Progress in

PHYSICAL ORGANIC CHEMISTRY

VOLUME 19

Editor

ROBERT W. TAFT, *Department of Chemistry*
University of California, Irvine, California

A Wiley-Interscience Publication

John Wiley & Sons, Inc.

New York / Chichester / Brisbane / Toronto / Singapore

Progress in

PHYSICAL ORGANIC CHEMISTRY

VOLUME 19

Progress in

PHYSICAL ORGANIC CHEMISTRY

VOLUME 19

Editor

ROBERT W. TAFT, *Department of Chemistry*
University of California, Irvine, California

A Wiley-Interscience Publication

John Wiley & Sons, Inc.

New York / Chichester / Brisbane / Toronto / Singapore

This text is printed on acid-free paper.

An Interscience® Publication

Library of Congress Cataloging in Publication Data:

Library of Congress Catalog Card Number: 63-19364

ISBN 0-471-52442-5

Printed in the United States of America

10 9 8 7 6 5 4 3 2 1

Contributors to Volume 19

José-Luis M. Abboud
Instituto de Quimica Fisica "Rocasolano"
CSIC
Madrid, Spain

Juan Bertràn
Department de Quimica
Universitat Autônoma de Barcelona
Bellaterra (Catalonia), Spain

Keith Bowden
Department of Chemistry and Biological Chemistry
University of Essex
Colchester, Essex, U.K.

Erwin Buncel
Department of Chemistry
Queen's University
Kingston, Canada

Ulf Edlund
Department of Organic Chemistry
Umeå University
Umeå, Sweden

Otto Exner
Institute of Organic Chemistry and Biochemistry
Czechoslovak Academy of Sciences
Prague, Czechoslovakia

Zdenék Friedl
Institute of Organic Chemistry and Biochemistry
Czechoslovak Academy of Sciences
Prague, Czechoslovakia

Edward J. Grubbs
Department of Chemistry
San Diego State University
San Diego, California

Mortimer J. Kamlet
Deceased

Rafael Notario
Instituto de Quimica Fisica "Rocasolano"
CSIC
Madrid, Spain

Miquel Solà
Department de Quimica
Universitat Autônoma de Barcelona
Bellaterra (Catalonia), Spain

Tessek Laboratory
Institute of Analytical Chemistry
Czechoslovak Academy of Sciences
Brno. Czechoslovakia

Introduction to the Series

Physical organic chemistry is a relatively modern field with deep roots in chemistry. The subject is concerned with investigations of organic chemistry by quantitative and mathematical methods. The wedding of physical and organic chemistry has provided a remarkable source of inspiration for both of these classical areas of chemical endeavor. Further, the potential for new developments resulting from this union appears to be still greater. A closing of ties with all aspects of molecular structure and spectroscopy is clearly anticipated. The field provides the proving ground for the development of basic tools for investigations in the areas of molecular biology and biophysics. The subject has an inherent association with phenomena in the condensed phase and thereby with the theories of this state of matter.

The chief directions of the field are: (a) the effects of structure and environment on reaction rates and equilibria; (b) mechanisms of reactions; and (c) applications of statistical and quantum mechanics to organic compounds and reactions. Taken broadly, of course, much of chemistry lies within these confines. The dominant theme that characterizes this field is the emphasis on interpretation and understanding which permits the effective practice of organic chemistry. The field gains its momentum from the application of basic theories and methods of physical chemistry to the broad areas of knowledge of organic reactions and organic structural theory. The nearly inexhaustible diversity of organic structures permits detailed and systematic investigations which have no peer. The reactions of complex natural products have contributed to the development of theories of physical organic chemistry, and, in turn, these theories have ultimately provided great aid in the elucidation of structures of natural products.

Fundamental advances are offered by the knowledge of energy states and their electronic distributions in organic compounds and the relationship of these reaction mechanisms. The development, for example, of enen an empirical and approximate general scheme for the estimation of activation energies would indeed by most notable.

The complexity of even the simplest organic compounds in terms of physical theory well endows the field of physical organic chemistry with the frustrations of approximations. The quantitative correlations employed in this field vary from purely empirical operational formulations to the approach of applying physical principles to a workable model. The most common

procedures have involved the application of approximate theories to approximate models. Critical assessment of the scope and limitations of these approximate applications of theory leads to further development and understanding.

Although he may wish to be a disclaimer, the physical organic chemist attempts to compensate his lack of physical regor by the vigor of his efforts. There has indeed been recently a great outpouring of work in this field. We believe that a forum for exchange of views and for critical and authoritative reviews of topics is an essential need of this field. It is our hope that the projected periodical series of volumes under this title will help serve this need. The general organization and character of the scholarly presentations of our series will correspond to that of the several prototypes, e.g., *Advances in Enzymology, Advances in Chemical Physics,* and *Progress in Inorganic Chemistry.*

We have encouraged the authors to review topics in a style that is not only somewhat more speculative in character but which is also more detailed than presentations normally found in textbooks. Appropriate to this quantitative aspect of organic chemistry, authors have also been encouraged in the citation of numerical data. It is intended that these volumes will find wide use among graduate students as well as practicing organic chemists who are not necessarily expert in the field of these special topics. Aside from these rather obvious considerations, the emphasis in each chapter is the personal ideas of the author. We wish to express our gratitude to the authors for the excellence of their individual presentations.

We greatly welcome comments and suggestions on any aspect of these volumes.

Robert W. Taft

Contents

One Century of Physical Organic Chemistry: The Menshutkin Reaction

BY JOSÉ-LUIS M. ABBOUD AND RAFAEL NOTARIO
Instituto de Quimica Fisica "Rocasolano," CSIC
Madrid, Spain

JUAN BERTRÁN AND MIQUEL SOLÀ
Departament de Quimica
Universitat Autònoma de Barcelona
Bellaterra (Catalonia), Spain

CONTENTS

I. MENSHUTKIN (1, 2) AND THE MENSHUTKIN REACTION

Born October 24, 1842, Nikolai Alexandrovich Menshutkin (3) spent most of his academic life at the University of Saint Petersburg, where he graduated in 1862.

Together with Butlerov and Mendeleiev, he was one of the founding fathers of the Russian Chemical Society (1869). He became the first editor of the *Journal of the Russian Chemical Society*, soon to be renamed the *Journal of the Russian Physical and Chemical Societies.* He held this post until 1900.

From 1902 until the time of his death on February 5, 1907, he occupied the chair of Analytical and Organic Chemistry at the then newly created Polytechnic Institute of Saint Petersburg. In this respect, it is of interest that his book *Analytical Chemistry* enjoyed a worldwide reputation.

His paper "Über die Affinitätkoeffizienten der Alkylhaloide und der Amine" was published in 1890 (4). At that time, the quaternization of amines was already known for several decades (5). Also known was that the rate constants of reactions taking place in solution are often solvent-dependent (6). However, Menshutkin's treatment of solvent effects on the second-order rate constant for the quaternization of triethylamine with ethyl iodide (Reaction 1) at 100°C

$$(C_2H_5)_3N + C_2H_5I \longrightarrow (C_2H_5)_4N^+I^- \qquad (1)$$

was probably the first *systematic* study in this field of physical organic chemistry. He was aware of the importance of his findings (7).

During 1877–1905 he published a number of papers dealing with structural and medium effects on reactivity (see Appendix I). They are "modern" in many respects, and most of his data are still valid. Clearly, Nikolai Alexandrovich Menshutkin was "avant la lettre," a quite brilliant physical organic chemist.

The IUPAC defines (2) the Menshutkin reaction (MR) as the trialkylammonio-dehalogenation of alkyl halides:

$$RHal \xrightarrow{(R'_3N)} RR'_3N^+ Hal^- \qquad (2)$$

Following the common practice we shall adopt here a somewhat broader definition, encompassing all S_N2 [or A_ND_N (8)] alkylation reactions of nitrogen bases in which the formal hybridization of the nitrogen atom is sp^2 or sp^3, with no restrictions imposed on the nature of the nucleofuge. In keeping with the spirit of the IUPAC definition, attention will be focused primarily on neutral electrophiles.

This review is organized as follows. In Sections II and III we examine the thermodynamic and kinetic data available thus far. A quantum-mechanical approach to the MR is given in Section IV. Relevant conclusions and prospects are summarized in Section V.

II. THERMODYNAMIC FEATURES OF THE MENSHUTKIN REACTION

All the experimental evidence seems to indicate that "gas-phase" MRs actually take place on the walls of the reaction vessel and/or on the solid salt (9). Quantitative studies on the systems $Me_3N(g)/MeI(g)$ (10) and $Et_3N(g)/MeI(g)$ (11) show that *activation energies are negative* and that the addition of gaseous dipolar materials has little effect on reaction rates.

In solution, the reversibility of MRs involving halides has long been known (12).

Consider the reaction between a nitrogen base B and an alkylating reagent RL (in principle, L is *any* nucleofuge) in *any* solvent:

$$B + RL \rightleftharpoons \underset{\text{separate ions}}{BR^+ + L^-} \rightleftharpoons \underset{\text{ion pairs}}{BR^+L^-} \rightleftharpoons \underset{\text{solid salt}}{BR^+L^-} \qquad (3)$$

In the general case, products appear as separate ions, ion pairs (13), and solid salt.

The situation is greatly simplified by using highly dilute solutions of the reagents in solvents able to strongly solvate the ionic products:

$$B + RL \underset{k_r}{\overset{k_f}{\rightleftharpoons}} BR^+ + L^- \quad K_c \tag{4}$$

In this case, both k_f and k_r can be obtained directly (14) from separate studies of the forward and reverse reactions. In some instances, both k_f and k_r can be obtained by simultaneously monitoring the concentrations of reactants in systems containing initially B, RL, and S *alone* (15). This method entails larger uncertainties (16).

Notice that K_c, the equilibrium constant for Reaction 4, equals k_f/k_r.

The Lewis concept of acids and bases links proton exchange to exchanges of other electron-accepting species (17):

$$B_1H^+ + B_2 \rightleftharpoons B_1 + B_2H^+ \quad \Delta\Delta H^\circ_{H^+},\ K_{H^+} \tag{5}$$

$$B_1R^+ + B_2 \rightleftharpoons B_1 + B_2R^+ \quad \Delta\Delta H^\circ_{R^+},\ K_{R^+} \tag{6}$$

$$B_1BF_3 + B_2 \rightleftharpoons B_1 + B_2BF_3 \quad \Delta\Delta H^\circ_{BF_3},\ K_{BF_3} \tag{7}$$

The relationship between the MR and alkyl cation exchange between two bases, B_1 and B_2, follows from the consideration of simultaneous equilibria (4) for B_1 and B_2:

$$K_{R^+} = \frac{K_c(B_2)}{K_c(B_1)} \tag{8}$$

Alkyl cation exchange can be observed experimentally (18). This provides a direct measure of K_{R^+}.

Relevant thermodynamic data for Reactions 5 and 7 are collected in Table 1, wherein pyridine has been chosen as the reference base B_1.

Figure 1 shows that, for a given base, differential methyl cation affinities (26), $\Delta\Delta H^\circ_{Me^+}$, are essentially independent of the solvent (27) (NB = $C_6H_5NO_2$; SU = sulfolane; 2NP = 2-nitropropane). This is probably a consequence of the small range of dielectric constants spanned by these solvents; $\Delta\Delta H^\circ_{Me^+}$(NB) is quite comparable to $\Delta\Delta H^\circ_{Et^+}$(2NP) (28).

Relevant relationships between $\Delta\Delta H^\circ_{Me^+}$(NB) and other thermodynamic data are as follows:

1. As shown in Fig. 2, $\Delta\Delta H^\circ_{Me^+}$(NB) and $\Delta\Delta H^\circ_{BF_3}(CH_2Cl_2)$ (differential BF_3 affinities) for 3- and 4-substituted pyridines are linearly related (14), (17).

TABLE 1
Thermodynamic Data for Reactions 5–7[a]

Base	$\Delta\Delta H^\circ_{Me^+}$(SU)	$\Delta\Delta H^\circ_{Me^+}$(NB)	$\Delta\Delta H^\circ_{Me^+}$(2NP)	$\Delta\Delta H^\circ_{Me^+}$(MeCN)	$\Delta\Delta H^\circ_{Et^+}$(2NP)	$\Delta\Delta H^\circ_{BF_3}(CH_2Cl_2)$	$\Delta\Delta G^\circ_{H^+}$(aq)
X-Pyridines							
4-NMe_2	—	−3.7[e]	—	−3.70[g]	—	−5.61[h]	−6.0[k]
4-OMe	−2.40 ± 0.35[c]	−1.46 ± 0.29[d]	—	—	—	−1.72 ± 0.10[i]	−1.9[k]
4-ter-C_4-H_9	—	−1.49 ± 0.49[d]	—	—	—	−1.40 ± 0.12[i]	0.6[k]
4-Me	−1.32 ± 0.26[c]	−1.75 ± 0.50[d]	—	—	—	−1.45 ± 0.15[i]	−1.1[k]
3-Me	—	−1.07[e]	−1.16 ± 0.39[d]	—	—	−0.68 ± 0.10[i]	−0.5[k]
3,5-Me_2	—	−0.78 ± 0.26[d]	—	—	—	—	—
H	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)
3-Cl	3.95 ± 0.24[d]	3.99 ± 0.36[d]	4.19 ± 0.44[d]	4.09 ± 0.32[d]	5.07 ± 0.44[d]	2.22 ± 0.10[i]	3.3[k]
4-CF_3	4.48 ± 0.15[c]	4.74[e]	—	—	—	2.95 ± 0.10[i]	3.4[k]
4-CN	4.61 ± 0.46[d]	4.91 ± 1.10[d]	4.80 ± 0.38[d]	5.50[g]	6.60 ± 0.38[d]	3.54 ± 0.10[i]	4.6[k]
3-Br	4.91 ± 0.26[d]	5.19[e]	5.36 + 0.12[d]	5.36 ± 0.12[d]	5.06 ± 0.12[d]	2.39 ± 0.14[i]	3.9[m]
3-F	—	3.39[e]	3.31 ± 0.06[d]	3.31 ± 0.06[d]	4.16 ± 0.06[d]	—	3.0[m]
3,5-Cl_2	7.59 ± 0.57[d]	8.11 ± 0.70[d]	7.40 ± 0.33[d]	7.72 ± 0.61[d]	7.11 ± 0.33[d]	4.44[j]	6.3[l]
2,4,6-Me_3	0.84 ± 0.26[d]	0.50 ± 0.46[d]	—	—	—	6.47 ± 0.07[i]	—
2-Cl	10.54 ± 0.72[d]	—	—	10.68 ± 0.62[d]	—	7.61 ± 0.11[i]	6.1[k]
Quinuclidine	−9.21 ± 0.24[c]	−9.7[e]	—	−8.91[g]	—	−5.25 ± 0.10[h]	−7.7[n]
N-Me-piperidine	—	−5.4[f]	—	−4.57[g]	—	—	−6.7[f]
Et_3N	—	—	—	−5.40[g]	—	—	−7.5[g]
DABCO[b]	—	−5.6[e]	—	−5.67[g]	—	—	−4.8[g]

[a] All values in kcal mol^{-1}.

[b] 1,4-diazabicyclo[2.2.2]octane.

[c] Ref. 19.

[d] Ref. 14.

[e] Calculated through linear relationships between values of $\Delta H^\circ_{Me^+}$ determined in nitrobenzene and in other solvents.

[f] Ref. 18.

[g] Ref. 20.

[h] Ref. 21.

[i] Ref. 22.

[j] Estimated value (see Fig. 2).

[k] Ref. 23.

[l] Estimated assuming the additivity of substituent effects.

[m] Ref. 24.

[n] Ref. 25.

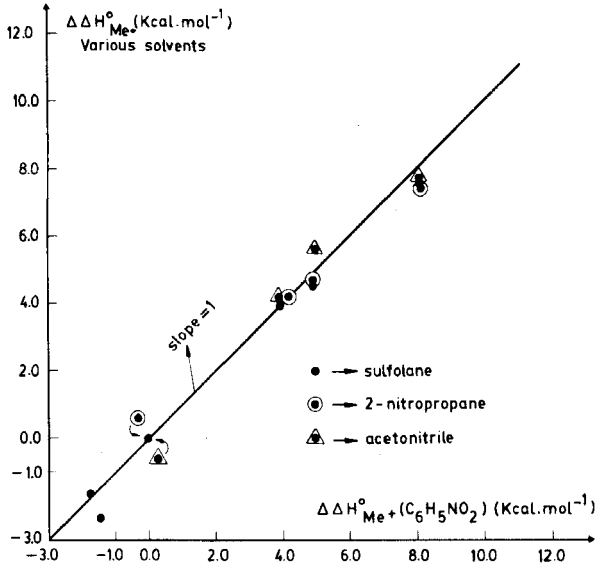


Figure 1 Differential methyl cation affinities for nitrogen bases (relative to pyridine) in various solvents versus the correspondent values in nitrobenzene solution.

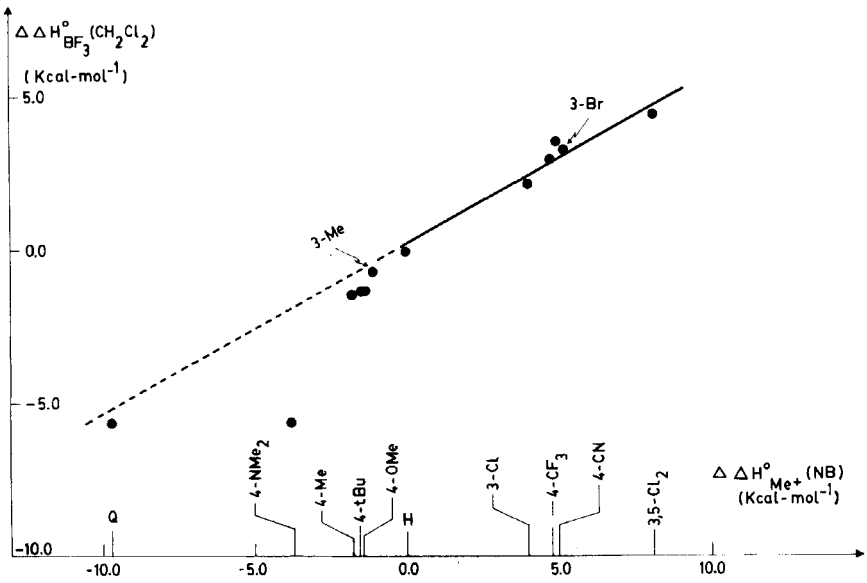


Figure 2 Differential methyl cation affinities $\Delta\Delta H^{\circ}_{Me^+}$(NB) versus differential standard enthalpy changes for Reaction 6 in CH_2Cl_2. Reference base is pyridine.

This does not apply to pyridines bearing electron-releasing (– R) substituents, indicating significant differences between Reactions 6 and 7 in terms of electron demand and, more likely, solvation.

2. Likewise, $\Delta\Delta H^{\circ}_{Me^+}$(NB) and $\Delta\Delta G^{\circ}_{H^+}$(aq) values (14,17) *for the same substituents* follow

$$\Delta\Delta G^{\circ}_{H^+}(aq) = (-0.34 \pm 0.38) + (1.32 \pm 0.12)\Delta\Delta H^{\circ}_{Me^+}(NB) \qquad (9)$$

where $n = 10$; $r^2 = .986$; $sd = 0.43$ kcal mol^{-1}.

It is known that polarizability contributions to $\Delta\Delta H^{\circ}_{BF_3}(CH_2Cl_2)$ (21) and $\Delta\Delta G^{\circ}_{H^+}$(aq) (23) are small, and it follows that the same holds for $\Delta\Delta H^{\circ}_{Me^+}$(NB).

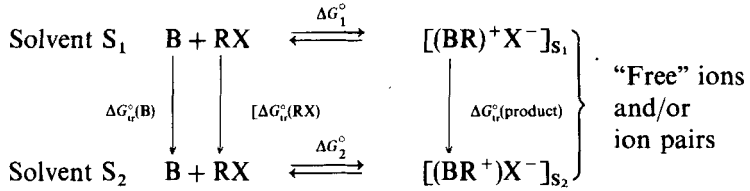
A wealth of kinetic data for forward and reverse alkylation reactions of pyridines and other heterocycles is available (29), indicating that they should provide reliable $\Delta\Delta G^{\circ}_{Me^+}$ values. Their usefulness for this purpose is, unfortunately, limited by the fact that they are obtained using very different temperatures and solvents.

Standard free-energy changes for the alkylation of *N,N*-dimethylanilines (30) [ΔG°_{MA}, Reaction 10] and pyridines (14) [ΔG°_{Py}, Reaction 11] with MeI under formal conditions of equilibrium are presented in Table 2.

$$XC_6H_4NMe_2 + MeI \longrightarrow XC_6H_4\overset{+}{N}Me_3I^- \quad \text{(ion pairs)} \qquad (10)$$

$$XC_5H_4N + MeI \longrightarrow XC_5H_4NMe^+ + I^- \quad \text{(separate ions)} \qquad (11)$$

For a given substituent X, ΔG°_{MA} is strongly solvent-dependent (30b, 31). This can be analyzed through the following cycle (32):



in which the "product" appears as "free" ions or ion pairs. For any species, ΔG°_{tr} is the corresponding standard free- energy change for the transfer from solvent S_1 into solvent S_2. Equation 12 follows:

$$\Delta G^{\circ}_2 - \Delta G^{\circ}_1 = \Delta G^{\circ}_{tr}(\text{product}) - [\Delta G^{\circ}_{tr}(RL) + \Delta G^{\circ}_{tr}(B)] \qquad (12)$$

In the absence of strong solvent–solute interactions (such as hydrogen

TABLE 2
Standard Free-Energy Changes for Reactions 10 and 11

	Reaction 10[a]					Reaction 11[a]
X	ΔG°_{MA}(NB)	$\Delta G^{\circ}_{MA}(Me_2CO)$[b]	$\Delta G^{\circ}_{MA}(C_6H_6)$[b]	ΔG°_{MA}(THF)[b]	ΔG°_{MA}(MeCN)[b]	ΔG°_{py}(MeCN)[d]
4-Me	−4.6[b]	−3.5	—	~0.0	—	—
3-Me	−3.5[b] (−3.3)[c]	−2.9	1.6	0.5	−4.6	—
H	−2.8[b] (−2.8)[c]	−2.5	—	0.9	−4.6	−12.00
3-Cl	−0.4[b]	−0.2	—	—	−2.6	−5.95
3-Br	—	—	—	—	—	−6.24
3-NO_2	1.0[b] (1.0)[c]	1.5	—	—	−0.9	—
3,5-diCl	—	—	—	—	—	−2.72
4-CN	—	—	—	—	—	−5.10
2-Cl	—	—	—	—	—	−2.72

[a] All values in kcal mol^{-1}. Values for Reaction 10 determined at 60°C; those for Reaction 11, at 25°C.
[b] From Ref. 30b.
[c] From Ref. 30a.
[d] From Ref. 14.

bonding) (32)

$$|[\Delta G^{\circ}_{tr}(RL) + \Delta G^{\circ}_{tr}(B)]| \ll |[\Delta G^{\circ}_{tr}\ (product)]| \tag{13}$$

So that

$$\Delta G^{\circ}_{2} - \Delta G^{\circ}_{1} \approx \Delta G^{\circ}_{tr}(product) \tag{14}$$

Equation 14 quantifies the differential effect of the solvent on the position of the equilibria involved in Equation 3.

The availability of experimental standard enthalpies of formation for a variety of ions in the gas phase allows a comparison between solution and gas-phase reactivities.

Let us consider Reaction 15 in the gas phase:

$$B(g) + RL(g) \longrightarrow BR^{+}(g) + L^{-}(g) \quad \Delta X^{\circ}_{(15)} \tag{15}$$

where $\Delta X^{\circ}_{(15)}$ is the change of the thermodynamic state function X for this reaction.

Reaction 15 is the sum of Reactions 16 and 17:

$$RL(g) \longrightarrow R^{+}(g) + L^{-}(g) \quad \Delta X^{\circ}_{(16)} \tag{16}$$

$$R^{+}(g) + B(g) \longrightarrow RB^{+}(g) \quad \Delta X^{\circ}_{(17)} \tag{17}$$

Hence

$$\Delta X^{\circ}_{(15)} = \Delta X^{\circ}_{(16)} + \Delta X^{\circ}_{(17)} \tag{18}$$

Equations 15–18 show that the outcome of the MR Equation 15 is determined solely by the difference between the alkyl cation basicities of L^{-} and B (33, 34).

For the gas-phase alkylation of pyridine with methyl iodide, $\Delta H^{\circ}_{(16)} = 216\,kcal\,mol^{-1}$ and $\Delta H^{\circ}_{(17)} \approx -127\,kcal\,mol^{-1}$ (35). Hence, $\Delta H^{\circ}_{(15)} \approx 89\,kcal\,mol^{-1}$; $\Delta G^{\circ}_{(15)}$ is expected to be close to this value. In MeCN, this same reaction is exergonic by $12.0\,kcal\,mol^{-1}$ and exothermic by $23.4\,kcal\,mol^{-1}$ (14). The difference between gas-phase and solution values of the reaction enthalpy amounts to $\sim 112\,kcal\,mol^{-1}$ and is due entirely to solvation, largely of the reaction products. As we shall discuss in Section IV, *solvation is able to profoundly modify the potential energy hypersurface of the MR.*

The formation of solid salt is a strong driving force, of great importance in poorly solvating media. Both solvation and the formation of solid salt

tend to drive MRs to completion, but in the absence of surface effects or micellar catalysis (36), only the solvent is able to lower the activation barrier of the elementary step:

$$B + RL \longrightarrow BR^+L^- \text{ (ion pair)} \tag{19}$$

Differential standard entropy changes for methyl cation exchange between pyridines in MeCN, $\Delta\Delta S^\circ_{Me^+}$(MeCN) are summarized in Table 3.

Experimental uncertainties are large. There is, however, a clear trend of decreasing $\Delta\Delta S^\circ_{Me^+}$(MeCN) with increasing (i.e., becoming less negative) $\Delta\Delta G^\circ_{Me^+}$(MeCN) (see Table 3). From the fact that within families of bases, $\Delta\Delta S^\circ_{Me^+}(g) \approx 0$ (37a), it follows that (a) $\Delta\Delta S^\circ_{Me^+}$(MeCN) originates in solvation effects and (b) solvent "freezing" is more important the less substituent-stabilized the *N*-methylpyridinium cations are. This interplay between substituent and solvent stabilization of organic ions has long been known (38).

To summarize:

1. Abraham (32) has unraveled the contributions of reagents and products to the thermodynamics of MRs in solution.
2. McMahon and Kebarle (37a) and Mautner (37b) have given means of estimating gas-phase methyl cation affinities of neutral species from proton affinities.
3. Arnett (14, 19), Kondo (20), Matsui and Tokura (30b), Rossell (30a), Lewis (39), and their coworkers have provided a small set of reliable thermodynamic data for MRs and other alkyl transfers in solution.
4. At this point, however, we lack a comprehensive view of structural effects on the thermodynamics of alkyl-transfer reactions (39a). In this respect, quantum chemistry seems bound to play a key role.

TABLE 3
Differential Standard Entropy and Free-Energy Changes, $\Delta\Delta S^\circ_{Me^+}$(MeCN) and $\Delta\Delta G^\circ_{Me^+}$(MeCN), for Reaction 11 in MeCN at 25.0°C (14)

X	$\Delta\Delta S^\circ_{Me^+}$(MeCN)[a]	$\Delta\Delta G^\circ_{Me^+}$(MeCN)[c]
H[b]	0.0 (±2.70)	0.0
3-Br	−1.43 (±0.53)	5.76
3-Cl	−3.73 (±1.16)	6.05
4-CN	−5.15 (±1.79)	6.90
3,5-diCl	−5.29 (±0.62)	9.28
2-Cl	+4.92 (±2.87)	9.28

[a] All values in cal mol^{-1} K^{-1}.
[b] Reference base: pyridine.
[c] In kcal $mole^{-1}$.

III. KINETICS OF THE MENSHUTKIN REACTION

A. The Database and Its Analysis

The truly impressive body of second-order rate constants k for Reaction 20 available nowadays is summarized in Appendix I.

$$B + RL \xrightarrow{k} \text{products} \tag{20}$$

("Products" can be either separate ions, ion pairs, or solid salt).

It is an experimental fact that k values are determined by the nature of the reagents (B, RL) and the solvent (S), as well as by the temperature (T) and the pressure (P). That is

$$k = f(B, RL, S, T, P) \tag{21}$$

wherein f is some (hitherto unknown) function of these variables.

Inspection of the original data shows that, under the same experimental conditions (S, T, P), the mutual agreement between k values for a given reacting system (B, RL) as obtained by different workers varies between excellent (i.e., well within the limits of the combined experimental errors) to poor (differences of the order of magnitude of the constants). This is a consequence of uncertainties originating in the reversibility of the MR, ion-pairing, secondary reactions involving reactants and/or products (self-catalysis) and, likely, traces of impurities affecting conductimetric titrations.

Frequently, uncertainties are largest for very reactive or very unreactive systems. This is unfortunate, given the importance of these data for correlation studies. In fact, while large-scale studies of medium effects on the k values of a constant (B, R, L) system are available, it is difficult to find extensive data sets for reactions involving a constant nucleophile (electrophile) and electrophiles (nucleophiles) having widely different structures, under conditions of constant S, P, and T.

Most of these studies are aimed at obtaining information on the structure of and the charge distribution within the transition state (TS). TSs are fleeting species (lifetimes of ~ 0.1 ps), which until recently (40) have escaped experimental detection. So far, TSs for MRs have not been detected. Analyses of experimental kinetic data are based on

1. The activated complex theory (41). Within its framework, the rate constant k for Reaction 20 and the standard free-energy change for the formation of the activated complex (BRL) (standard free-energy of

activation for Reaction 20) are related through

$$k = \frac{k_B T}{h} (^\circ C)^{-1} \Gamma e^{-\Delta G^\ddagger / RT} \tag{22}$$

where k_B and h respectively stand for Boltzmann and Planck's constants ($^\circ C = 1$ mole dm^{-3}). The term Γ is the ratio of the relevant activity coefficients (42):

$$\Gamma = \frac{\gamma(B)\gamma(RL)}{\gamma(BRL)} \tag{22a}$$

2. A principle of analogy, applying to
   a. Relationships between structural effects on the activation magnitudes $\Delta G^\ddagger$ and on $\Delta H^\ddagger$ and on the homologous thermodynamic magnitudes for model reactions. To this group belong the time-honored Brønsted (43) and Hammett (44) analyses.
   b. Relationships between medium effects on standard free-energies of transfer of TSs and model solutes (32, 45).

The results from Brønsted–Hammett treatments are generally discussed in terms of (a) Hammond's postulate (46), (b) Thornton (47) and Kurz's (48) rules, and (c) potential-energy surface plots (49) (PESPs).

All these methods fall short of providing a complete description of the TSs.

The dissection of intrinsic (kinetic) and thermodynamic contributions to $\Delta G^\ddagger$ values has been carried out along the lines of Marcus theory (50) by Albery and Kreevoy (51) and Murdoch (52) and Lee (53). Varandas and Formosinho (54) have developed a different approach to the problem.

At this point, the precise form of f in Equation 21 is unknown, but a less ambitious approach is possible. Let us a take as a reference a reacting system (B_0, R_0L_0) in a given solvent S_0. Temperature and pressure are fixed at the values T_0 and P_0. The rate constant then takes the value k_0. For a different system (B, RL_0) in S_0 at T_0 and P_0, the rate constant is k. If B and B_0 as well as R and R_0 are structurally related, it seems reasonable to link $k_{(B,RL)}$ and k_0 through a series expansion:

$$\log k_{(B,RL)} = \log k_0 + \left(\frac{\partial \log k}{\partial x}\right)(\Delta X) + \left(\frac{\partial \log k}{\partial Y}\right)(\Delta Y) + \left(\frac{\partial^2 \log k}{\partial X\, \partial Y}\right)(\Delta X \Delta Y) + \left(\frac{\partial^2 \log k}{\partial X^2}\right)(\Delta X)^2 + \left(\frac{\partial^2 \log k}{\partial Y^2}\right)(\Delta Y)^2 \tag{23}$$

where X and Y are structural descriptors of B and R and ΔX and ΔY measure the structural changes corresponding to $B_0 \rightarrow B$ and $R_0 \rightarrow R$.

The term $(\partial^2 \log k/\partial X \partial Y)(\Delta X \Delta Y)$ is an interaction term describing the mutual influence of the structural change undergone by the reagents, (i.e., $B_0 \rightarrow B$; $R_0 \rightarrow R$). Thus far, "square terms" such as $(\partial^2 \log k/\partial X^2)(\Delta X)^2$ have not been included in the actual analysis or have been found to be not statistically significant. The importance of cross-terms for mechanistic studies has been emphasized by Dubois et al. (55).

To our knowledge, an analysis along the lines of Equation 23 was first carried out on a MR by Kondo et al. (56). These workers studied the "cross-terms" arising in the study of the quaternization of substituted *N*,*N*-dimethylanilines with 2,4,6-trinitroanisole in various solvents at 50.0°C.

Expressions formally analogous to Equation 23 have been used by Claramunt et al. (57), who approached the problem from a purely statistical point of view. Changes of B, R, and T were simultaneously examined. This work is a prime reference regarding the use of optimal experiment design techniques and provides precise methodological guidelines.

The influence of B, R, L, and S has been treated by Quemeneur and Bariou (58).

It seems desirable that future work in this field would consider the fact that, while limiting the number of experiments is important (even elegant), the "statistically prescribed minimal number of highly informative experiments" may not be sufficient from a chemical point of view. This is so because large experimental errors might sometimes creep in the database and remain unnoticed in the absence of independent checks of the mathematical model.

In this section, we shall examine how k (or $\Delta G^{\ddagger}$) and $\Delta H^{\ddagger}$ are affected by the structure of the reagents (B,RL), the solvent (S), and the pressure (P).

B. The Role of the Nucleophile

1. Taft–Topsom Analyses

The influence of steric effects on the kinetics of MRs being important (17, 29b, 59–67), we shall first consider the case of molecules in which these effects remain essentially constant.

Quinuclidines (**1**) are endowed with an unhindered reactive site (62a) and a rigid framework. The alkylation of (**1**) with MeI has been systematically studied (68, 69); results in MeOH are summarized in Table 4.

1

TABLE 4
Rate Constants k for Quaternization of 4-X-Substituted Quinuclidines with MeI in MeOH[a]

X	$10^3 \times k$(10.0°C)[b]	$10^3 \times k$(25.0°C)[c]	σ_F[d]	σ_R^+[e]
H	4.39	10.35	0	0
t-C_4H_9	4.18		0	−0.07
i-C_3H_7	4.06		0	−0.07
C_2H_5	3.95		0	−0.07
CH_3	3.85	10.00	0	−0.08
CH_2OCH_3	3.57	0.14	−0.06	
CH_2OH	3.51	7.56	(0.14)	(−0.06)
C_6H_5	3.35		0.10	−0.22
$CH{=}CH_2$	3.26		0.06	−0.15
CH_2Cl	2.70	0.23	−0.06	
NH_2	2.60		0.14 (0.19)[f]	−0.52
$NHCH_3$	2.52		0.12 (0.19)[f]	−0.58
$N(CH_3)_2$	2.25		0.10 (0.19)[f]	−0.64
OH	2.11	6.80	0.30	−0.38
$CO_2C_2H_5$	2.02	5.17	0.24 (0.31)[f]	0.0
OCH_3	1.70		0.25 (0.28)[f]	−0.42
Br	1.29	3.67	0.45	−0.15
Cl	1.23	3.70	0.45	−0.17
F	1.06		0.44	−0.25
CN	1.00	2.73	0.60	0.0
NO_2	0.66		0.65	0.0
$CON(CH_3)_2$		7.00	0.19	0.0

[a] All values in liters mol^{-1} s^{-1}.
[b] Values taken from Ref. 69b.
[c] Values from Ref. 68.
[d,e] From Ref. 71.
[f] Enhanced values of σ_F suggested for the correlation of data in aqueous solution (Ref. 71 and references cited therein).

These results show that

1. Substituent effects in MeOH are very modest. At 10°C, $[k(X = NO_2)/k(X = H)] = 6.7$. This leveling effect is due largely to hydrogen-bonding interactions between the nitrogen of **1** and the solvent. Clearly, *the use of hydroxylic solvents for this sort of structural studies should be discouraged.*

2. The quantitative ranking of substituent effects is solvent-dependent, as shown in Table 5.

3. In both MeOH and MeCN, k values for alkyl derivatives increase with the degree of branching of the substituent: Me < Et < i-Pr < t-Bu. However, k(H) > k (Me). These results might be related to cavity and/or hydrophobic effects (70).