Reactivity Model for the Menschutkin Reaction. Methylation of Alkyl-Substituted and Heterosubstituted Pyridines[1]

John C. Schug* and Jimmy W. Viers*

Department of Chemistry, Virginia Polytechnic Institute and State University, Blacksburg, Virginia 24061

Jeffrey I. Seeman*

Philip Morris Research Center, P.O. Box 26583, Richmond, Virginia 23261

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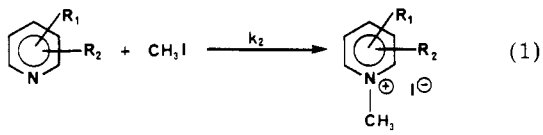
The relative activation energies for the methylation of pyridine, 37 alkyl-substituted pyridines, and 6 heterosubstituted pyridines were calculated by using semiempirical all-valence electron (MINDO/3) self-consistent-field procedures. The rates of alkylation covered more than 5 orders of magnitude. A reactivity model was constructed by placing a CH_3^+ moiety 1.88 Å from the pyridine nitrogen and completely optimizing the CH_3^+-substrate supermolecule. A transition-state (TS) model was determined by consideration of the dequaternization of the *N*-methylpyridinium cation. The energy difference between the TS model and the completely optimized ground-state molecule for the 44 compounds resulted in a good correlation with the logarithms of the methylation rate constants. Implications of this work to nonadditive steric and electronic effects are considered. The model is used to evaluate changes in the position of the TS in these methylation reactions.

I. Introduction

The Menschutkin reaction of substituted pyridines (eq 1) continues to provide a great deal of information regarding electronic, steric, and solvent factors in organic chemical reactions.[3] To date, most interpretations of the



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Menschutkin reaction have been carried out in the context of linear free-energy relationships (LFER).[3-9] Recently, a considerable and continuing debate[7d-f,h,9] concerning the nature of the pyridine alkylation transition state (TS) was provoked by an elegant study by Arnett and Reich.[8] We have been particularly interested in the Menschutkin reaction on the basis of our preliminary evidence that indicates excellent correlations between the alkylation rates of various substituted nicotines and their pharmacological activity.[10]

The Menschutkin reaction is an extremely interesting candidate for reactivity modeling. Kinetic data for the methylation of a very wide range of alkyl- and heteroatom-substituted pyridines are available, including compounds whose reactivities are dominated by steric effects and others controlled by electronic effects.[3,11-18] The interpretations of the relative reactivities of substituted pyridines by means of linear free-energy relations have generally been successful, except for 2,3- and 2,6-disubstituted pyridines, where large steric effects and nonadditivities become apparent. Brown and co-workers have made detailed studies of the latter cases and have suc-

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Table I. Methylation Rate Constants, MINDO/3-Calculated Relative Activation Energies, and Nonadditive Rate Factors [S^a] of 1-44

compd	k_{rel}	k_{calcd}[k]	S^a	$\Delta E^{\ddagger}$[l]	$\Delta E^{\ddagger}/RT$
pyridine (1)	1			0	0
2-picoline (2)	0.43[b]			1.7	2.9
3-picoline (3)	1.7[b]			−0.9	−1.5
4-picoline (4)	2.1[b]			−2.1	−3.6
2,3-lutidine (5)	0.43[b]	0.74	0.59	2.2	3.6
2,4-lutidine (6)	0.92[b]	0.90	1.0	−0.3	−0.5
2,5-lutidine (7)	0.82[b]	0.73	1.1	1.0	1.6
2,6-lutidine (8)	0.040[b]	0.18	0.22	5.5	9.2
3,4-lutidine (9)	3.4[b]	3.6	0.95	−2.8	−4.7
3,5-lutidine (10)	2.6[b]	2.9	0.90	−1.8	−3.1
2,4,6-trimethylpyridine (11)	0.11[c,d]	0.17	0.65	4.6	7.7
2,3,5,6-tetramethylpyridine (12)	0.013[e]	0.034	0.38	8.4	14.2
2,3,4,5,6-pentamethylpyridine (13)	0.015[e]	0.071	0.21	7.1	11.9
2-ethylpyridine (14)	0.22[f]			1.6	2.7
3-ethylpyridine (15)	2.2[c]			−1.5	−2.5
4-ethylpyridine (16)	2.3[c]			−2.6	−4.4
2-isopropylpyridine (17)	0.075[f,g]			1.5	4.1
3-isopropylpyridine (18)	2.4[c]			−1.0	−1.8
4-isopropylpyridine (19)	2.2[c]			−3.0	−5.1
2-*tert*-butylpyridine (20)	0.00020[f,g]			8.2	13.9
3-*tert*-butylpyridine (21)	2.8[c]			−1.9	−3.1
4-*tert*-butylpyridine (22)	2.2[c]			−3.4	−5.8
2-methyl-3-ethylpyridine (23)	0.48[c]	0.95	0.51	2.6	4.4
2-methyl-5-ethylpyridine (24)	1.1[c]	0.95	1.2	0.4	0.7
2-methyl-3-isopropylpyridine (25)	0.51[c]	1.0	0.49	2.4	4.0
2-methyl-5-isopropylpyridine (26)	1.2[c]	1.0	1.2	0.4	0.7
2-methyl-3-*tert*-butylpyridine (27)	0.33[c]	1.2	0.27	2.9	4.9
2-methyl-5-*tert*-butylpyridine (28)	1.3[c]	1.2	1.1	−0.03	−0.04
2-ethyl-3-methylpyridine (29)	0.24[c]	0.37	0.64	2.9	4.9
2-ethyl-5-methylpyridine (30)	0.54[c]	0.37	1.5	1.2	2.1
2-ethyl-6-methylpyridine (31)	0.0035[h]	0.095	0.037	6.6	11.2
2-isopropyl-3-methylpyridine (32)	0.0031[c]	0.13	0.024	5.2	8.8
2-isopropyl-5-methylpyridine (33)	0.17[c]	0.13	1.3	0.7	2.8
2,6-diethylpyridine (34)	0.0037[i]	0.048	0.076	6.9	11.7
2,6-diisopropylpyridine (35)	0.00015[i]	0.0056	0.027	8.5	17.2
2,3-cyclopentenopyridine (36)	1.9[b]	0.73	2.6	−2.3	−3.9
2,3-cyclohexenopyridine (37)	1.1[b]	0.73	1.5	−0.3	−0.4
2,3-cycloheptenopyridine (38)	0.30[b]	0.73	0.41	1.4	2.4
2-aminopyridine (39)	0.50[g]			−1.0	−1.8
4-aminopyridine (40)	36.0[j]			−8.4	−14.3
2-amino-6-methylpyridine (41)	0.050[j]	0.22	0.23	3.9	6.6
2-cyanopyridine (42)	0.0020[g]			4.7	7.9
4-cyanopyridine (43)	0.096[g]			0.8	1.3
3-methoxypyridine (44)	0.98[j]			−1.2	−2.0

[a] Nonadditive rate factor $S = k_{rel}/k_{calcd}$. Perfect additivity is obtained when $S = 1$. [b] Reference 6, acetonitrile, 25 °C. [c] Reference 11, nitrobenzene, 25 °C. [d] Reference 12, nitromethane, 60 °C. [e] Reference 13, acetone, 25 °C. [f] Reference 11a, nitrobenzene, 25 °C. [g] Reference 14, acetonitrile, 30 °C. [h] Reference 15, dimethyl sulfoxide, 23 °C. [i] Reference 16, acetone, 25 °C. [j] Reference 17, dimethyl sulfoxide, room temperature. [k] Calculated using relative rate constants for the monosubstituted pyridines and applying LFER. [l] Calculated using eq 2-3 (kcal/mol^{-1}).

ceeded in quantifying these kinetic steric effects.[11] In a very recent paper,[19] the present authors have also discussed the reactivities of 2,X-disubstituted pyridines and established that the nonadditivities are steric in origin. One of the most illuminating previous studies was that of Berg et al.[5b,14] in which the relative rate constants were empirically dissected into electronic and steric components.

While these earlier studies have clearly established the importance of both electronic and steric effects, and have in some cases quantitatively evaluated both components, little has actually been accomplished in terms of obtaining a basic understanding of the data. That is, no success has been achieved in calculating the relative reactivities from first principles. In the present paper, we take a step in this direction. We propose a model that allows for the unified treatment of electronic and steric effects. It accounts successfully for nonadditive substituent effects and allows the treatment of heteroatom substituents as well.

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Sections II and III of this paper deal with the construction of a model transition state for the Menschutkin reaction and the use of MINDO/3 calculations to calculate relative methylation activation energies for 44 pyridines (1–44, cf. Table I), including the most reactive alkylpyridine (toward iodomethane, 3,4-lutidine) to the least reactive (2,6-diisopropylpyridine) for which kinetic data are currently available. Also included in the series are six heterosubstituted pyridines, thereby extending the reactivity range examined herein to greater than 5 orders of magnitude. A good correlation between experimental rate constants and theoretical relative activation energies is obtained, indicating that the model is indeed capable of predicting electronic and steric effects. In section IV, we discuss possible variation in the TS structures for the series of substrates treated.

II. Reactivity Model

Two different theoretical approaches can be applied toward an improved understanding of chemical reaction rates in general. One approach involves obtaining a de-

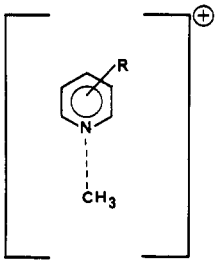
Table II. Comparison of Pyridine Alkylation Relative Rate Constants

	k_{rel}				
	methylation			ethylation	allylation
compd	CH_3CN/25 °C[a]	CH_3CN/30 °C[b]	$PhNO_2$/25 °C[c]	$PhNO_2$/60 °C[d]	$PhNO_2$/60 °C[e]
pyridine	1	1	1	1	1
2-picoline	0.43	0.50	0.47		0.16
3-picoline	1.7	2.1	2.1	2.0	1.5
4-picoline	2.1	2.2	2.2	2.1	1.8
2,3-lutidine	0.43		0.56		0.16
2,4-lutidine	0.92		1.1		0.32
2,5-lutidine	0.82		1.1		0.27
2,6-lutidine	0.040		0.042		~0.0039
3,4-lutidine	3.4	4.23		4.2	2.8
3,5-lutidine	2.6	3.97		4.0	2.4
	Statistical analyses[f]				
slope		0.897	0.977	0.760	0.641
intercept		−0.112	−0.149	0.042	0.387
r		0.986	0.996	0.997	0.989
n		6	8	5	10
p		0.00034	0.00009	0.00490	0.00001
SDR		0.139	0.115	0.128	0.205

[a] Reference 6b. [b] Reference 14. [c] Reference 11. [d] Reference 21. [e] Reference 12. [f] The reported correlations are linear relations between natural logarithms of the relative rates between each of the literature sets of data (columns 2–5) and our methylations in acetonitrile/25 °C; r is the correlation coefficient, n is the sample number, p is the probability, and SDR is the standard deviation of the residuals. Slope (m) and intercept (b) are for the relationship ln (column 1) = m ln (column x) + b.

tailed knowledge of the minimum energy reaction path on the multidimensional energy hypersurface for a particular set of reactants.[20] Because of the complexity of this type of investigation, studies to date have been limited to very simple types of reactions. The second approach involves the derivation of a suitable reactivity model, alternatively described as a model for the reaction transition state. Successful models for quantitation of steric hindrance in ester hydrolyses and S_N2 reactions have been reported by DeTar and his students,[21] and similar transition state models have subsequently been evaluated for other reactions by other groups.[22,23] Fundamental to this approach is the hypothesis that the model TS structures yield an estimate of steric and electronic factors affecting the transition state, and that the change in activation energy is proportional to these factors, as quantified by the chosen theory.

In the present study, we adopt the second approach discussed above and base our model on the postulate that relative activation energies can be estimated by considering interactions between CH_3^+ ions and the several molecules, as illustrated by **45**.



This model does not specifically consider solvent effects or charge separation and bond breaking associated with the nucleofuge. Abraham has shown that varying the solvent for a given pair of reactants can change the reaction rate by as much as several orders of magnitude;[24] Arnett and Reich have concluded that the energy requirement for bond breaking is the single most important factor in determining the rate.[8] Considerable controversy concerning TS structure in the Menschutkin reaction remains as evidenced by subsequent work by Johnson,[9] Abraham,[7d] and others.[7c,e,f,h]

To evaluate the need to consider unusual solvent and/or TS variation effects in these reactions, we have compared the rates of methylation shown in Table I with other available alkylation data. Table II shows the available data. The correlations presented in Table II are linear relations between the logarithms of the present experimental relative rate constants (column 1) and the logarithms of the relative rate constants determined by the other investigators. The most complete comparison of our methylation data is with the allylation results of Clarke and Rothwell[12] in different solvents (acetonitrile vs. nitrobenzene) and at different temperatures (25 vs. 60 °C). Additional comparisons include ethylations and methylations in alternative solvents and temperatures. From the excellent relationships that exist between these sets of alkylation rate constants (cf. the lower section of Table II, which lists the correlation coefficients and additional statistical parameters), we tentatively conclude that differential solvation and changes in leaving group will not invalidate correlations involving the logarithms of relative rate constants.[14]

We next had to choose a theoretical algorithm to use in conjunction with our TS model. Berg and Gallo have recently employed Allinger's molecular mechanics method to determine transition-state structures from estimated strain energies in the methylation of 2-alkylpyridines.[5b,25] Because a suitable force field for nitrogenous heterocycles was (and remains) unavailable,[26] Berg and Gallo used a

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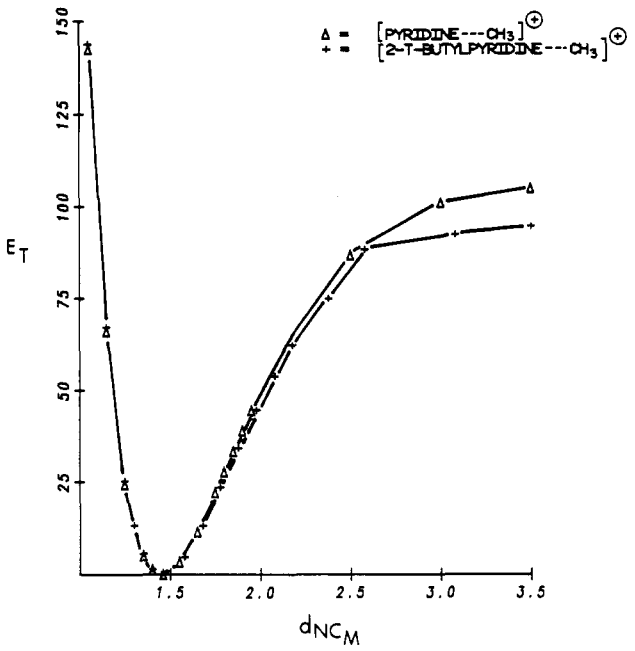

Figure 1. Total energy (kcal mol^{-1}) for [pyridine–CH_3]$^+$ and [2-*tert*-butylpyridine–CH_3]$^+$ supermolecules as a function of the N···C distance, d_{NC_M} (Å). E_T is given in each case relative to the value obtained for the equilibrium cation.

standard pyridine ring geometry for their calculations.[25] They also found it necessary to specify a particular geometry for the attacking CH_3^+ ion. From the results of several different force fields, they concluded that the best average transition state has a N···CH_3^+ distance (d_{NC_M}) of about 1.81 Å.

We decided to employ the MINDO/3 algorithm[27,28] since earlier studies have shown that this method correctly predicts energies and structural information for pyridines and the related *N*-methylpyridinium cations.[19] We have found that the nonadditive part of the iodomethylation rate constants for **2**, **5–7**, **23**, **25**, **27**, and **36–38** are highly correlated with the molecular position of their 2-alkyl substituent.[6] We have also reported an excellent correlation between experimental heats of reaction for a number of alkylpyridines and boron trifluoride and the MINDO/3 calculated heats of methylation.[19]

Numerous other studies have been reported that used the MINDO/3 method with carbocations and related species.[29,30] Although MINDO/3 was originally parameterized for equilibrium geometries of molecules, Dewar and co-workers[31] have applied the method to studies of a wide range of reaction mechanisms, including transition states of charged species, with considerable success.

When considerations are limited to CH_3^+–nucleophile interactions, no saddle point exists on the model reaction hypersurface. Consider for example the supermolecule obtained by placing a CH_3^+ moiety at some position along the C_4–N axis of pyridine at a reasonably large distance from the nitrogen atom. As the CH_3^+ ion is moved toward the nitrogen, the MINDO/3-derived total energy of the system continuously decreases until d_{NC_M} reaches its equilibrium value for the corresponding *N*-methylpyridinium cation. This is illustrated for pyridine and 2-*tert*-butylpyridine in Figure 1.

The functional behavior illustrated in Figure 1 is not limited to semiempirical treatments. Hariharan et al. and Kaufman et al. have carried out ab initio (model potential) self-consistent-field calculations for the attack of CH_3^+ on a ring nitrogen of guanine and have found a very similar total energy–d_{NC_M} relationship.[32,33] Without performing any geometry optimization, Hariharan et al. calculated an energy difference of about 107 kcal/mol between the separated CH_3^+ (planar)–guanine pair and the equilibrium guanine–CH_3^+ (tetrahedral) cation, the latter occurring at a d_{NC_M} distance of about 1.77 Å.[31] Our MINDO/3 calculations[28] yielded an equilibrium distance d_{NC_M} of 1.45 Å for the *N*-methylpyridinium cation, almost identical with the experimental value of 1.46 Å. The total energy increased by 105 kcal/mol when d_{NC_M} was increased from its equilibrium geometry value to 3.5 Å.

The forward (alkylation) and reverse (dequaternization) processes must pass through the same TS. By the principle of microscopic reversibility, the dequaternization reaction[34] can be employed to determine our TS model. Berg and Gallo have summarized the evidence that solvent effects should be very similar for the quaternary salt and the methylation transition state of pyridine.[25] Therefore, solvent effects need not be explicitly included for the reverse activation process.

For the dequaternization of *N*-methylpyridinium iodide, Arnett and Reich have determined the enthalpy of activation to be 36.35 kcal/mol,[8] and we matched this number to a calculated model activation energy. Starting from the optimized structure of *N*-methylpyridinium cation, which exhibited good agreement with the crystal structure of *N*-methylpyridinium iodide,[19] we moved the exocyclic methyl carbon atom (C_M) away from the nitrogen atom and, at each distance d_{NC_M}, optimized all other geometric parameters. As illustrated in Figure 1, the energy difference between each CH_3^+–pyridine supermolecule (**45**, R = H) and the optimized *N*-methylpyridinium cation increased essentially linearly with d_{NC_M} from 1.6 to 2.3 Å; a value of 36.35 kcal/mol was reached at a distance of d_{NC_M} = 1.88 Å. We adopted this value for d_{NC_M} for our reactivity model in the methylation of substituted pyridines **1–44**.

III. Relative Alkylation Rates of Substituted Pyridines

The relative rate constants for the methylation of pyridine, 37 alkylpyridines, and six heterosubstituted pyridines are listed in the first column of Table I. The data for compounds **1–10** and **36–38** were obtained by us at 25 °C in acetonitrile.[6] The relative rates for the remaining compounds are from Brown and his students,[11] Berg and Gallo,[14,18c] le Noble and Ogo,[16] Deady et al.,[15,17] and Clarke and Rothwell.[12] Attempting to reconcile data from different laboratories may cause some difficulty due to systematic errors. However, the complete set of data seems to be reasonably consistent (cf. Table II). Moreover, the

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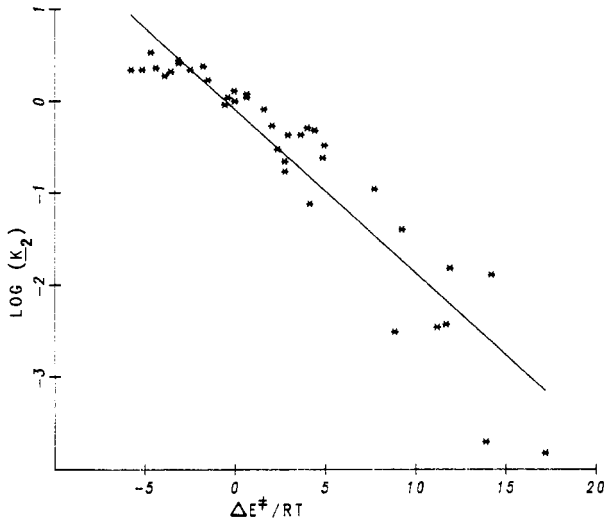

Figure 2. Relationship between the MINDO/3-calculated activation energy $\Delta E^{\ddagger}$ and the methylation rate constants for the alkylpyridines 1–38 (eq 4).

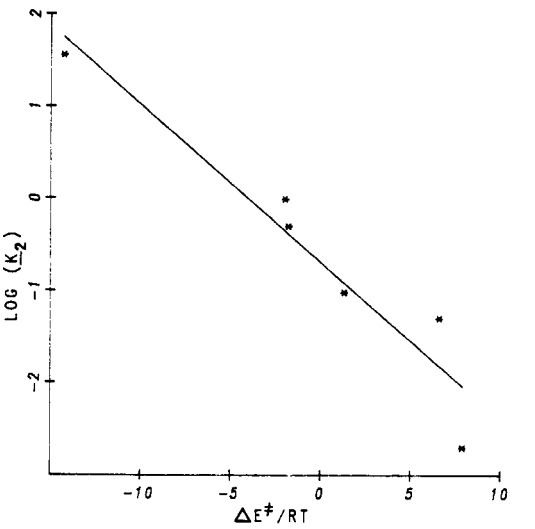

Figure 3. Relationshp between the MINDO/3-calculated activation energy $\Delta E^{\ddagger}$ and the methylation rate constants for the heterosubstituted pyridines **39–44** (eq 5).

total data give a wide range of relative rates, and the objectives and results of this study justify examination of the entire set.

All calculated results in this paper were obtained by using the GEOMO (MINDO/3) program, which incorporates geometry optimization.[28] Our approach was direct. For each nucleophile, we (a) optimized the geometry for the free base and obtained a total energy, E_{FB},[6] (b) constructed our reactivity model **45** with the attacking methyl carbon (C_M) 1.88 Å away from the pyridine nitrogen and minimized the energy with respect to all other geometric parameters, thereby obtaining a total energy for the model TS, E_{TS}, and (c) estimated the model activation energy relative to pyridine, $\Delta E^{\ddagger}_i$ by using eq 2–3. If the model is appropriate, we expect a good correlation of log (k_{rel}) with $\Delta E^{\ddagger}$.

$$\delta E^{\ddagger} = E_{TS} - E_{FB} \quad (2)$$

$$\Delta E^{\ddagger}_i = \delta E^{\ddagger}_i - \delta E_{pyr} \quad (3)$$

Figure 2 shows the correlation obtained for pyridines 1–38 (eq 4). To test the generality of our model, we

$$\log (k_{rel}) = -0.093 - 0.178(\Delta E^{\ddagger}/RT) \quad (4)$$

[r = 0.937, n = 38, p = 0.000 01, SD of residual = 0.414]

applied it to several pyridines involving substituents other than alkyl groups. As shown in Table I, we chose compounds that primarily exerted electronic effects (e.g., 4-aminopyridine) and substrates dominated by steric factors (e.g., 2-amino-6-methylpyridine). The procedure is identical with that described above for the alkylpyridines. The calculated results are listed in Table I, and Figure 3 shows a graph of log (k_{rel}) vs. $\Delta E^{\ddagger}/RT$ for these species (**39–44**) (including pyridine). The least-squares straight line is given by eq 5.

$$\log (k_{rel}) = -0.689 - 0.171(\Delta E^{\ddagger}/RT) \quad (5)$$

[r = 0.956, n = 6, p = 0.0026, SD of residual = 0.469]

If these six heterosubstituted pyridines are combined with the other 38 pyridines discussed earlier, the resulting correlation is given by eq 6. It appears that our model

$$\log (k_{rel}) = -0.192 - 0.171(\Delta E^{\ddagger}/RT) \quad (6)$$

[r = 0.921, n = 44, p = 0.000 01, SD of residual = 0.459]

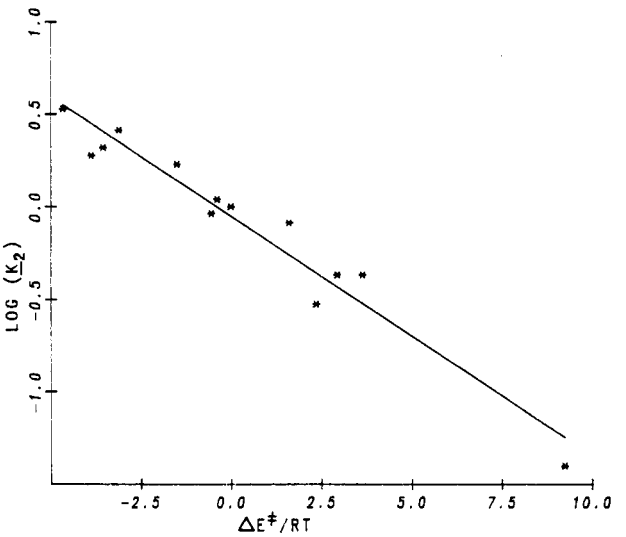

Figure 4. Relationship between the MINDO/3-calculated activation energy $\Delta E^{\ddagger}$ and the methylation rate constants for the entire set of pyridines for which experimental data were obtained in our laboratories (**1–10** and **33–36**). See eq 7.

is capable of correlating both alkyl-substituted and heterosubstituted pyridines simultaneously. Note that the slopes of eq 4–6 are nearly identical, indicating the compatibility of the treatment of alkyl-substituted and heterosubstituted pyridines.

It is important to note that the kinetics data used in the above correlations have experimental uncertainties, not only because they represent average values over limited sets of experiments but also because we have gathered together data from different sources. As indicated in Table I, the methylations were run in different solvents, and although the relative rate constants are highly correlated from one solvent to another (Table II), the slopes are not unity. In addition, there are unquestionably significant errors associated with the rate constants for the hindered pyridines, and it is for these that the deviations from the correlation lines are the greatest.

To investigate to what extent using data from different laboratories has biased the statistics of our reactivity model, we have correlated the model activation energies with relative rate constants using experimental results obtained exclusively in our laboratories (**1–10** and **36–38**). The resultant correlation (Figure 4 and eq 7), which spans

$$\log (k_{rel}) = -0.0522 - 0.1295(\Delta E^{\ddagger}/RT) \quad (7)$$

[$r = 0.973$, $n = 13$, $p = 0.000\,01$, SD of residual = 0.123]

nearly 2 orders of magnitude in rate, is much better in terms of linear free-energy relationships than the previous correlations. The utility of any theoretical model is dependent on the consistency of the experimental data. We conclude that the current model may actually be better than is indicated by the statistical parameters of the preceding correlations (eq 4–6), which utilize data from different laboratories.

The correlations (eq 4–7) are fairly impressive for a number of reasons. First, the correlations that incorporate large samples ($n = 38$ for eq 4 and $n = 44$ for eq 6) are significant to greater than one part in one hundred thousand. Second, it is striking that a theoretical study of this type, which included steric effects and electronic effects simultaneously, mimics experimental observations over such a wide range (for the alkylpyridines, 4 orders of magnitude; with the inclusion of the heterosubstituted pyridines **39–44**, 5 orders of magnitude). Third, we further emphasize that this model predicts reactivity trends for systems that incorporate dominant steric effects (e.g., 2,6-dialkylpyridines) as well as dominant electronic effects (e.g., 3,4-dimethylpyridine, 4-aminopyridine). In addition, the model successfully treats numerous pyridines that exhibit nonadditive kinetic effects. Each of the 14 2,3-disubstituted pyridines and four 2,6-disubstituted pyridines methylate in a nonadditive fashion, as indicated by a value of $S < 1$ (cf. Table I).

An unusual result occurred when we treated 2-fluoropyridine. The optimized ground-state structure was not exceptional, but in the model TS, the fluorine atom was displaced toward the carbon of the attacking methyl group, so that it was almost within bonding distances of the pyridine nitrogen, C_M, and one methyl hydrogen, as well as C_2 of the pyridine ring. This configuration was quite stable so that the calculated $\Delta E^{\ddagger}/RT$ was -50.78. This, of course, would predict a rate constant many orders of magnitude larger than that for pyridine rather than the experimentally observed $k_{rel} = 0.001\,31$. Interestingly, Dannenberg recently made an INDO study of the nucleophilic attack of F^- on methyl, ethyl, and isopropyl fluoride, and in the latter two cases, he observed deep minima corresponding to "specific interactions between F^- and hydrogen on the alkyl groups".[35] Dannenberg suggested that these minima would disappear in the presence of a solvent. Ab initio calculations at the STO-3G level also found a similar abnormality in the reaction of CH_3F with F^-, in that a lower energy stable intermediate rather than a transition state was produced; this abnormality disappeared when a 4-31G basis set was used.[36]

IV. Structures of Model Transition States

In all cases, the pyridine ring in the optimized model TS remains essentially planar, and the carbon atom (C_M) of the attacking $C_MH_3^+$ group is very close to being in the plane of the ring. The dihedral angles $\tau(NC_2C_3C_4)$ and $\tau(NC_6C_5C_4)$ measure nonplanarity of the pyridine ring, and all were found to be less than 1°. The dihedral angles $\tau(C_MNC_2C_3)$ and $\tau(C_MNC_6C_5)$ measure the deviation of C_M from the pyridine ring plane and were no larger than 1.5°.

Table III. Comparison of Methylation Activation Energies Relative to Pyridine

compd	$\Delta E^{\ddagger}_{expt}$[a] kcal mol^{-1}	$\Delta E^{\ddagger}_{calcd}$ (d_{NC_M} = 1.88 Å), kcal mol^{-1}	d_{NC_M}*,[b] Å
pyridine	0	0	1.88
2-picoline	0.1	1.7	1.87
3-picoline	−0.3	−0.9	1.89
4-picoline	−0.3	−2.1	1.90
2,6-lutidine	+1.2	+4.8	1.85
2-isopropylpyridine	+0.9	+1.5	1.87
2-*tert*-butylpyridine	+3.6	+9.4	1.83

[a] Data from ref 11a. [b] d_{NC_M}* is the distance between the pyridine nitrogen and C_M for which the calculated activation energy matches the experimental activation energy.

The largest deviations from coplanarity occurred for the most sterically hindered system.

For the symmetric compounds (e.g., **1**, **4**, **10**) and those with no ortho substituent (e.g., **3** and **9**), C_M is found to be essentially colinear with C_4–N. The 2,6-disubstituted compounds (**8**, **11–13**, **34** and **35**) deviate from colinearity here by about 1.5°, the methyl group being forced slightly out of the plane of the pyridine ring. For compounds having a single α-substituent, the methyl carbon C_M in the model TS is forced out of colinearity with the C_4–N axis but remains in the plane of the ring. For 2,3- and 2,5-lutidine, $\angle C_4NC_M$ is 173.7°, while for 2-picoline and 2,4-lutidine, it is 174.3°. Approximately the same lack of colinearity (6°) was found for cyclohexenopyridine (**37**) and cycloheptenopyridine (**38**), while for cyclopentenopyridine (**36**) the deviation was only 4°. In the series 2-methyl-, 2-ethyl-, 2-isopropyl-, and 2-*tert*-butylpyridine (**2**, **14**, **17**, and **20**), as the 2-substituent increases in size, C_M is driven continuously further off the C_4–N axis. The deviations from colinearity were found to be 5.7°, 6.5°, 7.2°, and 12.9°, respectively, for **2**, **14**, **17**, and **20**.

We have previously examined the effect of alkyl substituents on pyridines and on the corresponding *N*-methylpyridinium cations by MINDO/3-geometry optimization and have found significant internal bond angle variations as a function of substituent bulk.[19] Not surprisingly, alkyl substituents display similar effects on the bond angles for the model TS. For a monosubstituted system, the ipso angle decreases by ca. 4–6°, the α-angle increases ca. 3–4°, and there are minor changes for the β- and γ-angles.

When the pyridine is substituted in two adjacent positions, the optimized model TS structures exhibit nonadditive changes[37] in the internal as well as external ring angles. Such structural nonadditivities are similar to the results we reported earlier for the effect of adjacent substituted pyridines and the *N*-methylpyridinium cations.[19] As noted in an earlier paper,[19] nonadditive changes in structural parameters for the 2-substituted pyridines are well-correlated with their kinetic nonadditives. As noted in the preceding section of this paper, the present model calculations adequately account for these kinetic nonadditives in terms of changes in activation energies.

The question of possible variation of transition-state structure,[6,7] through the series can be addressed by comparison of our estimated relative activation energies with the experimental activation energies obtained several years

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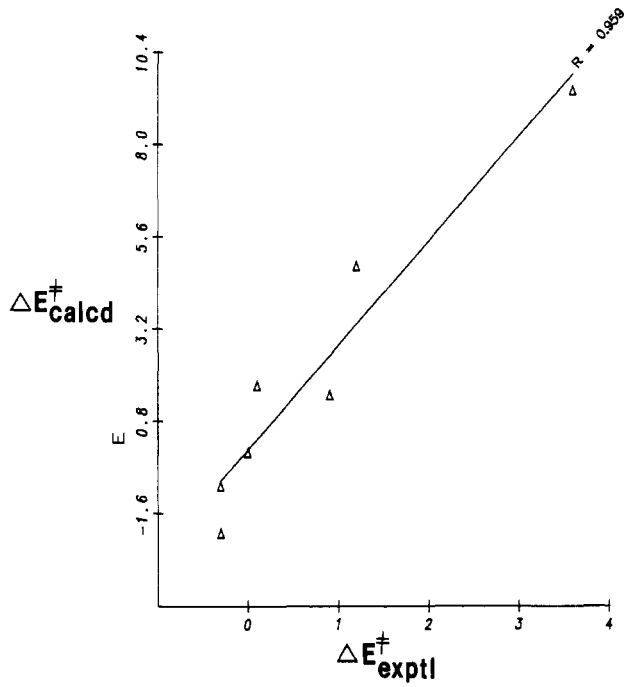

Figure 5. Experimental activation energies (kcal mol^{-1}) for the methylation of selected alkylpyridines vs. the MINDO/3-derived methylation activation energies (kcal mol^{-1}).

ago by Brown and co-workers.[11] The methylation activation energies of seven compounds relative to that of pyridine are shown in Table III, and Figure 5 shows a plot of $\Delta E^{\ddagger}_{exptl}$ vs. $\Delta E^{\ddagger}_{calcd}$. The least-squares straight line shown on this graph is given by eq 8.

$$\Delta E^{\ddagger}_{exptl} = 0.041 + 0.339\Delta E^{\ddagger}_{calcd} \quad (8)$$

[r = 0.959, n = 7, p = 0.001 19, SD of residual = 0.428]

If the slope of eq 8 is divided by ln 10, its value becomes comparable to those in eq 5–7. This gives credence to our modeling procedure, though the deviation of the slopes from the theoretical value of unity implies that the TS structure may not be uniform. In order to make the slope of eq 8 approach unity, the calculated values of $\Delta E^{\ddagger}$ must be reduced for the more hindered compounds and increased for the less hindered substrates. This can be accomplished by modifying d_{NC_M} in those compounds as follows.

Our calculations have shown that, on the average, as d_{NC_M} is increased, the calculated $\Delta E^{\ddagger}$ changes by ca. 110 kcal mol^{-1} Å^{-1}; this number does not vary by more than 10% for the compounds included in Table V. Using this average slope, we have calculated for each of the compounds the value d_{NC_M} should be (d_{NC_M}*) in order for the calculated and experimental relative activation energies to be equal, assuming that the distance of 1.88 Å is correct for pyridine. See Table III.

The required shifts in d_{NC_M} are rather small, the largest being 0.05 Å for the most hindered species, 2-*tert*-butylpyridine. These shifts are compatible with the Hammond postulate as related to the Menschutkin reaction by McKenna,[38] in that the more hindered species tend to require transition states that are more productlike in character. This is also in agreement with the finding of le Noble and co-workers on the basis of volumes of activation;[7a,16,39] however, it is not clear that such small changes in d_{NC_M} would lead to changes in activation volumes by factors of 2 or more.

Not too much quantitative significance should be placed on d_{NC_M}* because of the uncertainties in the experimental activation energies. Arnett and Reich[8] determined an energy of activation for pyridine methylation that differed from the value of Brown et al.[11] by more than 1 kcal mol^{-1}. This variation would effect the quantitative, but not the qualitative, nature of our conclusions. Uncertainties also exist in the calculated relative activation energies, $\Delta E^{\ddagger}_{calcd}$. Aside from leaving group and solvent effects, the large number of internal geometric degrees of freedom in the molecules considered causes additional calculational difficulties. Especially troublesome are the internal rotational degrees of freedom associated with ethyl, isopropyl, and *tert*-butyl groups. Our experience has shown that the energy surface in systems incorporating flexible side chains are very complicated and possess numerous local minima.[19] It is necessary to begin each geometry optimization at a large number of different starting points in the search for a true global minimum. In a number of cases, we have not made exhaustive searches due to the large amount of computational time required.

V. Conclusions

The Menschutkin reaction is of great importance as an archetype in physical organic chemistry. It has recently become controversial with the publication of Arnett and Reich's somewhat unorthodox description[8] and the numerous subsequent publications both criticizing it and defending it.[7,9] We have herein presented a transition-state model for the methylation of a series of alkyl-substituted and heterosubstituted pyridines that accurately correlates the rates of methylation for this series that spans 5 orders of magnitude in rate. The TS model is novel since there are few literature reports dealing with theoretical treatments of the nitrogen alkylation transition state, none to our knowledge that simultaneously model both electronic and steric contributions, and none that treats such a wide range of chemical reactivity and substituent patterns.

Recently, Menger and Williams[40] utilized their postulate of "reaction windows" to explain the nonadditive kinetics of alkylation of nitrogen heterocycles, including pyridines. In this hypothesis, "reactions do not occur by means of single definable transition states...there exist "cones" of trajectories; each trajectory is associated with a particular degree of bond formation and cleavage".[39] Our results indicate that relative activation energies estimated on the basis of a simple model adequately account for nonadditive effects, and there is no need for such phenomenological models as "reaction windows" at this time.

The utility of our model can be stated in another way: on the basis of our molecular orbital calculations for the free bases, we have attempted[41] to find correlations between relative reaction rates and π, total, or lone-pair charges on the nitrogen atoms. These attempts were doomed to failure because they do not take steric effects into account. The success of the current model is based upon the simultaneous treatment of both effects.

Acknowledgment. We thank Drs. James Kao and Victor Day and the Philip Morris Research Center Computer Applications Division and Ms. Kathy McCourt for their contributions to this work and to an anonymous

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referee of the preliminary communication[2] and to the referees of this paper for helpful comments, which were utilized herein. Thaks are also given to Drs. T. S. Osdene, E. B. Sanders, and R. B. Seligman for their encouragement and support.

Registry No. 1, 110-86-1; 2, 109-06-8; 3, 108-99-6; 4, 108-89-4; 5, 583-61-9; 6, 108-47-4; 7, 589-93-5; 8, 108-48-5; 9, 583-58-4; 10, 591-22-0; 11, 108-75-8; 12, 3748-84-3; 13, 3748-83-2; 14, 100-71-0; 15, 536-78-7; 16, 536-75-4; 17, 644-98-4; 18, 6304-18-3; 19, 696-30-0; 20, 5944-41-2; 21, 38031-78-6; 22, 3978-81-2; 23, 14159-59-2; 24, 104-90-5; 25, 80263-42-9; 26, 20194-71-2; 27, 80263-43-0; 28, 85735-96-2; 29, 56986-88-0; 30, 18113-81-0; 31, 1122-69-6; 32, 72693-04-0; 33, 6343-58-4; 34, 935-28-4; 35, 6832-21-9; 36, 533-37-9; 37, 10500-57-9; 38, 7197-96-8; 39, 504-29-0; 40, 504-24-5; 41, 1824-81-3; 42, 100-70-9; 43, 100-48-1; 44, 7295-76-3.

Organometallic Methylation of Nicotine and Nicotine *N*-Oxide. Reaction Pathways and Racemization Mechanisms[1]

Jeffrey I. Seeman,* Henry V. Secor, Charles R. Howe, Charles G. Chavdarian, and Larry W. Morgan

Philip Morris U.S.A. Research Center, Richmond, Virginia 23261

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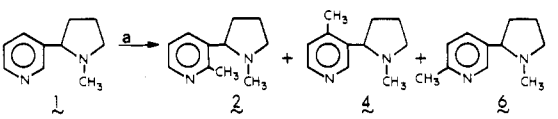
The reaction of nicotine with methyllithium leads to 2-methylnicotine as a major product in addition to the previously reported 4- and 6-methylnicotines. The reaction of nicotine *N*-oxide with methylmagnesium bromide furnishes both 2- and 6-methylnicotine. The product composition of these reactions is strongly dependent on the experimental conditions; the effects of solvent, temperature, and relative reagent concentration are presented. The methyllithium reactions lead to partially racemized methylnicotines, and the recovered nicotine is often nearly optically pure. Independently, (*S*)-(−)-6-methylnicotine was treated with methyllithium and was recovered with complete retention of optical activity. These results suggest that the loss of optical purity in the formation of methylnicotines in these methyllithium reactions occurs during the reaction itself and is not due either to racemization of the starting material or to subsequent racemization of the initially formed product.

Introduction

Investigations in the field of nicotine structure–activity remain a topic of considerable interest.[2] While almost all preparations of nicotine analogues involve lengthy synthesis from acyclic precursors,[3] some of these nicotinoids have been derived directly from nicotine itself.[4,5] This latter approach has appeal because optically pure (*S*)-nicotine is readily available as a starting material, and because this strategy can directly result in optically active analogues.

Some years ago, it was reported that reaction of nicotine (1) with methyllithium in a variety of solvents led to the isolation of 6-methylnicotine (6) with minor amounts of 4-methylnicotine (4) (eq 1).[6] In 1978, other workers reported repeating the original literature procedure and "obtaining essentially the same results" with the exception that the isolated 4 had a higher optical activity.[7,8]



(1)

(a) CH_3Li/toluene heat

Based on the well-documented propensity of alkyllithium reagents to attack in a regioselective manner at the 2-position of a 3-substituted pyridine in preference to the 6-position,[9] we were somewhat skeptical of the literature reports[6,7] which did not demonstrate the formation of 2-methylnicotine (2) as a reaction product. We were thus prompted to reexamine these methylations to confirm

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