

for the loss of methanol relative to *n*-propanol from the silver-bound dimer (Table I), but the difference in proton affinities for these two alcohols is only ~ 7 kcal/mol.¹¹ Absolute metal ion affinities are, in general, much smaller than the corresponding proton affinities^{12,1a} due to a much smaller degree of covalency in the metal cation-ligand bond, particularly for closed-shell cations where electrostatic models have been successful at predicting metal ion affinities.^{13,12b} Small metal ion affinity differences between H₂O and NH₃ relative to their proton affinity difference has also been observed for a number of metals.^{12c} This has been explained for alkali metals as resulting from a greater transfer of charge from the metal ion to NH₃ than to H₂O.^{12c} The tendencies of these bases for electron transfer to a proton are expected to have a more profound influence on their proton affinities,¹⁴ resulting in an enhanced affinity for NH₃ relative to H₂O. The closed-shell silver cation is expected to behave similarly to the alkali metal cations, and these findings support this expectation although the relative degrees of covalent interaction, ionic interaction, and electron transfer cannot be obtained from the data. The difference in the tendency for electron transfer of methanol and *n*-propanol is likely to be much smaller than that of NH₃ and H₂O so that 7 kcal/mol represents an upper limit to the differences in the silver ion affinities of methanol and *n*-propanol, with the actual difference likely to be somewhat less.

Acknowledgment. This work was supported by the National Science Foundation Grant CHE 80-11425. The laser was purchased with funds provided by Continental Oil Corporation. We acknowledge contributions to this study by D. Zakett. S.A.M. acknowledges receipt of an ACS Analytical Division Fellowship sponsored by the Perkin-Elmer Corporation.

Registry No. CH₃OH, 67-56-1; C₂H₅OH, 64-17-5; *n*-C₃H₇OH, 71-23-8; *i*-C₃H₇OH, 67-63-0; *n*-C₄H₉OH, 71-36-3; *t*-C₄H₉OH, 75-65-0; Ag⁺, 14701-21-4.

(11) Hartman, K. N.; Lias, S.; Ausloos, P.; Rosenstock, H. M.; Schroyer, S. S.; Schmidt, C.; Martinsen, D.; Milne, G. W. "A Compendium of Gas Phase Basicity and Proton Affinity Measurements"; 1979, NBSIR 79-1777.

(12) (a) Woodin, M. L.; Beauchamp, J. L. *J. Am. Chem. Soc.* **1978**, *100*, 501. (b) Davidson, W. R.; Kebarle, P. *Ibid.* **1976**, *98*, 6133. (c) Castleman, A. W. *Chem. Phys. Lett.* **1978**, *53*, 560.

(13) Davidson, W. R.; Kebarle, P. *J. Am. Chem. Soc.* **1976**, *98*, 6125.

(14) Kroeger, M. K.; Drago, R. S. *J. Am. Chem. Soc.* **1981**, *103*, 3250.

MINDO/3-Based Transition-State Models for the Menshutkin Reaction. Iodomethylation of Alkylpyridines

Jimmy W. Viers* and John C. Schug*

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

Jeffrey I. Seeman*

Philip Morris Research Center
Richmond, Virginia 23261

Received August 21, 1981

The Menshutkin reaction of substituted pyridines has provided an important basis for the assessment of electronic and steric effects in organic chemical reactions.^{1,2} A continuing challenge in the study of this important reaction is the elucidation of

mechanistic information for systems which incorporate both nonadditive steric effects and subordinate electronic features.^{3,4} Table I lists the rate constants for the iodomethylation of pyridines 1-21.⁴⁻⁶ We have recently shown⁴ that the nonadditive part of the iodomethylation rate constants for 2, 5-7, and 11-13 were highly correlated with the molecular position of their 2-alkyl substituent. We now report a theoretical model for correlation of the relative rates of iodomethylation of a series of alkyl-substituted pyridines (1-21), ranging from the most reactive pyridine (toward iodomethane; 3,4-lutidine) to the least reactive (2,6-diisopropylpyridine) for which kinetic data are currently available. These alkylations, which span four orders of magnitude in rate, are simultaneously controlled by steric and electronic effects. We propose the hypothesis that a set of pyridine iodomethylation rate constants are determined by the relative interactions of CH₃⁺-substrate pairs.

We have previously shown⁴ that complete geometry optimization using the MINDO/3 program of Rinaldi⁷ predicts appropriate trends in bond angles and lengths for pyridine and a series of analogous alkyl-substituted benzene derivatives, including the very sterically hindered *o*-di-*tert*-butylbenzene. The MINDO/3 algorithm has also been successfully used for the determination of the energetics of cations.⁸ In addition, we have found that the MINDO/3 optimized geometry of the *N*-methylpyridinium cation compares favorably with the X-ray structure of *N*-methylpyridinium iodide.⁹ We have further validated the use of MINDO/3 for these systems by obtaining an excellent correlation between experimental heats of reaction for a number of alkylpyridines and boron trifluoride reported by Brown et al.¹⁰ and the MINDO/3 calculated heats of reaction for the analogous iodomethylation reactions.¹¹

To provide a basis for correlating the relative rates, we constructed a model transition state (TS) for each substrate by placing the carbon atom of the CH₃⁺ ion at a reasonable TS distance from the nitrogen atom. It is not possible to determine an appropriate N \cdots CH₃⁺ separation (d_{NCM}) for the model TS by considering the forward (methylation) reaction since the calculation does not show an activation barrier in the absence of solvent and a leaving group. The activation energy for the demethylation of *N*-methylpyridinium iodide is known^{2a} (36.35 kcal/mol⁻¹), and by microscopic reversibility, it can be employed to determine the model TS. Starting from the optimized structure of *N*-methylpyridinium cation, we increased d_{NCM} , optimizing all other geometric parameters at each separation. The energy difference between equilibrium cation and the model TS equalled 36.35 kcal/mol⁻¹ when d_{NCM} equalled 1.88 Å. This distance was then used for the entire series of alkylpyridines. Previous successful calculations of steric effects on S_N2 reactions showed that complete molecular relaxation was required in order to obtain meaningful changes in activation energies.¹² We therefore minimized the energy of the supermolecule with respect to *all* geometric parameters except the 1.88-Å N \cdots CH₃ distance.

For each compound, we calculated an energy difference ΔE between the completely optimized CH₃⁺-substrate system and

(3) (a) DeTar, D. F. *J. Org. Chem.* **1980**, *45*, 5166-5174, 5174-5176. (b) Paquette, L. A.; Gardlik, J. M. *J. Am. Chem. Soc.* **1980**, *102*, 5033-5035. (c) Balliah, V.; Kanagasabapathy, V. M. *Tetrahedron* **1978**, *34*, 3611-3615. (d) Deady, L. W.; Finlayson, W. L.; Korytsky, O. L. *Aust. J. Chem.* **1979**, *32*, 1735-1742.

(4) Seeman, J. I.; Galzerano, R.; Curtis, K.; Schug, J. C.; Viers, J. W. *J. Am. Chem. Soc.* **1981**, *103*, 5982-5984.

(5) le Noble, W. J.; Ogo, Y. *Tetrahedron* **1970**, *26*, 4119-4124.

(6) Brown, H. C.; Cahn, A. *J. Am. Chem. Soc.* **1955**, *77*, 1715-1723.

(7) Rinaldi, D. *QCPE* **1978**, *11*, 360.

(8) Tasaka, M.; Ogata, M.; Ichikawa, H. *J. Am. Chem. Soc.* **1981**, *103*, 1885-1891.

(9) Lalancette, R. A.; Furey, W.; Costanzo, J. N.; Hemmes, P. R.; Jordan, F. *Acta Crystallogr., Sect. B* **1978**, *B34*, 2950-2953.

(10) Brown, H. C.; Gintis, D.; Domash, L. *J. Am. Chem. Soc.* **1956**, *78*, 5387-5394.

(11) Schug, J. C.; Seeman, J. I.; Viers, J. W., manuscript in preparation.

(12) (a) DeTar, D. F.; Luthra, N. P. *J. Am. Chem. Soc.* **1980**, *102*, 4505-4512. (b) DeTar, D. F. *Ibid.* **1974**, *96*, 1254-1255, 1255-1256. (c) Abraham, M. H.; Grellier, P. L.; Hogarth, M. J. *J. Chem. Soc., Perkin Trans. 2* **1975**, 1365-1371.

(1) Reviews: (a) Zoltewicz, J. A.; Deady, L. W. *Adv. Heterocycl. Chem.* **1978**, *22*, 71-121. (b) Tomasik, P.; Johnson, C. D. *Ibid.* **1976**, *20*, 1-64.

(2) (a) Arnett, E. M.; Reich, R. *J. Am. Chem. Soc.* **1980**, *102*, 5892-5902. (b) Johnson, C. D.; Roberts, I.; Taylor, P. G. *J. Chem. Soc., Perkin Trans. 2* **1981**, 409-413.

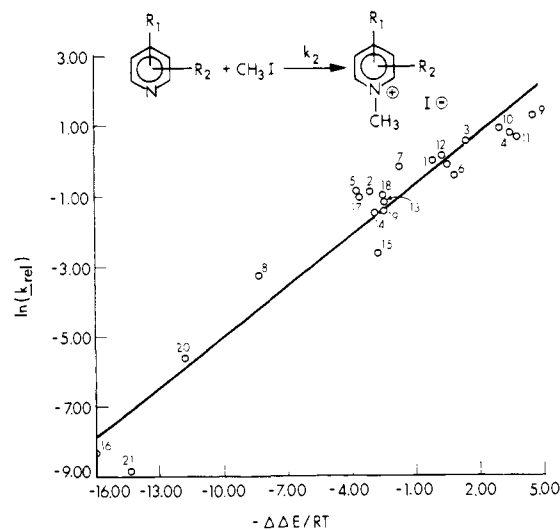


Figure 1. Relationship between the MINDO/3-calculated activation energy $\Delta\Delta E$ and the iodomethylation rate constants for 1-21.

that for the completely optimized substrate molecule by itself.⁴ ΔE spanned a range of 12.2 kcal mol⁻¹ from the most reactive to the least reactive pyridine. When ΔE was referenced to pyridine [$\Delta\Delta E_i = \Delta E_i - \Delta E(\text{pyridine})$], we obtained an excellent correlation between the logarithms of the experimental relative rate constants and $\Delta\Delta E$ as shown in Figure 1 and eq 1. We performed the TS

$$\ln k_{\text{rel}} = -0.259 - 0.481(\Delta\Delta E/RT) \quad (1)$$

$$[r = 0.964, r^2 = 0.928, p = 0.00001, n = 21, \text{sd of residuals} = 0.772]$$

analysis with complete geometry optimization for $d_{\text{NC}_M} = 1.75$ and 2.00 Å for 1-13 and found that the relative energies, $\Delta\Delta E$, are only slightly affected by this change, supporting the validity of the correlation.

A number of structural conclusions are possible from examination of the minimum energy geometries obtained. Relative to the ground-state structures, bond angles in the TS are affected in such a way as to reduce crowding in the vicinity of the nitrogen, e.g., the internal angles C_2NC_6 and the exterior angles NC_2H_2 and $NC_2C_{2\alpha}$ (when present) increase by several degrees. The presence of a 2-substituent in 2, 5-7, and 11-19 asymmetrically distorts the internal pyridine angles and forces C_M , the carbon atom of the CH_3^+ , off the C_4-N axis ($\angle C_4NC_M \sim 167.0^\circ$ for 16); C_M does remain in the plane of the pyridine ring. For these TS models, $\angle C_MNC_2$ and $\angle C_MNC_6$ range from ca. 121 to 126° and 106 to 113°, respectively, relative to 117° for the pyridine TS supermolecule.

The asymmetric distortions which obtain for the 2-monosubstituted pyridine TS do not occur for the 2,6-disubstituted pyridine TS: the $N-C_M$ axis is slightly deflected out of the plane of the ring, with the plane defined by C_M-N-C_4 perpendicular to the plane of the pyridine ring. The distortions induced in the pyridine ring by the presence of the attacking CH_3^+ clearly are not additive on progressing from pyridine to 2- and 2,6-substituted pyridines. These restrictions in the energetically available modes of molecular relaxation may account for the observed nonadditive reactivity of 2,6-disubstituted pyridines,^{5,10,13} in particular, and of other highly congested molecules in general.¹⁴

The slope of eq 1 can be made to approach the theoretical value of unity by appropriately modifying d_{NC_M} for each substrate,

Table I. Iodomethylation Rate Constants and MINDO/3-Calculated Relative Activation Energies of 1-21

| compound | iodo-methylation k_{rel}^a | $\Delta\Delta E_i^b$, kcal mol ⁻¹ | $\Delta\Delta E/RT$ |
|------------------------------------|-------------------------------------|---|---------------------|
| pyridine (1) | 1 ^{a,b} | 0 | 0 |
| 2-picoline (2) | 0.43 ^b | 1.74 | 2.94 |
| 3-picoline (3) | 1.7 ^b | -1.00 | -1.49 |
| 4-picoline (4) | 2.1 ^b | -0.809 | -3.55 |
| 2,3-lutidine (5) | 0.43 ^b | 2.15 | 3.64 |
| 2,4-lutidine (6) | 0.92 ^b | -0.387 | -0.654 |
| 2,5-lutidine (7) | 0.82 ^b | 0.953 | 1.61 |
| 2,6-lutidine (8) | 0.040 ^b | 4.83 | 8.17 |
| 3,4-lutidine (9) | 3.4 ^b | -2.76 | -4.66 |
| 3,5-lutidine (10) | 2.6 ^b | -1.84 | -3.11 |
| 2,3-cyclopentenopyridine (11) | 1.9 ^b | -2.30 | -3.88 |
| 2,3-cyclohexenopyridine (12) | 1.1 ^b | 0.228 | 0.385 |
| 2,3-cycloheptenopyridine (13) | 0.30 ^b | 1.38 | 2.34 |
| 2-ethylpyridine (14) | 0.22 ^c | 1.62 | 2.74 |
| 2-isopropylpyridine (15) | 0.072 ^c | 1.53 | 2.59 |
| 2-tert-butylpyridine (16) | 0.00023 ^c | 9.41 | 15.9 |
| 2-methyl-3-ethylpyridine (17) | 0.36 ^d | 2.10 | 3.55 |
| 2-methyl-3-isopropylpyridine (18) | 0.38 ^d | 1.38 | 2.33 |
| 2-methyl-3-tert-butylpyridine (19) | 0.24 ^e | 1.38 | 2.33 |
| 2,6-diethylpyridine (20) | 0.0037 ^f | 6.92 | 11.7 |
| 2,6-diisopropylpyridine (21) | 0.00015 ^f | 8.46 | 14.3 |

^a Relative to pyridine. Excellent linear correlations exist between iodomethylation of alkylpyridines in acetonitrile and in other solvents at similar temperatures. See ref 4. ^b Reference 4. ^c Reference 6. ^d Podall, H. Ph.D. Dissertation, Purdue University, West Lafayette, IN, 1955. ^e Howie, M. S. Ph.D. Dissertation, Purdue University, West Lafayette, IN, 1960. ^f Reference 5. ^g $\Delta\Delta E = \Delta E_i - \Delta E(\text{pyridine})$ where ΔE_i is the energy difference between the completely optimized CH_3^+ -substrate complex and the completely optimized substrate for the $d_{\text{NC}_M} = 1.88$ -Å TS model.

consistent with the current concepts of TS variation in the Menschutkin reaction.¹⁵ The energy of the model TS increased at a rate of 110 kcal mol⁻¹ Å⁻¹ with respect to changes in d_{NC_M} . The required shifts in d_{NC_M} were found to be quite reasonable, the largest being -0.05 Å for the highly hindered 2-tert-butylpyridine and +0.02 Å for 4-picoline.

In this study, we have successfully correlated the relative iodomethylation activation energies of 21 substituted pyridines which cover four orders of magnitude in alkylation rate. Complete TS geometry optimization was performed independent of the kinetic results, and the excellent correlation supports the use of the model for derivation of kinetic and TS structural information. Because complete geometry optimization was performed, the estimated relative activation energies of the model TS include steric as well as electronic effects. Studies of this type will be particularly valuable in analyzing nonadditive effects which are manifested by nonadditive molecular relaxation mechanisms and associated nontransferability of structure.

Acknowledgment. We thank Drs. T. S. Osdene and E. B. Sanders for encouragement and support, Dr. W. Dwyer for invaluable assistance during the initiation of this project, and the referees for helpful suggestions.

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, 533-37-9; 12, 10500-57-9; 13, 7197-96-8; 14, 100-71-0; 15, 644-98-4; 16, 5944-41-2; 17, 14159-59-2; 18, 80263-42-9; 19, 80263-43-0; 20, 935-28-4; 21, 6832-21-9; methyl iodide, 74-88-4.

(13) (a) le Noble, W. J.; Asano, T. *J. Am. Chem. Soc.* **1975**, *97*, 1778-1782. (b) Okamoto, Y.; Lee, K. I. *Ibid.* **1975**, *97*, 4015-4018. (c) Weber, H.; Pant, J.; Liedigk, M.; Wunderlich, H. *Chem. Ber.* **1981**, *114*, 1455-1563.

(14) Reviews: (a) Förster, H.; Vögtle, F. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 429-441. (b) Tidwell, T. T. *Tetrahedron* **1978**, *34*, 1855-1868.

(15) (a) le Noble, W. J.; Miller, A. R. *J. Org. Chem.* **1979**, *44*, 889-891. (b) Berg, U.; Gallo, R.; Metzger, J.; Chanon, M. *J. Am. Chem. Soc.* **1976**, *98*, 1260-1262. (c) Yamataka, H.; Ando, T. *Ibid.* **1979**, *101*, 266-267. (d) Abraham, M. H.; Nasehzadeh, A. *J. Chem. Soc., Chem. Commun.* **1981**, 905-906. (e) Harris, J. M.; Paley, M. S.; Prasthofer, T. W. *J. Am. Chem. Soc.* **1981**, *103*, 5915-5916. (f) Kevill, D. N. *J. Chem. Soc., Chem. Commun.* **1981**, 421-422. (g) Berg, U.; Gallo, R., submitted for publication.