $\Delta G^{\ddagger}{}_f/\Delta G°$, both properties relative to unsubstituted pyridine. [b] Calculated. Temperature at which $\Delta G° = 0$.

Table IX. Enthalpies of Activation and Reaction for Alkylation of Several Pyridines with Methyl Iodide at 25 °C in Acetonitrile

pyridine	$\Delta H^{\ddagger}{}_f$	$\Delta H^{\ddagger}{}_r$	$\Delta H°$, kcal/mol
H	12.96 ± 0.31	36.35 ± 0.27	−23.39 ± 0.41
3-Br	13.82 ± 0.15	31.95 ± 0.11	−18.13 ± 0.19
3-Cl	13.37 ± 0.21	33.17 ± 0.24	−19.30 ± 0.32
4-CN	14.41 ± 0.31	32.31 ± 0.22	−13.31 ± 0.38
3,5-diCl	14.75 ± 0.30	30.42 ± 0.53	−15.67 ± 0.61
2-Cl	15.78 ± 0.40	23.49 ± 0.47	−12.71 ± 0.62

Table X. The Entropies of Activation and Reaction for the Alkylation of Several Pyridines with MeI at 25 °C in Acetonitrile

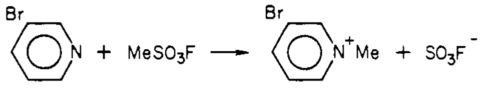
pyridine	$\Delta S^{\ddagger}{}_f$	$\Delta S^{\ddagger}{}_r$	$\Delta S°$, eu	$\Delta S°/\Delta G° \times 10^3$
H	−30.84 ± 0.18	7.61 ± 2.70	−38.45 ± 2.70	3.2
3-Br	−32.09 ± 0.21	7.79 ± 0.49	−39.88 ± 0.53	6.4
3-Cl	−32.13 ± 0.29	10.15 ± 1.66	−42.28 ± 1.16	6.4
4-CN	−32.27 ± 0.15	12.33 ± 1.79	−44.60 ± 1.79	8.8
3,5-diCl	−33.33 ± 0.27	7.79 ± 0.56	−43.74 ± 0.62	16.1
2-Cl	−31.07 ± 0.34	2.46 ± 2.87	−33.53 ± 2.87	12.3

Table XI. Comparison of Results from this Study with Published Values from other Laboratories for Reaction of Pyridine with Methyl Iodide

solvent	property	this study[a]	lit. value
acetonitrile	$\Delta H^{\ddagger}$	12.96	
	$\Delta S^{\ddagger}$	−30.84	
	k_f (25[d])	35.9×10^{-5}	
nitrobenzene	$\Delta H^{\ddagger}$		13.3[b,c]
	$\Delta S^{\ddagger}$		−29.8[b,c]
nitrobenzene	k_f (25)		34.5×10^{-5} [b]
	k_f (40)		17.2×10^{-4} [e]
	k_f (30)		48.4×10^{-5} [f]

[a] See Tables VIII–X. [b] Reference 17b. [c] Coppens, G.; Declerc, F.; Gillet, C.; Nasielski, J. *Bull. Soc. Chim. Belg.* 1963, *72*, 25. [d] °C. [e] Clarke, K.; Rothwell, K. *J. Chem. Soc.* 1960, 1885. [f] Hartman, H.; Kelm, H.; Rinck, G. *Z. Phys. Chem.* 1965, *44*, 335. This reference provides rate and activation data for reaction of methyl iodide with halogen-substituted pyridines in nitrobenzene, thus supplementing those of Brown[17] for alkyl halides.

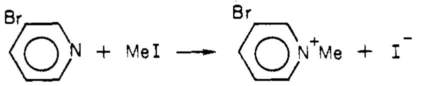
This shows that the relative heats of methylation using enthalpies of activation for MeI as the alkylating agent are consistent with independent calorimetric data taken directly. A further check on self-consistency comes from combining reactions 12 and 13,



(12)

$$Bu_4N^+I^- + MeSO_3F \rightarrow MeI + Bu_4N^+ + SO_3F^- \quad (13)$$

whose heats of reaction have been measured calorimetrically, to obtain reaction 14. The $\Delta H°$ of 14 has been calculated from



(14)

activation parameters and agrees within experimental error with the value calculated from reactions 12 and 13:

$$\Delta H_{14} = -15.67 \text{ kcal/mol} \pm 0.61 \text{ (activation parameters)} \quad (15)$$

$$\Delta H_{14} = \Delta H_{12} - \Delta H_{13} = -15.31 \text{ kcal/mol} \pm 0.48 \text{ (calorimetry)} \quad (16)$$

In view of the large range of temperature extrapolations and many other possible sources of error which have concerned other authors, the agreement is very satisfactory.

Combination of Thermochemical and Rate Data. Using reaction combinations similar to the above, it was possible to determine the heats of reaction for the alkylation of 3*H*-, 3-chloro-, 3-bromo-, 4-cyano-, 3,5-dichloro-, and 3-chloropyridine with MeI. The forward activation parameters for the above reactions were then determined by conductance in the usual manner. By measuring the free energy of activation for the reverse reactions by high-performance LC at one temperature and combining this with the heats of reaction and the activation parameters for the forward reaction, the complete kinetic and thermodynamic parameters for the above reactions could be calculated. These are shown in Tables VIII–X.

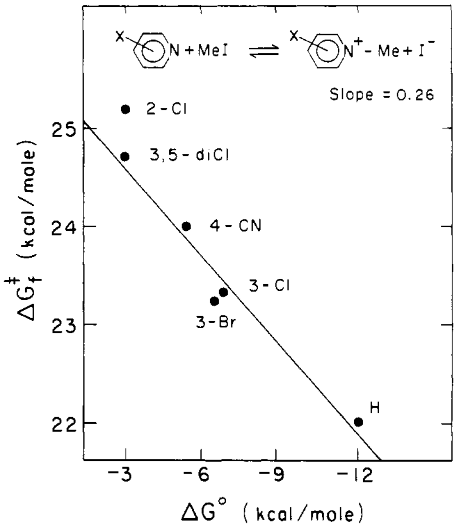


Figure 4. Free energy of activation vs. free energy of reaction for the methylation of substituted pyridines with methyl iodide in acetonitrile.

Comparison with Published Values. Table XI provides some checks of our data against published values for the most relevant systems we can find. Although there are no comparisons at exactly equivalent conditions, the agreement is good enough to support the methods which we have used.

Discussion

Extended Brønsted Treatment. The goal of this study is to determine kinetic and thermodynamic properties for the alkylation of a series of substituted pyridines and to compare the results with other measures of charge development in the Menschutkin transition state and in the pyridine nucleus. Figures 4 and 5 compare the free energies and enthalpies of activation for methylation with the corresponding thermodynamic properties for complete reaction—presumably to separated ions—in acetonitrile

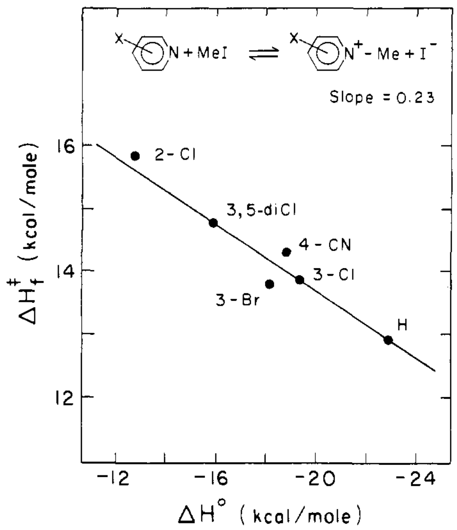


Figure 5. Enthalpy of activation vs. enthalpy of reaction for the methylation of substituted pyridines with methyl iodide in acetonitrile.

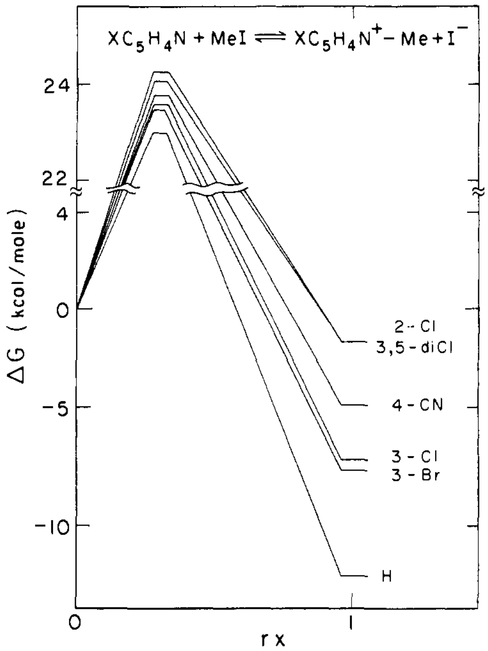


Figure 6. Free energy–reaction coordinate diagram for the methylation of substituted pyridines with methyl iodide in acetonitrile. See text regarding positions of transition states.

at 25 °C. We shall refer to the slope of the correlation line in Figure 4 as α_{Me} since it corresponds operationally to the Brønsted α for proton transfer. Excluding the 2-chloro compound, the only one for which steric factors can be invoked, a slope of 0.26 can be assigned to the free energy plot and 0.23 to the enthalpy one. Since the same initial state is being converted into a transition state and into final products in each case, these figures give us a clear reading on the relative sensitivity to substitution on the pyridine ring of the transition state and in the product ions. By these criteria <30% of the final charge has developed at the transition state for the forward reaction. Figures 5–7 present "reaction coordinate plots" of free energies and enthalpies. We have not used the usual curved plots since we only know three energies for each compound—those of the initial, final, and transition states. The position of the transition state on the reaction coordinate is placed to correspond to the degree of charging as detected in the pyridine members at that point. This cannot be related directly to the length or strength of any particular bond, and so is a purely arbitrary choice.

The only directly comparable data of which we are aware are those of Matsui and Tokura[14] for methylation of substituted

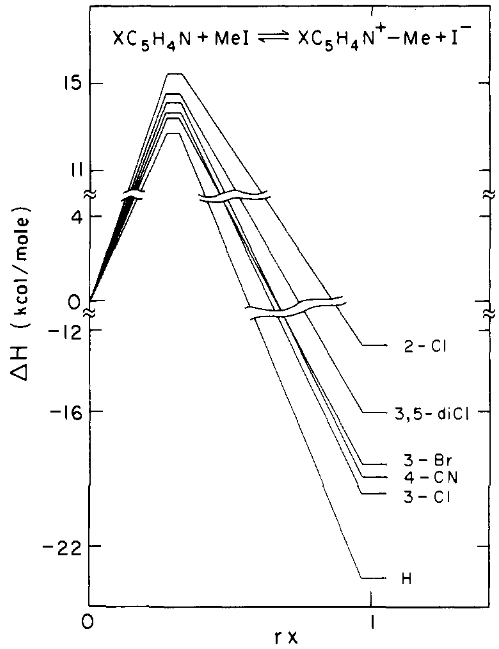


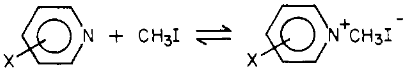
Figure 7. Enthalpy–reaction coordinate diagram for the methylation of substituted pyridines with methyl iodide in acetonitrile. See text regarding position of transition state.

N,N-dimethylanilines in nitrobenzene at 50 °C from which a slope of ~0.48 may be estimated.

The slope of Figure 4 corrected to 50 °C is still 0.26, and relative values in both series seem to be rather insensitive to solvent effects. Therefore, the most likely cause of the difference in slope lies in a difference in steric factors at the transition state. There would be a much steeper slope (approaching 0.5) to the Brønsted-type line of Figure 4 if heavy weight were given to the point for 2-chloropyridine. Hindrance to the approach of the alkylating agent to the nucleophilic center would reasonably lead to a more product-like transition state.

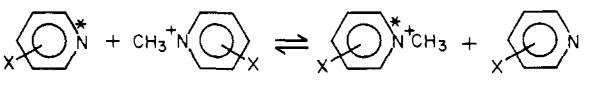
Very recently, Albery and Kreevoy[37,38] have extended the theory of Marcus to transalkylation reactions. In view of the success of Marcus theory in relating rates and thermodynamics for electron-transfer and proton-transfer reactions, it is reasonable to apply the same basic approach for methyl transfer reactions.

The Albery–Kreevoy–Marcus (AKM) theory considers the overall symmetry of the transition state for pyridine quaternization with methyl iodide (eq 17) in terms of the activation barriers for



(17)

the two symmetrical exchange reactions, for which $\Delta G° = 0$, where



(18)

$$\mathrm{CH_3I + I^{-*} \rightleftharpoons CH_3I^* + I^-} \tag{19}$$

the asterisks represent an appropriate label, such as radioactivity, for following the exchange reaction. Rates for reactions 18 and 19 could be measured readily to test the application of AKM theory to our data. Unfortunately, we know of no directly applicable reports which could be applied at this time[44] and so will forego further discussion of this interesting approach toward relating $\Delta G^{\ddagger}$ and $\Delta G°$.

Other Probes of the Menschutkin Transition State. Matsui and Tokura[14] not only compared rates and equilibria for the reaction of several 3- and 4-substituted N,N-dimethylanilines with methyl iodide, they did so in several solvents. Little sensitivity of relative rates to solvent change was observed for most of the bases. Solvent effects as a function of substituents were nearly the same for methylation of pyridines as for the N,N-dimethylanilines. They determined $\Delta G^{\ddagger}$ and $\Delta G°$ for reaction of m-methyl-N,N-di-

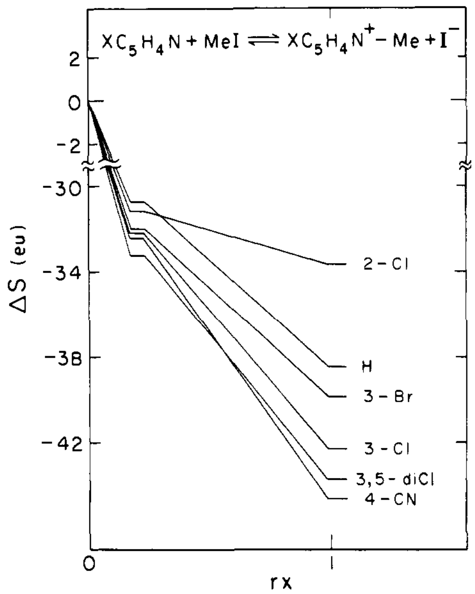


Figure 8. Entropy–reaction coordinate diagram for the methylation of substituted pyridines with methyl iodide in acetonitrile. See text regarding position of transition state.

methylaniline with methyl iodide in six solvents and obtained a slope of ~0.38 as a measure of the response of transition state to solvent variation relative to that of the products.

Abraham and Grollier[20b] compared solvent effects on rates for many Menschutkin reactions and found that all correlated well (but with somewhat different slopes), against their standard system, tri-*n*-propylamine + methyl iodide in 39 solvents. Their elegant dissection of the triethylamine–ethyl iodide reaction into solvent effects on the transition state compared with those on the products gave 0.37–0.45 as the measure of charge development by several criteria. A calorimetric dissection of solvent effects on enthalpies of reaction and activation[48,49] agrees with Abraham's conclusion that most of the influence of solvent variation on the Menschutkin reaction is exerted on the transition state rather than on the reactants.

The response of quaternization reactions to pressure leads to an estimate of ~0.30 for charge development in the transition state of pyridine with methyl iodide in acetonitrile from the ratio of $\Delta V^{\ddagger}/\Delta \bar{V}^{\circ}$.[50] Steric effects on the forward reaction of sterically hindered pyridines are about three times as severe for the forward Menschutkin reaction as for the reverse one.[17]

The Question of Activation Entropies. All of the experimental criteria presented so far for comparing the response of transition state and product ions with a variety of perturbations (solvent, pressure, reagent structure) agree that considerably <50% of full charge has been developed at the S_N2 transition state for this series of transalkylations. The first attempt to address this question,[30] however, was based on a comparison of entropies ($\Delta S^{\ddagger}$ vs. ΔS°) and came to the entirely opposite conclusion—that the transition state was almost entirely like the products. Kreevoy[31] raised the reasonable objection that the essential bimolecular character of the S_N2 transition state precluded separated ions as an appropriate model and suggested that the true product upon which the entropy argument was based was an ion pair.

Our data (Table X, Figure 8) and those of other workers (Table X) are all in substantial agreement that $\Delta S^{\ddagger}$ for the quaternization reaction by a variety of neutral alkylating systems in nonaqueous media is in the range of −35 to −40 gibbs/mol which is only slightly less negative than that for the overall ionization reaction. Oddly enough, this range of values is remarkably insensitive to the partners involved in the reaction or their concentrations, even when variation in rate behavior suggests that the degree of ion pairing is changing.[24,25] This in turn implies, at least for the present case, that there is probably little difference in entropy between the solvated pyridinium iodide ion pair and that of the separated ions. This conclusion is supported in part by the careful study of Mackay and Poziomek,[46] who determined the ion-pair dissociation constant of 4-cyano-1-ethylpyridinium iodide in acetonitrile ($K_D = 10.4 \times 10^{-3}$ M) and showed that, in terms of activity coefficients or reactivity, the ions and ion pair were virtually identical. We note at this point that, although the S_N2 geometry of the transition state for the quaternization of pyridines with methyl iodide requires a colinear N–C–I arrangement, the usual geometry of pyridinium iodide ion pairs is probably different with the iodide ion above the ring in a charge-transfer complex. The relaxed ion pair is a poor model for the transition state.

The experimental evidence shows clearly that, *although the degree of charging at the transition state is only ~30–40%, that in the fully charged ions as registered by the effect of pyridine substituents, solvent change, and volume change for free energy or enthalpy, the entropy change for activation is almost the same large negative number as that for the complete reaction.* Two major factors could contribute to the entropy change in the Menschutkin reaction. One is the change in translational entropy from bringing the reactants together to the transition state. However, by the same argument, translational entropy should be lost in the reverse Menschutkin reaction for which $\Delta S^{\ddagger}$ is actually a small positive value. Thus, although translational entropy changes must be considerable, say 10–15 gibbs/mol, for both the forward and reverse reaction, other factors must be more important. The major source of large negative $\Delta S^{\ddagger}$ and ΔS° for quaternization is electrostatic solvation of the charges produced. This point is tested easily by finding an average ratio of 5.4×10^{-3} for $\Delta S^{\circ}/\Delta G^{\circ}$ of the 3- and 4-monosubstituted pyridines in Tables VIII and X. For a purely electrostatic system[51,52]

$$\Delta S^{\circ} = -\Delta G^{\circ}(\mathrm{d}\ \ln \epsilon/\mathrm{d}t) \qquad (20)$$

the value for $\mathrm{d}\ \ln \epsilon/\mathrm{d}t$ for several dipolar aprotic solvents of dielectric properties similar to acetonitrile is exactly in the range of $4\text{–}6 \times 10^{-3}$.[52] Since the entropies of activation for quaternization are nearly the same as those for complete ionization, and the latter are dominated by electrostatic solvation, it follows that the overwhelming contribution to $\Delta S^{\ddagger}$ is solvation of the ion-pair-like transition state. Furthermore, there is good reason to attribute virtually all of this entropy change to reorganization of solvent around the iodine atom as it is converted from the negative end of a weak dipole into an almost fully charged iodide ion. Our support for this claim is as follows.

(a) There is a discrepancy between the modest degree of charge development in the pyridine ring in the transition state and the large corresponding change in entropy.

(b) The entropies of activation for methylation of all our pyridines are nearly the same (−32 ± 1 gibbs/mol) while ΔS° covers a wider range and seems to be more responsive to charge variation in the pyridinium ion.

(c) The $\Delta S^{\ddagger}$ for reaction of each pyridine with ethyl iodide (Table VI) is within experimental error of that for its reaction with methyl iodide (Table X), although rate differences are considerable.

(d) The $\Delta S^{\ddagger}$ is much lower for reaction of free triphenylmethyl carbonium ions with pyridine in nitromethane—under conditions where there is no leaving group.[53]

(e) The change in $\Delta S^{\ddagger}$ for transferring the reaction of *N,N*-dimethylaniline with methyl iodide from acetonitrile to acetone is −4.51 gibbs/mol.[14] The corresponding single ion entropy of

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(50) Kondo, Y.; Shinzawa, M.; Tokura, N. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 713. See also a discussion by Asano, T.; Le Noble, W. J. *Chem. Rev.* **1978**, *78*, 407.

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(53) Kim, C. B.; Leffek, K. T. *Can. J. Chem.* **1975**, *53*, 3408.

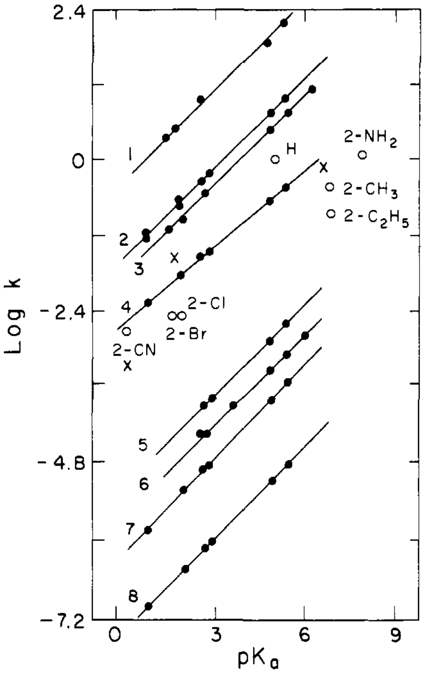

Figure 9. Comparison of log k for alkylation of substituted pyridines by a variety of alkylating agents. Parallel lines include points for 3- and 4-substituted pyridines only for the following reactions. (1) Reaction with MeOCCl in H_2O, 25 °C: Bond, P. M.; Castro, E. A.; Moodie, R. B.; *J. Chem. Soc., Perkin Trans. 2* **1976**, *68*. (2) $MeSO_3F$ in 2-nitropropane, 25 °C. (3) $C_6H_5SO_2Cl$ in H_2O, 25 °C; Rogne, O. *J. Chem. Soc. B* **1970**, 728. $EtSO_3F$ in 2-nitropropane, 25 °C. (5) Alkyl bromide in nitromethane, 40 °C: Clark, K.; Rothwell, K. *J. Chem. Soc.* **1960**, 1885. (6) MeI, nitrobenzene, 25 °C: Coppens, G.; Declerk, F.; Gillet, C.; Nasielski, J. *Bull. Soc. Chem. Belg.* **1963**, *72*, 25. Ortho substituted: Deady, L. W.; Zoltewicz, J. A. *J. Org. Chem.* **1972**, *37*, 603. (7) MeI, 2-nitropropane, 25 °C. (8) EtI, 2-nitropropane, 25 °C. Open circles refer to relative methylation rates for 2-substituted pyridines with MeI in Me_2SO at 23 °C: ref 17c. *X* refers to relative rates for 2-substituted pyridines with $MeSO_3F$ in benzene: ref 63.

transfer, ΔS_{tr}, for iodide ion is −5.4 gibbs/mol.[20f] Although this evidence does not fit the present case precisely, it is consistent with the other facts. Matsui and Tokura[14] showed that $\Delta S^{\ddagger}$ for this reaction depends both on substitution and on solvent. Unfortunately, no other ΔS°_{tr} values for I^- are presently known in solvents where $\Delta S^{\ddagger}$ values have been measured which would allow us to test this question further.

It is particularly important to realize how misleading the usual way of writing displacement reactions really is—see for example equations 18 and 19—which totally neglect the crucial role of solvent in symbolizing this ostensibly "simple" reaction. Ritchie's[54] bold claim "all patterns of reactivity and selectivity in S_N2 reactions arise primarily from solvent and not from some inherent property of the solute reactants" has at least partial support from the demonstration by Olmstead and Brauman[55] that simple ion–molecule displacement reactions do not follow the S_N2 mechanism. Solvation of the transition state is therefore a prerequisite for many, if not all, S_N2 reactions, and no other relevant property is more apt to reflect solvent reorganization than entropies of activation or reaction.

Solvation enthalpies and free energies quite often are closely parallel to the inherent gas-phase properties, so that in many cases the observed reactivity patterns in solution do accurately reflect the inherent ones.[56] However, there are so many cases where the exact opposite is true[57] that Ritchie's warning should be taken as a wise point of departure. The many attempts to analyze reactivity patterns in these systems in terms of quantum mechanical formulations which totally ignore the overwhelming role of solvation are clearly inappropriate. We shall see in the following section further evidence that the enormous variations in rates of Menschutkin reactions can scarcely be viewed in simple terms of a variable bimolecular transition state.

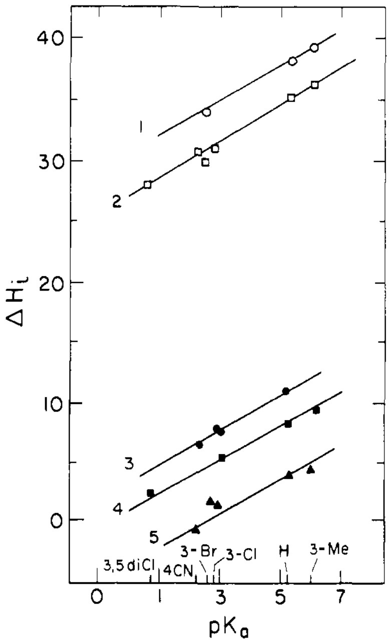

Figure 10. Effect of substituents on standard enthalpies for various processes which develop positive charge on the pyridine nucleus in solution. (1) Heat of protonation in HSO_3F. (2) Heat of methylation by $MeSO_3F$: this study. (3) Heat of reaction with $BF_3 \cdot THF$: M.S. Thesis of H. F. Hillegas, University of Pittsburgh, 1977. (4) Heat of protonation with F_3CCOOH in CCl_4: Arnett, E. M.; Chawla, B. *J. Am. Chem. Soc.* **1978**, *100*, 217. (5) Heat of ionization in water from values tabulated by Arnett, E. M.; Scorrano, G. *Adv. Phys. Org. Chem.* **1976**, *13*, 84.

Variation of the Alkylating Agent. In an earlier communication[16] we drew attention to the fact that the relative rates of methylation and ethylation of the 3- and 4-substituted pyridines are remarkably insensitive to the reactivity of the alkylating agent. Figure 9 extends this observation to include published data from a wide range of other alkylating agents under quite different conditions than those used here. Although our rate data fit a Hammett plot well ($\rho = -2.63$), we choose to use the pK_a's for the pyridines, since those data apply directly to charging of the pyridine nucleus (rather than to deprotonation of benzoic acids) and they have been determined for an enormous variety of groups and substitution patterns.[58] Figure 9 shows that the participation of 3 and 4 substituents in stabilizing the transition states for alkylation (and even some related reactions) is remarkably unaffected by the nature of the leaving group or the conditions over a rate range of nearly a billion! Figure 10 demonstrates that the response of 3 and 4 substituents on the pyridine ring to positive charge development from coordination of the nitrogen is almost unaffected by the nature of the process or of the acid.

Figures 9 and 10 provide very strong support for the notion advanced in the previous section, that the bond from the methyl group to the leaving group is almost completely ruptured (and the leaving group almost completely solvated) at the transition state, even though charge development as detected in the pyridine nucleus is only ~30% complete. If this conclusion is correct, then the primary factor which determines the rates of alkylation is the

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(54) Ritchie, C. D. In Coetzee, J. F.; Ritchie, C. D. "Solute-Solvent Interactions", Marcel Dekker: New York, 1976; Vol. 2, p 265.

(55) Olmstead, W. N.; Brauman, J. *J. Am. Chem. Soc.* **1977**, *99*, 4219.

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(57) (a) Arnett, E. M.; Jones, F. M., III; Taagepera, M.; Henderson, W. G.; Beauchamp, J. L.; Holtz, D.; Taft, R. W. *J. Am. Chem. Soc.* **1972**, *94*, 4724. (b) Arnett, E. M.; Abboud, J. L. M. *Ibid.* **1975**, *97*, 3865. (c) Arnett, E. M.; Small, L. E.; Oancea, D.; Johnston, D. *Ibid.* **1976**, *98*, 7346.

(58) We find as a rule of thumb that all free energy and enthalpy properties known to us which involve charging 3- or 4-substituted pyridines yield good linear coorelations when plotted vs. aqueous pK_a's.

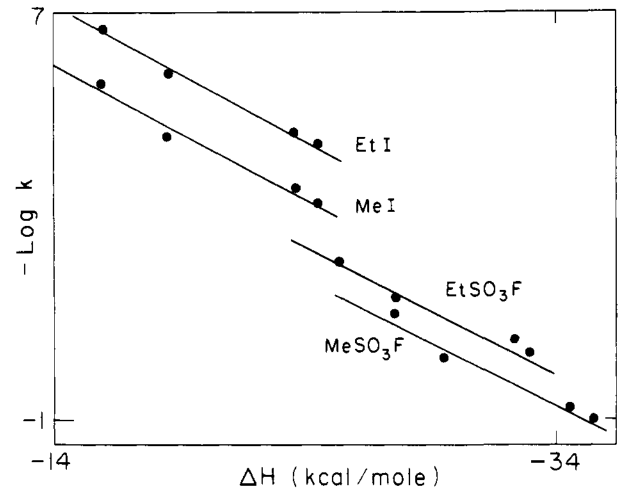

Figure 11. Log k vs. $\Delta H°$ for the alkylation of meta- and para-substituted pyridines: $XC_5H_4N + RY \rightarrow XC_5H_4N^+R + Y^-$; RY = EtI, MeI, $EtSO_3F$, and $MeSO_3F$.

strength of the bond between the alkyl group and the leaving group. Figure 11 provides strong support for this proposal. Clearly the only differentiating factor in the relative heats of reaction of the four pyridines shown is the alkylating agent. Since the same anion is produced by each of the iodides and by each of the fluorosulfonates the only difference between the position of each line is the relative strength of the bond from the alkyl group to the leaving group and the bond formed to each pyridine, including solvation enthalpies of initial and final states.

Figures 4 and 5 showed linear correlations of $\Delta G^\ddagger$ vs. $\Delta G°$ and of $\Delta H^\ddagger$ vs. $\Delta H°$ for methylations with methyl iodide. Figure 11 implies strongly that such correlations would be found for the other alkylation reactions since parallel linear $\Delta G^\ddagger$ vs. $\Delta H°$ correlations are found for these four alkylating agents although their reactivities are enormously different. Our results provide strong support for Leffek's suggestion[53] (based on very fast alkylations with free triaryl carbonium ions) that bond breaking to the leaving group is the main factor in determining rates of Menschutkin reactions and that electrostatic solvation is largely reflected in $\Delta S^\ddagger$.

The nature of the transition state from the vantage point of the methyl group has been provided by a series of elegant secondary deuterium isotope studies in Leffek's laboratory[59] which show a virtually constant k_H/k_D ratio of 0.89 ± 0.01 for reaction of six tertiary amines with CD_3I and CH_3I. Very careful chlorine kinetic isotope effects for alkylation with methyl chloride[60] also imply relatively little carbon–nitrogen bond formation at the transition state.

Reactivity–Selectivity Behavior. We have cited a wealth of evidence from this study and many others which implies a transition state for the Menschutkin reaction that is remarkably insensitive to both the nature of the tertiary amine base and of the alkylating agent as far as total charge development is concerned. This picture is a flagrant violation of the oft-cited reactivity–selectivity principle (RSP) which imputes greater selectivity to less reactive reagents. The RSP seems to be such a reasonable proposition that there have been a number of attempts to justify it on more or less theoretical grounds[61] and to relate it to the Hammond postulate.[33] However, as the RSP has been subjected to increasing scrutiny, its credibility has eroded steadily. It now seems plain that, *although the concept of the principle is attractive, it is virtually useless in practice as a general rule* since the number of times it does not work[61] is approaching the number of times that it does. Jencks has suggested wisely that the RSP be abandoned as a general principle.[62d]

Alkylation of the pyridines provides a clear dichotomy between the 2-substituted bases which are a classic example of RSP behavior[63] and the 3- and 4-substituted pyridines which we have shown do not follow it. The conclusion that the deciding factor is special steric requirements imposed by substituents at the 2 position on formation of an early transition state is obvious. Figure 4 shows clearly the different relationship between $\Delta G^\ddagger_f$ and $\Delta G°$ for methylation of 2-chloropyridine relative to the correlation line for the other bases. Figure 8 reveals that the relation between $\Delta S^\ddagger$ and $\Delta S°$ is again quite different for 2-chloropyridine, although its position on the $\Delta H^\ddagger$ vs. $\Delta H°$ plot (Figure 5) is normal. If enthalpy terms reflect primarily bonding and entropy changes manifest solvent reorangization, it appears that the 2-chloro group weakens the $N-CH_3$ bond both in the transition state and in the ion but has an even greater influence on solvation in both states. It seems likely, in the case of pyridine alkylation, that adherence (or lack of it) to the RSP is related to some complex relation between steric effects, bonding and solvent reorganization at the transition state. In the absence of reliable theories for predicting any of these three factors, we see little point in further speculation at this time on what appears to be a complex interplay of poorly understood influences.

We are well aware that both phenomenological patterns can be "explained" and, if desired, reconciled by invoking apropriate arguments. Our principal concern is that such rationalizations seem to be so facile and adaptable for interpretive purposes but of so little predictive power.

It is instructive to note the variety of conditions under which RSP behavior fails in nucleophilic substitution. Ritchie's[62b] N^+ correlation has been explored mostly for reactions of anionic nucleophiles with resonance delocalized carbonium ions in aqueous media. Bordwell[62c] has used charge-delocalized carbanions in Me_2SO in reaction with benzyl halides and we report here the alkylation of neutral pyridines with neutral alkylating agents. Resonance-stabilized carbonium ions,[56a] carbanions,[56c] and pyridinium ions[56b] all show nearly the same substituent effects on free energies in the gas phase as they do in solution and so might be considered as ideal substrates for revealing inherent free energy patterns. Yet all three series violate the RSP.

Conclusions

A consistent picture of the quaternization of many tertiary bases emerges from an unusually large number of studies over the last 90 years in which solvent, pressure, temperature, base, and alkylating agent have been varied. For this prototypical bimolecular displacement, the following generalizations can be made, provided that severe steric hindrance or strongly hydrogen-bonding solvents are not involved.

(1) The activation process produces about one third the degree of charge development in the bases as that generated by total formation of the quaternary salt. Within the present series of 3- and 4-substituted pyridines, an extension of the Brønsted type of correlation between $\Delta G^\ddagger$ and $\Delta G°$ for quaternization with methyl iodide has a slope, α_{Me}, of ~0.3. The pyridines which are most basic to protons (in terms of aqueous pK_a's) are most nucleophilic (in terms of $\Delta G^\ddagger$) and show the most reactant-like transition states (in terms of small α_{Me}) as calculated by extending the Brønsted equation to methyl transfer.

(2) Although the bond from the alkyl group to the pyridine nitrogen is only ~30% developed at the transition state, the bond

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[60] Bore, T. M.; Hershey, N. D.; House, H. O.; Swain, C. G. *J. Org. Chem.* **1972**, *37*, 997.

[61] (a) Pross, A. *Adv. Phys. Org. Chem.* **1977**, *14*, 69; *J. Chem. Soc., Perkins Trans. 2* **1979**, 595, 857; *J. Am. Chem. Soc.* **1976**, *98*, 776. (b) Giese, B.; Heuk, K. *Chem. Ber.* **1978**, *111*, 1384. Giese, B. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 125. These articles provide excellent coverage of the past and present status of the reactivity–selectivity principle.

[62] The following recent articles document some failures of the reactivity–selectivity principle: (a) Johnson, C. D. *Chem. Rev.* **1975**, *75*, 755. (See, however, McLennan, D. J. *Tetrahedron* **1978**, *34*, 2331.) (b) Ritchie, C. D. *Acc. Chem. Res.* **1972**, *5*, 348. Ritchie, C. D.; Grandler, J. *J. Am. Chem. Soc.* **1979**, *101*, 7318. Also many previous articles are of interest. (c) Bordwell, F. G.; Hughes, D. L. *J. Org. Chem.*, in press. (d) Young, P. R.; Jencks, W. P. *Ibid.*, in press. (e) Gilbert, J. J.; Johnson, C. D. *Ibid.* **1974**, 96, 5846. (f) Koshy, K. M.; Roy, D.; Tidwell, T. T. *Ibid.* **1979**, *101*, 357. (g) Bradamante, S.; Pagani, G. A. *J. Org. Chem.* **1979**, *44*, 4735. (h) References 13 and 16.

[63] Berg, U.; Gallo, R.; Metzger, J.; Chanon, M. *J. Am. Chem. Soc.* **1976**, *98*, 1260.

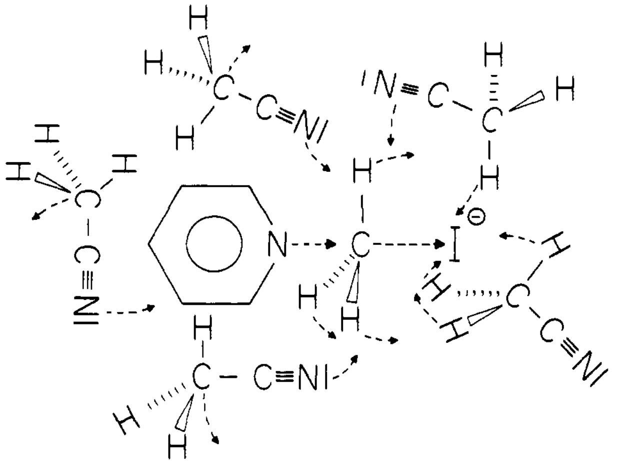

Figure 12. A purposely vague picture of the transition state for the quaternization of pyridines. The N–CH_3 bond is <30% formed while the CH_3–I bond is highly polarized, and solvent reorganization is very far advanced. Note that the solvated ion pair suggested here, with N–C–I bonds colinear, is quite different from the well-known pyridinium iodide charge transfer ion pair, which would be detected by spectroscopy or conduction. Motion (represented by arrows) of an unknown number of solvent molecules, as well as of the atoms in the reacting bonds, is an important feature of reorganization in the transition state which differentiates it ipso facto from even the best models based on relaxed molecules or ions in solution.

to the leaving group is highly polarized and solvent reorganization is nearly complete. The rate of the reaction is dominated by the strength of the bond from the alkyl group to the leaving group. Charge development on the methyl group at the transition states for methyl iodide methylation reactions is almost unaffected by variation of the base. We question the frequent use of such terms as "early" or "late" transition states since that for the Menschutkin quaternization is apparently "early" at one end and "late" at the other and we can say nothing about the number of solvent molecules involved or the strength of bonds to them. If only the covalent bond being formed (N–CH_3) and that being broken (CH_3–I) are considered, the total bonding is much less than unity at the transition state. However, this ignores the contribution of electrostatic bonding to the solvent molecules which is a determining factor in the reaction.

(3) Nearly a century of careful study shows that the reaction rates for quaternization are very sensitive to solvent variation which primarily affects the transition state rather than the reactants.[20] This is not surprising in view of growing evidence that solvent reorganization is a major factor in S_N2 reactions[54] and may even be a requirement for this mechanism.[55]

(4) Solvent reorganization around the iodide leaving group at the transition state is nearly complete in the reaction of methyl iodide with pyridines even though bonding of the methyl group to nitrogen has just begun. This interpretation accommodates the apparent discrepancy between the behavior of entropy parameters and all other factors in the reaction if we consider that changes in entropy are primarily a reflection of solvent reorganization.

(5) Relative rates of alkylation of 3- and 4-substituted pyridines are virtually insensitive to changes in reactivity of the alkylating agent even over a billionfold range in rates. In contrast, 2-substituted pyridines follow the RSP. We find that the free energy and entropy properties for activation and reaction of 2-chloropyridine are clearly differentiated from those of the 3- and 4-substituted compounds in this study. The reasons for adherence (or lack of it) to the RSP probably involves a complex interaction of poorly understood steric and solvation factors.

A Skeptical Epilogue Regarding the Use of Free Energy Analysis to Elucidate Transition-State Structures. The present view of the Menschutkin reactions provides an interesting test case of the current state of mechanism study in solution. The reaction is a prototype for S_N2 displacements which are probably very common and are conceptually simple (at least superficially) since only one transition state is involved. From a phenomonological viewpoint the agreement between many different mechanistic comparisons of the activation parameters with thermodynamic properties for the reaction is comforting. Conceptually, the actual nature and variation of the total transition-state structure remains vague since all stages of the reaction are dominated by solvation reorganization factors (see Figure 12).

Transition-state language (and its derivatives such as Hammond's postulate) is indeed useful for the discussion of reaction mechanisms in solution, since it is reasonable that they occur by continuous correlated changes in energy and geometry. However, in our view, many present attempts to deduce detailed structures for bimolecular transition states in displacement, addition, or elimination reactions are seriously overextended for at least two reasons. The first is that the transition state is usually very far removed in structure and potential energy content from both the initial and final states, thus preventing the rigorous use of Hammond's postulate. The second is that the energetics of the reaction are dominated by solvation dynamics into which there is only the most primitive insight at present.[54]

The transition-state theory has provided a theatre for untestable speculation about an inherently elusive entity (the transition state) which has scarcely had a parallel since the close of medieval scholasticism. The danger in such speculations is that they suggest to the unwary that we have detailed knowledge about the *structure* of the transition state when in fact for many cases, such as the present one, it is only feasible to make gross *energetic comparisons* with other clearly defined states such as reactants or products. As Hammond stressed,[33] transition states which are far removed in potential energy (not to mention free energy) from either reactant or products refer to structures which do not correspond to conventional molecular ones.

Energy correlations between kinetics and thermodynamics are certainly of inherent value since they provide a means for prediction and interpolation. However, when extended to discussion of transition-state structure, it is not unusual to treat the same data in terms of an immutable transition[64] state (e.g., through the Hammett equation) or, with equal facility, in terms of a variable transition state (e.g., through extentions of the Brønsted equation). Since both approaches are reasonable and are ultimately untestable, we see little value in arguments which depend on either one for discussing the structures of transition states that are far removed in energy from other states of the system.

In our view, the energy correlations are fundamentally valuable. However, they are basically unprofitable for the discussion of transition-state structure (e.g., in terms of its position along the reaction coordinate) unless the case fits Hammond's original criteria very closely.

Acknowledgments. We are most appreciative for support of this study through National Science Foundation Grant No. CHE-7622369. We also acknowledge helpful communications with Professors Albery, Harris, Jencks, Kreevoy, and Lewis, all of whom also generously provided us with valuable unpublished results.

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