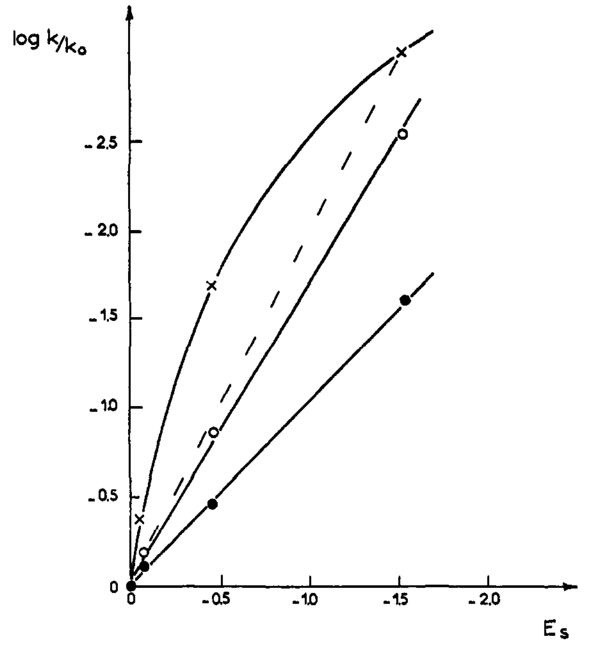
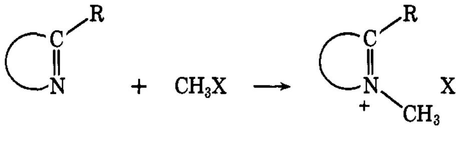


Figure 1. Log $k/k_0$ for quaternization of alkylthiazoles *vs.* Taft's $E_S$ parameters: (●) 2-alkylthiazoles; (○) 2-methyl-4-alkylthiazoles; (×) 2,5-dimethyl-4-alkylthiazoles.

However, recently Pryor[10] pointed out that the extension of the linear relationship log $k/k_0 = \delta$ log $(k/k_0)$ to any system may be dangerous when applied directly to the elucidation of a mechanism, since the true significance of the obtained linearity remains unknown.

We wish to report here results obtained in the quaternization of ortho-substituted heterocyclic bases (reaction 2) which clarify the origin of linear free-energy relationship in term of the $E_S$ scale.



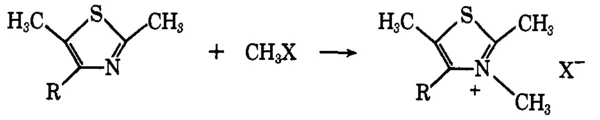
(2)

The extension of the Taft relation to this type of quaternization reaction is shown by fairly good correlations obtained for reaction 2 when one considers the usual α series from methyl to *tert*-butyl (Table I). It should be pointed out that the substituent effect observed here has been shown to be essentially steric in character.[11,12] On the other hand, when the quaternization reaction was studied on a 2,5-dimethyl-4-alkylthiazole series (reaction 3) the relation obtained was not linear.

Table I. Reaction Base + $CH_3X$ in Aprotic Polar Solvent

| Compounds | δ value[a] | Corr coeff |
|---|---|---|
| 2-Alkylthiazoles[c] | 0.96 | 0.9985 |
| 2-Alkylpyridines[b] | 2.09 | 0.9954 |
| 2-Alkylthiadiazoles[c] | 1.02 | 0.9989 |
| 2-Alkyl-4-methylthiazoles | 1.57 | 0.9976 |
| 4-Alkyl-2-methylthiazoles | 1.63 | 0.9994 |

[a] Log $k/k_0 = \delta E_S$ at 25° (R = Me, Et, *i*-Pr, *t*-Bu). [b] H. C. Brown and A. Cahn, *J. Amer. Chem. Soc.*, 77, 1715 (1955). [c] Reference 12.



(3)

The main difference between the two series of quaternization reactions (reactions 2 and 3) lies in the presence of a conformational preference[13,14] in one case (reaction 3) and its almost complete absence in the other (reaction 2). It is plausible that in the latter case the free rotation of dissymmetric groups ($CHX_2$, $CH_2X$) gives an average steric requirement. Thus, almost complete lack of conformational preference in monosubstituted heterocycles (reaction 2), which can be deduced from observation done in analogous benzenic series,[15] explains the linearity of the log $k/k_0$ plot *vs.* $E_S$ for reaction 2. The obvious conformational preference induced by the 5-methyl group in reaction 3 explains the observed nonlinearity (Figure 1).

We may therefore state that *$E_S$ values from the Taft's scale will correlate structural or reactivity data provided that the concerned groups are in a structural surrounding which does not induce an important conformational preference of the group.* This statement, which seems to limit the application of Taft's $E_S$ scale, suggests on the other hand a novel way to take advantage of it. For instance, in the above example of nonlinearity, the convexity of the curve is due to a lower reactivity of the predominant conformer. One might thus expect that the search for nonlinear $E_S$ relationships in enzyme–substrate systems, for instance, will give valuable information on the conformation induced by the enzyme on the substrate.

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(10) W. A. Pryor and K. Smith, *J. Amer. Chem. Soc.*, **92**, 2731 (1970).

(11) R. Cottet, R. Gallo, J. Metzger, and J. M. Surzur, *Bull. Soc. Chim. Fr.*, 4502 (1967).

(12) R. Gallo, M. Chanon, H. Lund, and J. Metzger, *Tetrahedron Lett.*, 3857 (1972).

(13) H. C. Brown, *J. Chem. Educ.*, **36**, 424 (1959).

(14) C. Roussel, M. Chanon, and J. Metzger, *Tetrahedron Lett.*, 1861 (1971).

(15) W. J. Hehre, L. Radom, and J. A. Pople, *J. Amer. Chem. Soc.*, **94**, 1496 (1972).

**André Babadjamian, Michel Chanon**
**Roger Gallo, J. Metzger***
*Institut de Petroleochimie et de Synthese Organique Industrielle*
*Université de Provence*
*Centre de Saint-Jérome, 13013-Marseille, France*

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## Concerning the Mechanism of the Hydrolysis of *N*-Salicylylpyrrole in Alkaline Solution

*Sir:*

A mechanism (Figure 1) has recently been proposed by Menger and Donohue[1] for the alkaline hydrolysis of *N*-salicylylpyrrole. The mechanism is partly based on a sigmoid pH–rate profile showing an increase of rate with hydroxide ion concentration in the pH range 8–11 and a plateau in the pH range 11–13 (Figure 2).

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(1) F. M. Menger and J. A. Donohue, *J. Amer. Chem. Soc.*, **95**, 432 (1973).

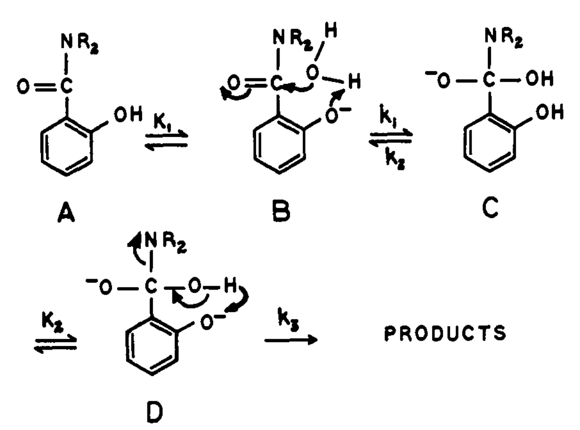

Figure 1. Mechanism of hydrolysis of *N*-salicylylpyrrole (F. M. Menger and J. A. Donohue, *J. Amer. Chem. Soc.*, **95**, 432 (1973)).

The rate law (eq 6) corresponding to the proposed mechanism can be derived (eq 1–5) by application of the steady-state method.

$$-\frac{d[A_T]}{dt} = k_3[D] \qquad (1)$$

$$[A_T] = [A] + [B] \qquad (2)$$

$$\frac{d\{[C] + [D]\}}{dt} = k_1[B] - k_2[C] - k_3[D] = 0 \qquad (3)$$

$$K_1 = [B]/[A][OH^-] \qquad (4)$$

$$K_2 = [D]/[C][OH^-] \qquad (5)$$

$$-\frac{d[A_T]}{dt} = k[A_T] = \frac{k_1k_3K_1K_2[OH^-]^2[A_T]}{\{1 + K_1[OH^-]\}\{k_2 + k_3K_2[OH^-]\}} \qquad (6)$$

$$k = k_1 \text{ for } K_1[OH^-] \gg 1 \text{ and } k_3K_2[OH^-]/k_2 \gg 1 \qquad (7)$$

Menger and Donohue on the basis of an incorrect rate expression indicated that the acid dissociation constant for the tetrahedral intermediate, C, can be obtained. The rate law for the mechanism proposed by Menger and Donohue is given in eq 6 and indicates that the dissociation constant, $K_2$, cannot be evaluated from their kinetic data apart from $k_3K_2/k_2$. A value of $3.2 \times 10^{-3}$ sec$^{-1}$ for the rate constant for the reaction of the *N*-salicylylpyrrole anion, B, with water, can be obtained from the kinetic data[1] as the limiting value of $k$ at high pH (eq 7). Using this value for $k_1$, a value of $1.1 \times 10^4$ for $k_3K_2/k_2$, and the p$K_a$ value of 8.59 for *N*-salicylylpyrrole reported by Menger and Donohue, a plot of $k$ (theoretical) *vs.* pH is compared with the experimental data in Figure 2.

Although an interpretation in terms of an ionization of a steady-state intermediate is probably correct, it is not required by the kinetics of the reaction. The mechanism may be written as

$$A + OH^- \underset{}{\overset{K_1}{\rightleftharpoons}} B + H_2O$$

$$B + H_2O \underset{k_2}{\overset{k_1}{\rightleftharpoons}} C$$

$$C + OH^- \xrightarrow{k_4} \text{products}$$

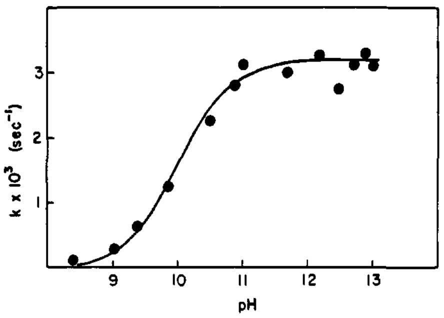

Figure 2. Theoretical variation of observed rate constant, $k$, with pH. Data points are taken from F. M. Menger and J. A. Donohue, *J. Amer. Chem. Soc.*, **95**, 432 (1973).

The steady-state rate law corresponding to this mechanism is

$$-\frac{d[A_T]}{dt} = \frac{k_1k_4K_1[OH^-]^2[A_T]}{\{1 + K_1[OH^-]\}\{k_2 + k_4[OH^-]\}}$$

Thus, a measurable acidity of a steady-state intermediate is not entirely justifiable by the kinetic data.

**Carl R. Wasmuth,* David A. Copeland**
*Department of Chemistry, University of Tennessee at Martin*
*Martin, Tennessee 38237*

*Received March 22, 1973*

## Substituent-Induced $^{13}$C Chemical Shifts. A Perturbation Approach

*Sir:*

It is generally agreed that $^{13}$C chemical shifts are proportional to the total electron density at carbon in systems where bond polarization effects and the presence of low-lying energy states are relatively unimportant.[1,2] Accordingly, the recent report[3] that substituent-induced variations in the $^{13}$C shifts (SCS) of trans 1-substituted butadienes alternate *in magnitude and sign* along the carbon chain may be interpreted as verification of the alternating induced charge (AIC) effect first noted in the CNDO calculations of Pople and Gordon.[4] Application of first-order perturbation theory to the calculation of substituent-induced chemical shifts indicates (1) that the AIC effect appears to be a general phenomenon, at least for carbon in $\pi$ systems, and (2) that there should exist a linear correlation between $\Delta\delta_c$ in derivatives and long-range coupling constants in parent hydrocarbons.

The effect of a substituent on the electron distribution within a $\pi$ system can be assessed in terms of perturbational molecular orbital (PMO) theory.[5] Assuming the substituent not to interact mesomerically with the $\pi$ system, its primary effect will be to alter the effective electronegativity of the atom to which it is bound. Within the Hückel approximation, this case

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[1] J. E. Bloor and E. L. Breen, *J. Phys. Chem.*, **72**, 716 (1968).

[2] T. Tokuhiro and G. K. Fraenkel, *J. Amer. Chem. Soc.*, **91**, 5005 (1969).

[3] O. Kajimoto and T. Fueno, *Tetrahedron Lett.*, 3329 (1972).

[4] J. A. Pople and M Gordon, *J. Amer. Chem. Soc.*, **89**, 4253 (1967).

[5] M. J. S. Dewar, "Molecular Orbital Theory of Organic Chemistry," McGraw-Hill, New York, N. Y., 1969, Chapter 6, and references therein.