the failure to observe the aminophosphorane using ^{31}P spectroscopy, the lack of incorporation of ^{18}O label from the solvent, and the absence of general-base catalysis are also consistent with such an explanation, but they are not compelling reasons for choosing between a concerted and nonconcerted process. However, an interesting possibility arises from this discussion since the concerted mechanism clearly requires inversion of the configuration about phosphorus and the other allows pseudorotation. While a distinction cannot be made with the present system, a suitable phosphate diester coordinated to the cobalt moiety would allow it provided pseudorotation does occur.

The acceleratory effect in the base hydrolysis of $[Co(NH_3)_5O_3POC_6H_4NO_2]^+$ relative to uncoordinated nitrophenylphosphate presumably arises largely from the proximity of the coordinated nucleophile NH_2^- to the phosphorus center and the rapid decay of the aminophosphorane which is generated. There are four ammonia molecules in the complex which are cis to the bound ester. During rotation of the ester about the Co–O bond the P center never escapes the nucleophile. Presumably the rate gain from the loss of translational entropy by carrying out the reaction in an intramolecular manner is maximized ($\sim 10^8$) since there are minimal losses from vibrational and rotational degrees of freedom.[51] Note also that no detectable intermolecular hydrolysis occurred. It is surprising perhaps that the rate enhancement is so substantial when strain is introduced by ring formation in the aminophosphorane. The contribution of strain to a decrease in hydrolysis rate would be expected to be even more substantial in the decomposition of the five-coordinate molecule where a chelated four-membered ring is generated at the tetrahedral P center. The other factor which could contribute substantially to the rate enhancement compared to the uncoordinated molecule is the neutralization of charge on the phosphorus residue by coordinating it to the metal ion. While it is clear that the metal ions are not as efficient in this manner as H^+, they do make it much easier to add an electron-rich reagent to what is basically an anionic residue. Even so, addition of a simple trivalent metal ion to neutralize the charge on the phosphorus residue is insufficient to completely account for the rate enhancement observed here.[10]

The chemistry described indicates how a substantial increase in rate can be obtained for attack of an amine nucleophile at a phosphorus center by using a restricted intramolecular pathway despite the ring strain involved in making the chelate. It is conceivable that the metal ion in the enzymic phosphoryl amino transferases functions partly in this way by grouping the reagents so that efficient intramolecular transfer from an oxygen to a nitrogen base can occur.

Acknowledgment. We are indebted to Dr. K. Barrow of the Biochemistry Department, University of New South Wales, Dr. D. Fenn and Mr. M. Whittaker of ANU for the ^{31}P spectra, and the Microanalytical Unit of ANU for C, H, N, Co, and P analyses.

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Steric Effects in Conformationally Mobile Systems. The Iodomethylation of 1-Methyl-2-arylpyrrolidines Related to Nicotine[1]

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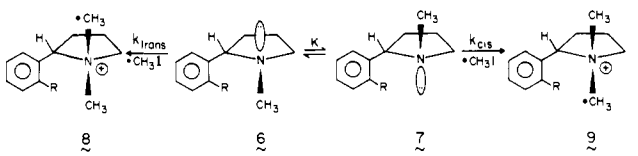
Abstract: The ground-state equilibrium distribution, the total observed iodomethylation rate constant, and the corresponding iodomethylation stereoselectivity were determined for 1-methyl-2-phenylpyrrolidine and the related 1-methyl-2-(2-alkylphenyl)pyrrolidines where the alkyl substituents include methyl, ethyl, isopropyl, and *tert*-butyl. From these parameters, the iodomethylation rate constants for attack cis and trans to the aromatic ring (k_{trans} and k_{cis}) were calculated by using the Curtin–Hammett and Winstein–Holness equations. The dependence of k_{cis} and k_{trans} on K was evaluated. The results are examined in light of the three important conformational features present in these systems: nitrogen inversion, rotation about the aromatic ring–pyrrolidine ring C–C single bond, and rotation about the bond linking the ortho substituent to the aromatic ring. Implications of the combined usage of the Curtin–Hammett/Winstein–Holness equations are analyzed.

An understanding of the role of steric interactions in organic chemistry has been advanced by various statistical treatments and enhancements of the Taft equation.[2] The concept that substituents have specific spatial requirements[3] has engendered attempts to quantitate steric phenomena independent of localized (field and/or inductive) and delocalized (resonance) electronic effects.[4] One approach has focused on the evaluation of steric parameters as a function of branching of alkyl substituents.[4e] Alkyl groups have relatively minor electronic effects which are usually unrelated to

Scheme I



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(1) (a) Presented in part at the Second Chemical Congress of the North American Continent, 180th National Meeting of the American Chemical Society, Las Vegas, NV, August 24-29, 1980; American Chemical Society: Washington, D.C., 1980; Abstract No. ORGN-335. (b) For the previous paper in this series, see Seeman, J. I.; Sanders, E. B.; Farone, W. A. *Tetrahedron* **1980**, *36*, 1173-1177.

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Table I. Observed Total Rate Constant, Product Stereoselectivity, and Ground-State Equilibrium Distribution of 1-5[a]

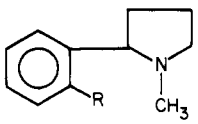
compd	$10^4 k_{W-H}$	k_{W-H} (rel)	[9]/[8]	K
R = H-, 1	30.0 ± 0.6	24	1.72 ± 0.02	17
R = CH_3-, 2	7.61 ± 0.08	6.1	1.4 ± 0.02	>30
R = CH_3CH_2-, 3	6.17 ± 0.02	4.9	1.3 ± 0.05	>30
R = $(CH_3)_2CH$-, 4	5.31 ± 0.07	4.2	1.3 ± 0.03	>30
R = $(CH_3)_3C$-, 5	1.25 ± 0.06	1	0.28 ± 0.01	>40

[a] See Scheme I and eq 1-4.

the size of the alkyl group itself. The quantitation of steric effects becomes exceedingly complex for reactions involving molecules capable of existing in multiple conformations.[5] Consequently we have undertaken a study aimed at evaluating the role of conformation on reactivity in a system having a number of independent internal motions, each of which was considered capable of affecting the observed kinetics.

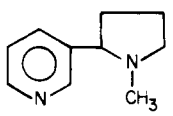
Results and Discussion

Scheme I summarizes the kinetic features which describe the alkylation of **1-5**.[6] The equilibrium constant K reflects the



1, R = H-
2, R = CH_3-
3, R = CH_3CH_2-
4, R = $(CH_3)_2CH$-
5, R = $(CH_3)_3C$-

distribution of free-base invertomers **6** and **7** at equilibrium. The rate constants k_{cis} and k_{trans} refer to alkylation of the trans (*N*-methyl group relative to the aromatic ring) and cis free-base invertomers, respectively. On the basis of the results for nicotine[7a] (**10**) and other amines,[8] it is clear that the rates of iodomethylation



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are many orders of magnitude less than the rates of nitrogen inversion. Thus, the Curtin-Hammett (C-H) (eq 1) and Winstein-Holness (W-H) (eq 2) approximations accurately describe Scheme I.[1b,7b] In order to derive k_{cis} and k_{trans} from eq 1 and 2, one needs to determine experimentally three parameters: the product ratio, $P = [P_c]/[P_t]$ (=[9]/[8]); the empirical rate constant, k_{W-H}; and K (=[7]/[6]).

$$[P_c]/[P_t] = [9]/[8] = Kk_{cis}/k_{trans} \quad \text{where } K = [7]/[6] \quad (1)$$

$$k_{W-H} = (k_{cis}K + k_{trans})/(K + 1) \quad (2)$$

Three independent experiments were required to determine $[P_c]/[P_t]$, k_{W-H}, and K. The product ratio was obtained by ^{13}C NMR analysis of the total crude reaction mixture of the substrate in question and $^{13}CH_3I$ in acetonitrile as described previously.[7a,9] The assignments were based on ^1H NOE experiments, interrelationships between ^1H and ^{13}C NMR resonances, and chemical shift correlations.[7a,9] The observed rate constant k_{W-H} was determined by conductometric analysis[10] of the alkylation mixtures by using a large (>100-fold) excess of iodomethane and assuming pseudo-first-order kinetics. The equilibrium distribution of invertomers was determined by kinetic, irreversible quenching of the inverting amines by strong acid under the appropriate experimental conditions.[7a,11,12b]

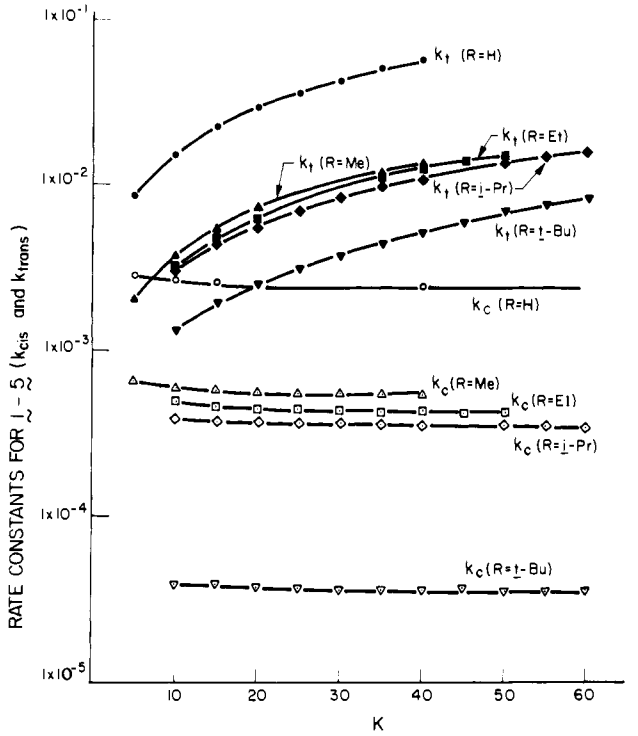

Figure 1. Alkylation rate constants for the nitrogen invertomers of **1-5** as a function of the value of the equilibrium constant K (see Scheme I).

Table I lists the results of the determination of the product ratios, equilibrium distribution, and observed iodomethylation rate constants for **1-5**. While k_{W-H} and $[P_c]/[P_t]$ can be determined with reasonable accuracy, K is rather difficult to establish precisely for compounds in which K is large (>10). This is because K is determined by NMR analysis under slow exchange conditions (either at low temperature or in strong acid); when the system is heavily biased in favor of one of the two components, the relative area of a resonance of the smaller component can only be measured with a large error associated with it.

Reaction Rate Constants

As shown in Table I, ortho alkyl substituents clearly affect K, which has a value of ca. 17 for the parent compound **1** and is greater than 40 for the *tert*-butyl derivative **5**. In all cases, the major isomer is the one in which the *N*-methyl group is trans to the aromatic ring. The observed iodomethylation rate constants

(5) See, for example: (a) Brown, H. C. *J. Chem. Soc.* **1956**, 1248-1268; (b) Brown, H. C.; Cahn, A. *J. Am. Chem. Soc.* **1955**, *77*, 1715-1723; (c) Cherest, M.; Felkin, H.; Tacheau, P.; Jacques, J.; Varech, D. *J. Chem. Soc., Chem. Commun.* **1977**, 372-373.

(6) The stereoselectivity of alkylation of **1** with iodomethane-d_3 and other alkylating agents has been reported previously along with a ^1H NMR assignment of the quaternary methyl groups by using chemical shift analogies. See: (a) Solladié-Cavallo, A.; Solladié, G. *Tetrahedron Lett.* **1972**, 4237-4240; (b) Solladié-Cavallo, A.; Solladié, G. *Org. Magn. Reson.* **1975**, *7*, 18-22.

(7) (a) Whidby, J. F.; Seeman, J. I. *J. Org. Chem.* **1976**, *41*, 1585-1590. (b) Seeman, J. I.; Farone, W. A. *Ibid.* **1978**, *43*, 1854-1864.

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(10) For previous uses of the conductometric procedure for kinetic analysis of the Menschutkin reaction, see: (a) Baker, V. J.; Blackburne, I. D.; Katritzky, A. R. *J. Chem. Soc., Perkin Trans. 2* **1974**, 1557-1561; (b) Imbach, J.-L.; Katritzky, A. R.; Kolinski, R. A. *J. Chem. Soc. B* **1966**, 556-562; (c) Grob, C. A.; Schlageter, M. G. *Helv. Chim. Acta* **1977**, *60*, 1884-1889; (d) Wylde, R.; Saeluzika, J. G.; Lanfumey, M. *J. Org. Chem.* **1975**, *40*, 1308-1312.

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Table II. Calculated Iodomethylation Rate Constants for 1-5

compd	k_{cis}	k_{cis}(rel)	k_{trans}	k_{trans}(rel)
R = H-, 1	$(2.0 \pm 0.1) \times 10^{-3}$	71	$(2.0 \pm 0.4) \times 10^{-2}$	5.0
R = CH_3-, 2	$(4.6 \pm 0.01) \times 10^{-4}$	16	$(9.8 \pm 0.3) \times 10^{-3}$	2.5
R = CH_3CH_2-, 3	$(3.6 \pm 0.03) \times 10^{-4}$	13	$(8.0 \pm 1.5) \times 10^{-3}$	2.0
R = $(CH_3)_2CH$-, 4	$(3.0 \pm 0.02) \times 10^{-4}$	11	$(6.9 \pm 1.5) \times 10^{-3}$	1.7
R = $(CH_3)_3C$-, 5	$(2.8 \pm 0.02) \times 10^{-5}$	1	$(4.0 \pm 0.5) \times 10^{-3}$	1

[a] The deviations are approximated by using the error analysis described in the text. See Scheme I and eq 3 and 4.

$k_{W\text{-}H}$ for **1-5** fall into three general ranges: the parent compound, **1**, has the largest $k_{W\text{-}H}$; the ortho methyl, ethyl, and isopropyl derivatives, **2-4**, respectively, have approximately the same $k_{W\text{-}H}$ which is ca. one-fifth that found for **1**; and the *tert*-butyl homologue **5** is ca. one-fourth that found for **2-4**.

Equations 3 and 4 indicate the dependence of k_{cis} and k_{trans} on $k_{W\text{-}H}$, K, and $[P_c]/[P_t]$.[12] Note that eq 3 and 4 are derived directly from eq 1 and 2.

$$k_{cis} = k_{W\text{-}H}[(K + 1)/K][P/(P + 1)] \quad \text{where } P = [P_c]/[P_t] = [\mathbf{9}]/[\mathbf{8}] \quad (3)$$

$$k_{trans} = k_{W\text{-}H}[(K + 1)/(P + 1)] \quad (4)$$

It is important to evaluate the dependence of k_{cis} and k_{trans} on K. Note that Scheme I has been defined such that $K > 1$. Equations 5 and 6 show the variability of k_{cis} and k_{trans} with respect

$$\partial k_{cis}/\partial K = -k_{W\text{-}H}[P/(P + 1)](1/K^2) \quad (5)$$

$$\partial k_{trans}/\partial K = k_{W\text{-}H}/(P + 1) \quad (6)$$

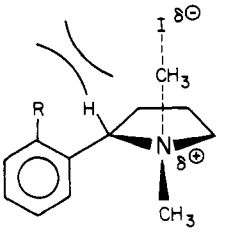
$$\partial k_{trans}/\partial k_{cis}|_K = -K^2/P \quad (7)$$

to K, and eq 7 combines these expressions, leading to the interesting result that k_{trans} is significantly more sensitive to a possible inaccurate value of K than is k_{cis}. This mathematical relationship is illustrated in Figure 1 which plots the values of k_{cis} and k_{trans} for **1-5** as a function of K. It is evident that k_{cis} for **1-5** is nearly independent of K when $K > 10$ while k_{trans} is markedly dependent on K for all values shown. Two particular features of Figure 1 should be noted. First, the ordinate of Figure 1 represents the rate constants and is illustrated by using a logarithmic scale for convenience in order to be able to represent the two rate constants on one graph. Second, Figure 1 indicates the variations of the rate constants for values for K ranging from 10-60. With use of this additional information, one is able to approximate the range of values likely for k_{cis} and k_{trans} for **1-5**.[12b]

Equation 7 indicates the sensitivity (or lack thereof) of k_{trans} (relative to k_{cis}) to K. It is to be noted again that we have arbitrarily defined Scheme I such that $K > 1$. When K is large but of inaccurate value, x_{trans}, the mole fraction of the trans invertomer **7**, is close to unity while x_{cis}, the mole fraction of the cis invertomer **6**, is small. Any error in the measurements of K will lead to errors in both x_{cis} and x_{trans}. However, the percentage error in x_{trans} will be much smaller than the percentage error in x_{cis}. Since the total empirical rate constant $k_{W\text{-}H}$ is equal to the sum of the product of individual mole fractions and their respective alkylation rate constant (eq 8), any deviation in the mole fraction of the ith component must be compensated for by a change in that component's reaction rate constant. Note that in eq 8 and Scheme I, the cis invertomer **6** (x_{cis}) alkylated in a trans fashion (k_{trans}).

$$k_{W\text{-}H} = x_{cis}k_{trans} + x_{trans}k_{cis} \quad (8)$$

Table II lists the k_{cis} and k_{trans} values along with an error associated not with the experimental determination of $k_{W\text{-}H}$ but with the error associated with K. Also shown in Table II are the relative values of k_{cis} and k_{trans}. Just as $k_{W\text{-}H}$ fell into *three distinct sets* (see above), k_{cis} and k_{trans} also fall into these three ranges. The more significant variation is in k_{cis}, which for the parent compound is 4 to 7 times faster than the ortho methyl, ethyl, and isopropyl derivatives (**1-4**) and is almost 70 times faster than the *tert*-butyl compound **5**. On the other hand, the values of k_{trans} vary by only a factor of 5 within the series **1-5**. That an ortho substituent would have any significant steric effect on k_{trans} is interesting because it indicates that sufficient flexibility exists in the pyrrolidine ring iodomethylation transition state for a 1,2-trans nonbonded interaction to occur (cf. **11**).



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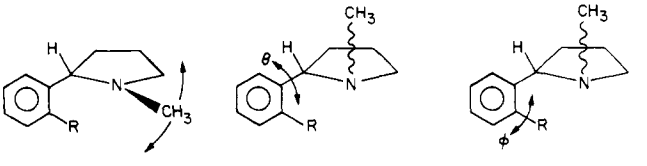
Three important conformational processes are occurring simultaneously in these systems: (1) inversion of the pyrrolidine *N*-methyl group[7a] (cf. **12**); (2) rotation about the sp^2-sp^3 pyrrolidine-phenyl C-C bond[18] (cf. **13**); and (3) rotation about the sp^2-sp^3 C-C ortho substituent-phenyl ring bond (cf. **14**).



12 **13** **14**

The only mathematical construct available which relates the observed total reaction rate constant for a molecule which exists in a number of reactive conformations to the reaction rate constant

(12) (a) The Winstein-Holness equation was originally derived[13] and subsequently used[13,14] in an effort to derive the ground-state equilibrium distribution of a conformationally mobile compound. Much criticism has been leveled against this usage of the W-H equation.[15] The validity or invalidity of this criticism does not mitigate against the use of the W-H equation in combination with the Curtin-Hammett Principle to describe a kinetic system such as Scheme 1. This is because the C-H and W-H equations are valid approximations to such systems.[7b] Katritzky and his group have used the C-H/W-H combined approach to analyze the alkylation of various piperidines, initially[10b,16] to determine the stereochemistry of the reactions, and later to determine the reaction rate constants.[10a,17] We are unaware of any work which has examined the error analysis of this system. This is quite important as the value of the equilibrium constant K is generally not accurately known.[11] (b) The use of eq 3 and 4 requires the experimental determination of $k_{W\text{-}H}$, K, and P. It is to be noted that these three parameters cannot be determined in a single experiment; e.g., K is obtained by the kinetic quenching procedure in strong acid while $k_{W\text{-}H}$ and P are obtained in acetonitrile solutions of different concentrations. The combined usages are an assumption of this treatment. This assumption has been previously reported in the literature; see, for example, Duke, R. P.; Jones, A. Y.; Katritzky, A. R. *J. Chem. Soc.* **1973**, 1553-1557.

(13) (a) Winstein, S.; Holness, N. J. *J. Am. Chem. Soc.* **1955**, *77*, 5562-5578. (b) Eliel, E. L.; Ro, R. S. *Chem. Ind. (London)* **1956**, 251-252.

(14) Eliel, E. L.; Allinger, N. L.; Angyal, S. J.; Morrison, G. A. "Conformational Analysis", Wiley: New York, 1965; Chapter 2.

(15) (a) Kwart, H.; Takeshita, T. *J. Am. Chem. Soc.* **1964**, *86*, 1161-1176. (b) Eliel, E. L.; Biros, F. J. *Ibid.* **1966**, *88*, 3334-3343. See, however: (c) Brown, D. R.; Leviston, P. G.; McKenna, J.; McKenna, J. M.; Melia, R. A.; Pratt, J. C.; Hutley, B. G. *J. Chem. Soc., Perkin Trans. 2* **1976**, 838-841 and references cited therein.

(16) Jones, R. A. Y.; Katritsky, A. R.; Mente, P. G. *J. Chem. Soc. B* **1970**, 1210-1217.

(17) Baker, V. J.; Blackburne, I. D.; Katritzky, A. R.; Kolinski, R. A.; Takeuchi, Y. *J. Chem. Soc., Perkin Trans. 2* **1974**, 1563-1568.

(18) (a) Whidby, J. F.; Edwards, W. B. III; Pitner, T. P. *J. Org. Chem.* **1979**, *44* 794-798. (b) Pitner, T. P.; Edwards, W. B. III; Bassfield, R. L.; Whidby, J. F. *J. Am. Chem. Soc.* **1978**, *100*, 246-251. (c) Pitner, T. P.; Whidby, J. F.; Edwards, W. B. III *Ibid.* **1980**, *102*, 5149-5150.

for each of these conformations is the Winstein–Holness equation which was discussed above for the specific case of two reacting isomers (eq 2) but is shown in eq 9 for numerous reaction con-

$$k_{W\text{-}H} = \sum x_i k_i \text{ for all conformations where } x_i \text{ is the mole fraction of the } i\text{th component} \quad (9)$$

formations. The procedure to determine k_{cis} and k_{trans} involves (1) the identification and characterization of the equilibrating conformations, (2) the evaluation of their respective mole fraction, (3) the experimental determination of the total reaction rate constant, and finally, (4) the solution of eq 9 and the determination of each conformation's rate constant.

Step 2 above is in general particularly difficult and, in the case at hand, would seemingly require the ground-state conformational profiles of the cis and trans isomers (**6** and **7**, respectively) as a function of two geometrical variables, θ and ϕ (cf. **13** and **14**). We have already discussed the difficulties in determining the relative populations of **6** and **7**, neglecting these other conformational freedoms.

However, from a qualitative sense, eq 9 suggests that minor components of a conformationally mobile system would play an insignificant role in the observed kinetics *unless* these minor components reacted significantly faster than the more populated states. Consider the case of the ortho-substituted derivatives **2–5** relative to the parent **1**. Theoretical calculations on the ground-state potential energy surfaces of nicotine and related compounds have been reported over the last few years.[19] While complete agreement is lacking in these studies, two minima and two maxima have been found in each. These calculations and molecular models clearly indicate that a wide range of conformations are particularly destabilized by cross-ring interactions. These conformations, which should be less reactive toward iodomethane,[4d] are far less populated than rotamers in which the ortho substituent is pointed away from the pyrrolidine ring. Consideration of eq 9 would suggest that the overall rate of alkylation would not be significantly affected by these minor forms. However, Table I clearly indicates that these ortho substituents have a significantly decelerating effect on the rate constants. That the rate constants k_{cis} and k_{trans} do fall into different ranges indicates that the effect of the conformational mobility of the aromatic ring with respect to the pyrrolidine ring *as well as* the mobility of the ortho substituent with respect to the aromatic ring cannot be treated as a set of independenct equilibrating, reactive conformations.

We favor an analysis which incorporates a dynamic approach rather than a thermodynamic view of the molecular events. Undoubtedly there are numerous combinations of directions that the substrate amines **1–5** could collide with the alkylating reagent. Before any collision results in product formation, the atoms of the reacting complex are adjusting to various energetic and geometric constraints. Kinetic energy is not the sole determinant of successful reaction for any of the multiple trajectories possible. Amines **1–5** have numerous conformations available to them, each of which plays a dynamic role in affecting the molecular motions of the reacting complex. These motions may be either dependent on each other or independent.[20]

The three conformational processes discussed above are particularly pertinent. Rotation about the C–C bond linking the ortho substituent and the aromatic ring as well as the rotation about the C–C bond linking the two rings is rapid. These two motions are occurring simultaneous to the rapid, though somewhat slower, nitrogen inversion processes. The approach of the alkylating agent

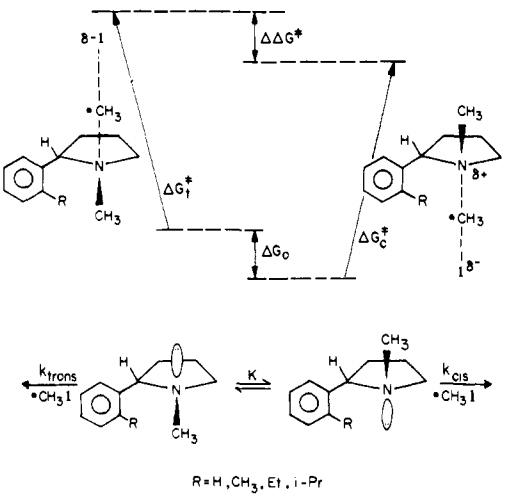


Figure 2. Energetics of the alkylation system shown in Scheme I for **1–4**.

with respect to the tertiary amine and the subsequent collision is a far slower and higher activation process. Consequently, the conformational processes (cf. **12–14**) affect in an interactive fashion the alkylation reaction.

These considerations also are reflected in the observed values of K. While we cannot with certainty distinguish between K for **2–4**, it is clear that $K(1) < K(2) \approx K(3) \approx K(4) < K(5)$. Thus, a minor ring–ring conformation can have a significant effect on the overall composition of the free-base equilibrating invertomer mixture.

Both enthalpic and entropic steric effects could be responsible for the decrease in observed iodomethylation rate constants. The bulky ortho substituents could cause a reduction in the number of available energy levels in the diastereomeric transition states. An enthalpic effect is also likely, especially if one considers that in one of these transition states the already bonded *N*-methyl group is cis to the aromatic ring and in the other the dissociating iodomethane is cis to the aromatic ring. Compared to the free-base invertomers, the transition states leading to the quaternary ammonium salts have considerably more hindrance. This is not merely because of the additional bulky groups which add to the possible nonbonded interactions but also because modes of strain relief present in the free-base isomers no longer are available in the alkylation transition states. An example of this would be the movement of the *N*-methyl group in **1–5** toward the plane of the pyrrolidine ring to relieve possible nonbonded interactions between it and other ring substituents. As nitrogen quaternization proceeds, more strict geometrical requirements are placed on the pyrrolidine nitrogen atom.

Product Ratios

As shown in Table I, the product ratio $[P_c]/[P_t]$ is greater than one for **1–4** (for the parent compound and when the substituent is methyl, ethyl, and isopropyl) but less than one for the *tert*-butyl derivative **5**. In Figure 2, the diastereomeric transition states for cis and trans iodomethylation are drawn along with the free-energy levels for each of these transition states. According to the C–H principle, this difference in free energy, $\Delta\Delta G^{\ddagger}$, is related to the product ratio $[P_c]/[P_t]$ (eq 10). Clearly, when $\Delta\Delta G^{\ddagger} < 0$, the

$$[P_c]/[P_t] = e^{-\Delta\Delta G^{\ddagger}/RT} \quad (10)$$

free energy of the trans alkylation transition state is larger than that for the cis alkylation reaction. Examination of the interactions shown in Figure 2 in a pairwise comparison procedure offers an indication as to the controlling features present in this system. Thus, the transition-state free-energy difference (cf. Figure 2) is attributable to the lack of symmetry caused by the aromatic ring.

Consider the substituents on the pyrrolidine nitrogen. The already bonded N–CH_3 interacts with the aromatic ring and with the pyrrolidine ring in $\Delta G_c^{\ddagger}$ in a manner analogous to the interaction between the attacking iodomethane and the aromatic

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(20) For a similar argument but one which relates to the steric isotope effect, see: Carter, R. E.; Melander, L. In "Advances in Physical Organic Chemistry", Streitweiser, A., Taft, R. W., Eds.; Wiley: New York, 1973; Vol. 11, pp 1–27.

Scheme II

$$A_1 \xleftarrow{k_{21}} A_2 \underset{k_{32}}{\overset{k_{23}}{\rightleftharpoons}} A_3 \xrightarrow{k_{34}} A_4$$

and pyrrolidine rings in $\Delta G_t^{\ddagger}$; similarly, the N–CH_3 interacts with the pyrrolidine ring substituents in $\Delta G_t^{\ddagger}$ analogous to the interaction between the iodomethane and the pyrrolidine ring substituents in $\Delta G_c^{\ddagger}$. When cis attack occurs preferentially, the pairwise comparisons cited above indicate that the already bonded N–CH_3 group has a larger steric requirement than the $N^{\delta+}\cdots CH_3\cdots I^{\delta-}$ in the transition state(s).[9a] This is the case for **1–4**. However, for the *tert*-butyl compound **5**, $[P_c]/[P_t] < 1$, indicating that the already bonded N–CH_3 has a smaller steric requirement than the $N^{\delta+}\cdots CH_3\cdots I^{\delta-}$ in the alkylation transition states of **5**.

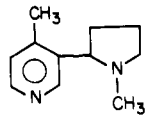
It is interesting to analyze the phenomenological cause for the inversion in $[P_c]/[P_t]$ from greater than one to less than one in the progression from the isopropyl compound **4** to the *tert*-butyl compound **5**. The implication is that the already bonded N–CH_3 becomes smaller in a steric fashion than the incoming iodomethane moiety in the transition state. The Menschutkin reaction is known to have an early transition state.[21] However, in a series of reactants, as the reaction becomes slower, the transition state becomes more product-like; i.e., it becomes later along the reaction path.[21,22] K is a function of the compound and not of the particular reaction. For any single compound, a later transition state will enhance nonbonded interactions, thereby increasing the influence of k_{cis} and k_{trans} on the value of $[P_c]/[P_t]$ (eq 1) while not changing the value of K. Thus, at some point, an inversion in product stereoselectivities should occur. This is true not only when varying the substrate, e.g., changing the ortho substituent for the same alkylating agent, but also when varying the alkylating agent while holding the substrate constant.

The reaction rate constants decrease substantially as the *ortho* substituent becomes increasingly larger. This implies a later transition state in this substitution sequence, thereby increasing the effective size of the incoming iodomethane moiety, even as the C- - -I bond is being broken. In addition, the Menschutkin reaction is well-known to be facilitated by solvent effects which stabilize the formation of the charged species.[21a] Undoubtedly, the reaction rate constants and $\Delta\Delta G^{\ddagger}$ reflect solvation effects. Pictorial descriptions of the Menschutkin reaction (see, for example, Figure 2) would more properly illustrate solvent molecules. A later transition state such as obtained for the *tert*-butyl compound **5** would require greater solvation around the pyrrolidine nitrogen. This would further increase the effective size of the alkylating agent, especially in the cis alkylation mode.

It is interesting to note that the product distribution in many C–H/W–H systems (eq 1 and 10) is close to unity.[8,9,10a,10b,16,17,22,23] This is true even for compounds in which there exists considerable biasing in the ground-state distribution of interconverting isomers, (cf. Scheme II). This generalization is especially true when the *N*-alkyl substituent is the same moiety present in the alkyl halide. A relatively balanced product distribution is likely to be the result of this type of "symmetrical" system in which those features which favor one isomer over the other, e.g., A_3 over A_2, are the same factors which decrease the relative reactivity of A_3 with respect to A_2. That is, if A_3 is more stable than A_2, it is likely that $k_{21} > k_{34}$ in such a fashion that $[A_4]/[A_1] = Kk_{34}/k_{21} \approx 1$.

Nicotine Analogue Pharmacology

These results bear on our study involving structure-activity relationships in nicotine pharmacology. We have been quite interested in the observation of Haglid that 4-methylnicotine (**15**)



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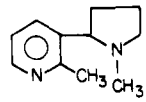

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was many orders of magnitude less active than nicotine (**10**) in a variety of pharmacological tests.[24] Haglid suggested that the low activity of 4-methylnicotine was due to its inability to adopt ring–ring conformations necessary for receptor binding and/or activation.[24] We subsequently prepared 2-methylnicotine (**16**) and found that it too was significantly less active than nicotine.[19b] Based on these observations and on biological and chemical evaluations of a number of nicotine analogues, we recently postulated that the inactivity of 2-methyl- and 4-methylnicotine is due to steric congestion at the pyrrolidine nitrogen due to the pyridine methyl group in these analogues.[19c] Our results in this series of 1-methyl-2-(2-alkylphenyl)pyrrolidines allow an evaluation of the role of pyridine substituents ortho to the *N*-methylpyrrolidine ring in nicotine structure-(re)activity relationships.

Iodomethylation is an excellent model to analyze nitrogen congestion because of the well-known steric effects on the Menschutkin reaction. As discussed above, the overall W–H rate constant as well as k_{cis} are significantly decreased when being compared to the unsubstituted parent **1**; k_{trans} is also smaller. In addition, the ground-state distribution of **5** is more biased toward the trans form than that found for **4**. Thus, these chemical models support the suggestion[19b] that long-range ring–ring steric effects are important in these conformationally mobile systems.

Comments on Curtin-Hammett/Winstein-Holness Kinetics

The derivation of the individual reaction rate constants for the iodomethylation of **1–5** as shown in Scheme I is based on the use of the C–H approximation (eq 1 and 10) and the W–H equation (eq 2 and 9).[12] Much continued controversy has surrounded the use of the W–H equation in the field of conformational analysis.

It may well be asked: *are the C–H and W–H equations valid within the context of their use in this work*?

A clear distinction must be made between the criticized uses of the W–H equation in the literature and the use of the W–H equation in this work. The kinetic method of conformational analysis[13,14] has been the major utilization of the W–H equation to date, and it is this use which has received much criticism[15a,15b,11,25] and some recent support.[11b,15c] Equation 2 can be solved for K, the ground-state distribution of isomers $A_2 \rightleftarrows A_3$, transforming it to eq 11 (see Scheme II). In this procedure, molecules with functional groups in well-defined special orientations and lacking conformational mobility are chosen as reactivity models; the rate constants for these models for particular reactions are then assumed to be equal to the corresponding rate constants for the conformationally mobile system. Equation 11 is then used

$$K = (k_{21} - k_{W\text{-}H})/(k_{W\text{-}H} - k_{34}) \qquad (11)$$

to calculate the ground-state equilibrium distribution of the mobile system.[13,14] For example, the independently measured and presumably homogeneous rate constants of a reaction of the fixed *cis*- and *trans*-4-*tert*-butylcyclohexanols are assumed equal to the axial and equatorial rate constants, respectively, of the conformationally mobile cyclohexanol.

Unfortunately, the kinetic method of conformational analysis often leads to equivocal results because the models fail to perfectly represent the actual systems due to polar and steric effects as well as ring distortion effects.[15]

Nonetheless, the W–H equation is always the proper, valid kinetic description of all systems which are mechanistically consistant with Scheme II *when* the rates of isomer interconversion

(21) By an early transition state, we are particularly referring to the N–CH_3 bond being made and the CH_3–I bond being broken rather than solvation phenomena. See (a) Arnett, E. M.; Reich, R. *J. Am. Chem. Soc.* **1980**, *102*, 5892–5902. (b) le Noble, W. J.; Miller, A. R. *J. Org. Chem.* **1979**, *44* 889–891. (c) Wigfield, D. C.; Lem, B. *Tetrahedron* **1975**, *31*, 9–11.

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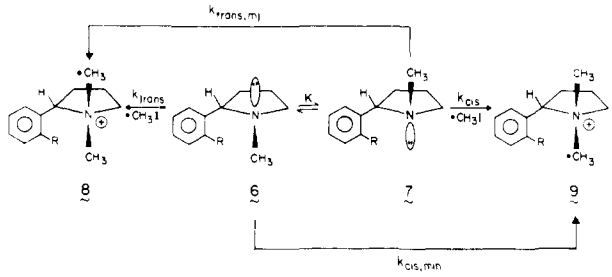
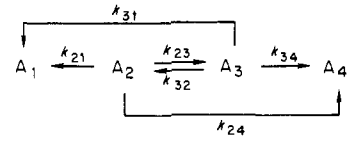
Scheme III



Scheme IV



are significantly faster than the rates of product formation (k_{23}, $k_{32} \gg k_{21}$, k_{34}).[1b,7b] The criticisms of the W–H equation[15] are based on the inapplicability of model systems for conformational analyses and not on its use as the valid descriptor of Scheme II kinetics. These two uses must be recognized as separate and unrelated applications of the C–H/W–H equations.

The C–H principle is describable by two different but mathematically equivalent expressions (eq 1 and 10). The former relates the product distribution to the ratio of reaction rate constants times the ground-state equilibrium distribution of isomers; the latter relates the product distribution to the difference in energy of the two reaction transition states ($\Delta\Delta G^{\ddagger}$) (cf. Figure 2).

Depending on the information and comparisons desired, one can choose either eq 1 or eq 10 (or both) without prejudice. Ground-state conformation is relevant to product distribution, as shown by eq 1. One cannot say that ground-state conformation and barrier to interconversion are relevant (which is true) and conclude (falsely) that eq 10 is irrelevant simply because ground-state conformational weights do not appear in this equation. This is because $\Delta\Delta G^{\ddagger}$ (eq 10) does take K, k_{21}, and k_{34} into consideration.

Similarly, ground-state conformational distribution plays a significant role in the overall rate of reaction, not because of the operative nature of the C–H/W–H equations but because of the ideal law of mass action on which the C–H/W–H concepts were developed (see eq 2). The C–H and the W–H equations are *both* based on the relevancy of the ground-state energy profiles.[7b]

Definition of the Reaction System

It is true that the initial steps of any kinetic investigation are defining the reaction(s) and determining the relationship between the rate and the composition of the reaction system.[26a] An inherent assumption made in the calculations above (cf. eq 3 and 4 and Tables I and II) is that Schemes I and II do, in fact, accurately describe the iodomethylations of **1–5**.

A valid question now arises: *is Scheme I the appropriate kinetic description of the reaction system?*

An alternative kinetic description of the iodomethylations of **1–5** is indicated by Scheme III which incorporates the potentiality of cross-products in these alkylations. In Scheme III, it is suggested that alkylation cis to the pyridine ring can occur both (a) by cis alkylation (k_{cis}) of the major free-base invertomer **7** and (b) by cis alkylation ($k_{cis,min}$) of the minor free-base invertomer **6** (see Scheme III). Similar logic holds for the two modes of trans alkylation. There is no theoretical reason why these iodomethylations cannot involve routes in which a change in nitrogen configuration is coupled with alkylation.

Cram,[27] Hutchins,[28] and more recently Zefirov[29] have considered some of the kinetic consequences of Scheme IV (and thus Scheme III). Assuming that the rates of interconversion of $A_2 \rightleftarrows A_3$ are significantly greater than the rates of reaction (the C–H/W–H assumptions!),[7b] the time independent value of $[A_4]/[A_1]$ is shown by eq 12.[27-29]

$$[A_4]/[A_1] = (k_{34}K + k_{24})/(k_{31}K + k_{21}) \qquad (12)$$

In order to solve for the reaction rate constants (k_{21}, k_{24}, k_{31}, and k_{34} from eq 12), one has use of the W–H equation (eq **9**) and three independent experimentally determined parameters, k_{W-H}, K, and $[A_4]/[A_1]$ as described above. Unfortunately, no unique solution for the reaction rate constants can be obtained from the resultant two equations and four unknowns.

McKenna has discussed the issue of cross-products in quaternization reactions in a number of review articles[8b,11b,30] and has concluded that "the analytical result is that the system reacts *as if* each base conformer were converted only into the stereochemically analogous product".[30] McKenna later concluded that cross-products "would not affect the kinetic analysis".[8b]

There is a significant volume of additional literature which has analyzed nitrogen quaternizations using Scheme II.[8,9a,10,11,22,23] The consensus approval of Scheme II is justifiable from the view that these investigations have resulted in the major experimental basis for many quantitative and systematic relationships in the Menschutkin reaction. Indeed, it is somewhat striking that so many other bimolecular reactions which have been treated by using Scheme II kinetics can be described by Scheme IV kinetics as well, e.g., elimination reactions[31] of a variety of acyclic compounds including dehydrohalogenation of monohalides[26b] and reaction of 1,2-dibromides with the iodide ion,[32] reduction of acyclic ketones[33] as well as other addition reactions to carbonyl compounds,[34] formation of amine oxides from tertiary amines,[35] etc.

Since we at present cannot distinguish between these two mechanisms (Schemes II and IV), it is of importance to consider whether or not these are really alternatives.[26c] Since this distinction "is irrelevant to any presently observable phenomena"[26b] and since significant mechanistic conclusions have been reached by considering only Scheme II in this and other work, we contend that the use of Scheme II and eq 3 and 4 for the derivation of rate constants is meaningful and valid.

Experimental Section

Methods and Materials. Amines **1–4** were prepared via a sequence initiating with condensation of the respective ethyl *o*-alkylbenzoates or ethyl benzoate with *N*-(trimethylsilyl)pyrrolidinone and LDA following the procedure of Hoffman applied to the synthesis of myosmime, nornicotine, and nicotine.[9a] The resultant 2-aryl-1-pyrrolines were reduced to the corresponding 2-arylpyrrolidines with sodium cyanoborohydride in acidic methanol. Methylation was performed by using the standard Clarke–Eschweiler conditions. 1-Methyl-2-(2-*tert*-butylphenyl)-pyrrolidine (**5**) was prepared by methylation of 2-(2-*tert*-butylphenyl)-pyrroline (**17**) with iodomethane in acetonitrile at 80 °C followed by sodium cyanoborohydride reduction of the resultant iminium salt following procedures published by us previously. Imine **17** was prepared by the reaction of *tert*-butylmagnesium chloride with 2-(2-methoxy-

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Table III. CH_3-N^+-CH_3 Chemical Shifts[a]

	^{1}H NMR (δ)		^{13}C NMR (δ)	
compd[b]	trans	cis	trans	cis
1-CH_3I	3.20	2.78	51.13	46.28
2-CH_3I	3.06	2.78	51.61	46.82
3-CH_3I	3.10	2.83	51.40	46.93
4-CH_3I	3.08	2.81	51.13	46.93
5-CH_3I	3.23	2.73	54.84	49.84

[a] In acetonitrile-d_3. [b] Refers to the mixtures of 8 + 9.

phenyl)-1-pyrroline, the latter prepared as described above for the imine precursers for **1-4**. Details of these preparations will be published in a full paper delineating the synthesis of a variety of nicotine analogues.

^{1}H and ^{13}C NMR spectra were obtained on either a Varian XL-100 NMR spectrometer equipped with a Digilab NMR-3 FT accessory or a Bruker WP-80 spectrometer operated in the FT mode. Spectroscopic grade acetonitrile was used as received for the kinetic experiments. Hexadecane was distilled prior to use and trifluoroacetic acid-*d* was used as obtained from Aldrich.

Kinetic Experiments.[10] Typically, a solution of iodomethane in ca. 49 mL of acetonitrile which had equilibrated at 25.00 ± 0.01 °C was added all at once to an equilibrated solution of amine in acetonitrile at 25.00 ± 0.01 °C. The resultant solution was always $<1 \times 10^{-3}$ M in amine and always >0.1 M in iodomethane, thereby ensuring a greater than 100:1 iodomethane:amine ratio. The reaction was run in a specially constructed conductivity cell purchased from Beckman Instruments (Cat. No. CEL-3L01-Special) which had platinum electrodes, 250-mL volume, and a flow-through cell construction such that rapid stirring within the reaction flask caused the solution to pass through and over the cell in a continuous fashion. The cells used had cell constants of ca. 0.1. Conductivity readings were made on a Beckman Instruments RC-18A conductivity bridge. Standard curves were generated from the purified quaternary salt product in each case. The experimental data was converted to time–concentration data and analyzed by using nonlinear least-squares analysis. Extremely small deviations were obtained. The pseudo-first-order rate constant derived in this manner was transformed to the second-order rate constant by dividing by the concentration of the iodomethane. At least four runs were performed for each compound.

Kinetic Quenching Experiments.[11] Typically, a solution of amine (ca. 20 mg) in 1 mL of anhydrous hexadecane was added dropwise to a rapidly stirred mixture of 1 mL of trifluoroacetic acid-*d* and 2 mL of hexadecane under argon in a previously flame-dried pear-shaped flask. Following the addition process, the mixture was allowed to stir an additional 1-2 min and then allowed to sit unperturbed for 1 min. The bottom layer was then carefully removed by pipet and transferred to a dry NMR tube for analysis.

Product Ratio Alkylation Experiments. Typically, 10–25 mg of **1-5** were dissolved in ca. 0.2 mL of anhydrous acetonitrile-d_3 in an NMR tube. Following equilibration at 25.00 ± 0.01 °C, a solution of iodomethane-^{13}C in acetonitrile-d_3 was added *via* syringe to the equilibrated amine solution. The resultant mixture was allowed to stand at that constant temperature for >14 h before NMR analysis. Because of the potential for different relaxation rates, a delay period of >6 s was used between successive FID. Typically 100 FIDs were collected for each spectrum, and at least three alkylations were performed for each sample. The deviations were typically less than 5%. ^{1}H and ^{13}C NMR spectra were obtained for each alkylation reaction, and the pure products were isolated and characterized by elemental analysis.

The assignments of the trans and cis alkylation products (**8** and **9**, respectively) for **1-5** were made on the basis of nuclear Overhauser enhancement experiments reported previously[7a,9a] and on chemical shift analogies.[6] Consistancy was observed between the assignments shown in Table III, the coupling patterns and integrations in the ^{1}H NMR spectra and the integrations and chemical shifts in the ^{13}C NMR spectra.

1,1-Dimethyl-2-phenylpyrrolidinium iodide (1-CH_3I): mp 155–156 °C (lit.[36] mp 156–157 °C).

1,1-Dimethyl-2-(2-methylphenyl)pyrrolidinium iodide (2-CH_3I): mp 205–206°. Anal. Calcd for $C_{13}H_{20}NI$: C, 49.22; H, 6.35; N, 4.42. Found: C, 49.05; H, 6.12; N, 4.39.

1,1-Dimethyl-2-(2-ethylphenyl)pyrrolidinium iodide (3-CH_3I): mp 190–191 °C. Anal. Calcd for $C_{14}H_{22}NI$: C, 50.76; H, 6.69; N, 4.23. Found: C, 50.47; H, 6.78; N, 4.22.

1,1-Dimethyl-2-(2-isopropylphenyl)pyrrolidinium iodide (4-CH_3I): mp 237–238 °C. Anal. Calcd for $C_{15}H_{24}NI$: C, 52.18; H, 7.01; N, 4.06. Found: C, 52.12; H, 6.89; N, 4.08.

1,1-Dimethyl-2-(2-*tert*-butylphenyl)pyrrolidinium iodide (5-CH_3I): mp 223–224 °C. Anal. Calcd for $C_{16}H_{26}NI$: C, 53.49; H, 7.29; N, 3.90. Found: C, 53.24; H, 7.33; N, 3.80.

Acknowledgment. We thank Dr. E. B. Sanders for suggesting the procedure for synthesizing 2-(2-*tert*-butylphenyl)pyrroline and for many helpful conversations, Dr. Jerry F. Whidby and Mr. Ronald Bassfield for assistance in obtaining and interpreting the NMR spectra, Mr. Charles E. Thomas for assistance in establishing the conductometric system, Ms. Diane C. DeNagel for technical assistance, and the Philip Morris R&D Computer Group for their invaluable cooperation. We also thank the reviewers for a number of helpful criticisms and suggestions. We especially thank Dr. T. S. Osdene and Mr. Frank E. Resnik for their continued encouragement and support.

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Solvent Effects in the Photochemistry of Xanthone[1]

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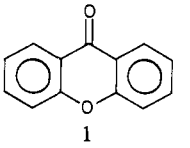
Abstract: The hydrogen-bonding properties of the media play a dominant role in the photochemistry of xanthone; for example, the bimolecular rate constant for the reaction of the triplet state with 2-propanol changes from 1.1×10^8 M^{-1} s^{-1} in carbon tetrachloride to 2.2×10^5 M^{-1} s^{-1} in neat 2-propanol. The change is attributed to an inversion of the n,π* and π,π* triplet states; while the effect is not uncommon, its magnitude is unprecedented. Self-quenching in xanthone is considerably faster than in the case of other aromatic ketones (e.g., benzophenone) and shows marked solvent dependence. The activation energy for energy transfer to γ-methylvalerophenone changes from 2.3 to 6.6 kcal/mol when the solvent is changed from carbon tetrachloride to methanol.

Introduction

Aromatic ketones have been the subject of numerous photochemical studies. Xanthone (**1**) is structurally quite similar to benzophenone, and its triplet energy is almost identical with that of acetophenone;[2] however, the few studies published on xanthone



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reveal striking differences between its behavior and that of other aromatic ketones. For example, studies of its phosphorescence reveal a strong dependence of the nature of the lowest lying triplet

(1) Issued as NRCC-18712.
(2) Herkstroeter, W. G.; Lamola, A. A.; Hammond, G. S. *J. Am. Chem. Soc.* **1964**, *86*, 4537.

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