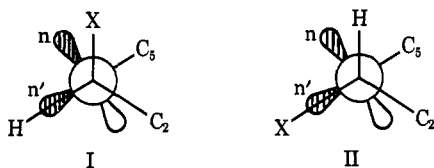
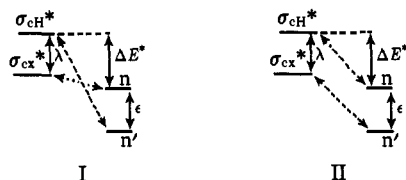


and II ( $C_1X$  equatorial). The bond  $\leftrightarrow$  lone-pair inter-



actions each involve four electrons and X is electro-negative. Let us consider then the attractive interactions between the two lone-pair orbitals and the two empty orbitals  $\sigma_{CX}^*$  and  $\sigma_{CH}^*$ . The important interactions are shown with dotted arrows and the corre-



sponding energies are approximately<sup>13</sup>

$$I \begin{cases} \text{(for } n) & -2h^*{}^2/(\Delta E^* - \lambda) \\ \text{(for } n') & -2h^*{}^2/(\Delta E^* + \epsilon) \end{cases}$$

$$II \begin{cases} \text{(for } n) & -2h^*{}^2/\Delta E^* \\ \text{(for } n') & -2h^*{}^2/(\Delta E^* + \epsilon - \lambda) \end{cases}$$

Orbital  $n$  favors I while orbital  $n'$  favors II. The differential energy in favor of I is  $4h^*{}^2\lambda\epsilon/(\Delta E^*)^3$ , where  $2h^*{}^2\lambda/(\Delta E^*)^2$  can be approximated by the energy difference between eclipsed and bisected conformations of  $XCH_2-CH_2-$  (15.7 kcal/mol for  $X = Cl^1$ ), the splitting  $\epsilon$  is 17 kcal/mol (*an initio* calculation on tetrahydropyran), and  $\Delta E^*$  is of the order of 160 kcal/mol.<sup>14</sup> The conformational preference is then  $\sim 3.3$  kcal/mol for  $X = Cl$ . The experimental value is 2.7 kcal/mol,<sup>9b</sup> while an ST0-3G *ab initio* calculation on 1-chlorotetrahydropyran yields a conformational preference of 1.2 kcal/mol (identical bond lengths in the two conformations) and 3.7 kcal/mol (relaxed bond lengths).

In highly polar solvents, orbitals  $n$  and  $n'$  are both stabilized, whence an increase in  $\Delta E^*$  and a decrease in conformational preference, as observed.<sup>15</sup>

We have not examined the repulsive energies corresponding to eq 1 and we cannot rule out the possibility that the preference for I is due to a smaller repulsion energy. However, this is unlikely since a calculation similar to the previous one—keeping only the four largest orbital interactions and choosing a common pair of ( $h$ ,  $S$ ) values—yields zero conformational preference. The observed solvent effect also argues against any exclusion-repulsion control. Indeed, it can be shown<sup>4</sup> that the repulsive energy change with substitution ( $H \rightarrow X$ ), for any individual (nonbonding orbital, subadjacent orbital) pair, is independent of the energy gap between the orbitals. Thus, superjacent orbital con-

(13) Overlap seems to discriminate only slightly between I and II (whence the common value of  $h^*$ ). For instance,  $\langle n/\sigma_{CC1}^* \rangle = 0.062$  in I while  $\langle n'/\sigma_{CC1}^* \rangle = 0.052$  in II.

(14) This number is chosen as half the natural frequency (13.5 eV) of electronic excitation  $\sigma_{CH} \rightarrow \sigma_{CH}^*$  for an isolated C-H bond (J. W. Raymond and W. T. Simpson, *J. Chem. Phys.*, **47**, 430 (1967)).

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rol by the  $C_1X$  antibonding orbital, as first suggested by Altona, and the energetic nonequivalence of the oxygen lone pairs seem to be significant factors in determining the anomeric effect.

For X less electronegative than H, the same superjacent orbital interactions favor II (equatorial X) over I, thereby providing at least some rationalization for the *reverse* anomeric effect.<sup>16</sup>

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### Conformational Limitation for the Applicability of the Taft $E_s$ Parameters

*Sir:*

The steric parameters obtained from the linear free-energy relationship (eq 1) proposed by Taft, for the

$$\log k/k_0 = E_s \quad (1)$$

evolution of rate constants in acid-catalyzed hydrolysis of esters,<sup>1</sup> have been applied to a wide variety of reactions.

These parameters have been subjected, however, to various criticisms; among the most important ones are: the lack of accounting for the difference in hyperconjugative ability between the various alkyl groups<sup>2</sup> and the close relation between  $E_s$  and  $\sigma^*$  observed by Russian workers.<sup>3</sup>

It is noteworthy, however, that in spite of these criticisms the  $E_s$  parameters have a surprisingly large range of applications such as: organic reactivity,<sup>4</sup> spectroscopy,<sup>5</sup> enzymatic catalysis,<sup>6</sup> and drug design.<sup>7</sup> Moreover, Charton has shown, in a recent statistical analysis, that the  $E_s$  parameters are a function only of the van der Waals radii.<sup>8,9</sup>

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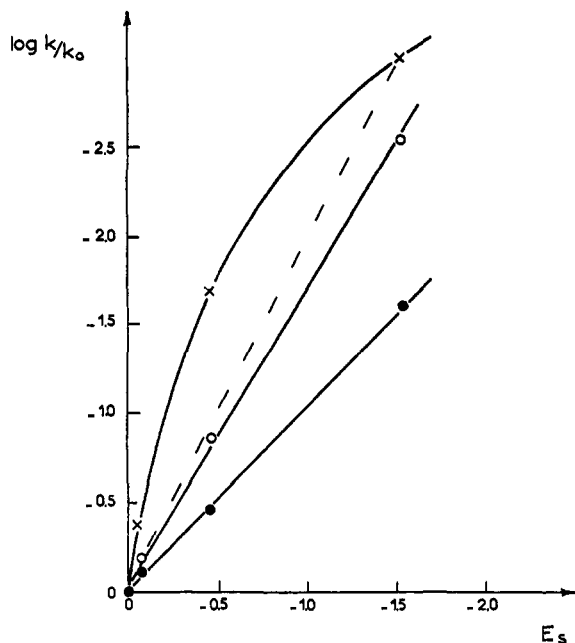
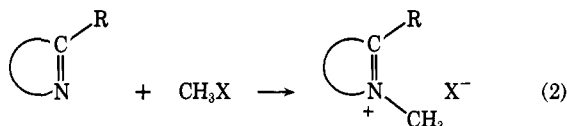


Figure 1.  $\log k/k_0$  for quaternization of alkylthiazoles vs. Taft's  $E_s$  parameters: (●) 2-alkylthiazoles; (○) 2-methyl-4-alkylthiazoles; (×) 2,5-dimethyl-4-alkylthiazoles.

However, recently Pryor<sup>10</sup> 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.



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  $\alpha$  series from methyl to *tert*-butyl (Table I). It

Table I. Reaction Base +  $\text{CH}_3\text{X}$  in Aprotic Polar Solvent

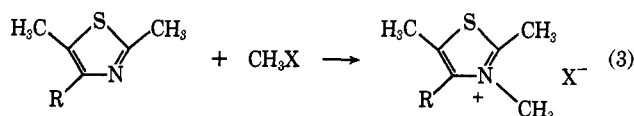
Compounds	$\delta$ value <sup>a</sup>	Corr coeff
2-Alkylthiazoles <sup>c</sup>	0.96	0.9985
2-Alkylpyridines <sup>b</sup>	2.09	0.9954
2-Alkylthiadiazoles <sup>c</sup>	1.02	0.9989
2-Alkyl-4-methylthiazoles	1.57	0.9976
4-Alkyl-2-methylthiazoles	1.63	0.9994

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

should be pointed out that the substituent effect observed here has been shown to be essentially steric in

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

character.<sup>11,12</sup> 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.



The main difference between the two series of quaternization reactions (reactions 2 and 3) lies in the presence of a conformational preference<sup>13,14</sup> 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 ( $\text{CHX}_2$ ,  $\text{CH}_2\text{X}$ ) 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,<sup>15</sup> 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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### Concerning the Mechanism of the Hydrolysis of *N*-Salicylpyrrole in Alkaline Solution

Sir:

A mechanism (Figure 1) has recently been proposed by Menger and Donohue<sup>1</sup> for the alkaline hydrolysis of *N*-salicylpyrrole. 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).

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