

TRANSMISSION OF SUBSTITUENT EFFECTS IN HETEROCYCLIC SYSTEMS. THE CORRELATION AND PREDICTION OF SOLVOLYSIS RATES FOR HETEROARYLMETHYL DERIVATIVES.¹

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Recent studies indicate a renewed interest in the mode of interaction of substituents with reaction sites in heterocyclic systems.^{3,4} We have investigated this question further through use of the solvolysis reaction; a very useful reaction in this respect, as it shows high sensitivity to resonance and field effects, and may be carried out on compounds of a wide range of reactivity under neutral conditions.

We wish to report notable success in dealing with the relative rates of solvolysis of a number of substituted heteroarylmethyl compounds, including α -heteroarylethyl *p*-nitrobenzoates of 2-furyl, 3-furyl, 2-benzofuryl, 3-benzofuryl, and 2-thienyl systems.

Bancroft and Howe⁵ have shown that the Dewar-Grisdale equation⁶, when calibrated with Brown's⁷ σ^+ constants rather than Hammett σ constants gives greatly improved results in correlating the measured rates of detritiation of substituted naphthalenes. Eaborn and Fischer⁸ have extended these observations.

We report here the successful application of a modification of the Dewar-Grisdale equation to the treatment of substituent effects in the solvolysis of heteroarylmethyl compounds. The Dewar-Grisdale equation (1) possesses a term ($q_{ij}M_x$) representative of resonance effects. M_x is a parameter indicative of the

$$(\sigma_{ij})_x = \frac{F_x}{r_{ij}} + q_{ij}M_x \quad (1)$$

resonance capability of substituent x , and q_{ij} is a measure of the transmission of resonance effects from a substituent attached to ring carbon i to the carbon (j) bearing the reaction center. The term q_{ij} is derived from Huckel molecular orbital theory. In solvolysis the delocalization of charge from the side chain to the carbon bearing the substituent, rather than polarization of the ring by the substituent, is of prime importance. Furthermore, the appreciable polarization of neutral heterocyclic systems necessitates consideration of the charge distribution of the un-ionized initial state as well. Accordingly, we define the term Δq_{ij} as the difference in regional charge⁹ at atom i in the un-ionized molecule and the heteroarylmethyl cation. Use of the Δq_{ij} term in the framework of equation (1) gives the modified Dewar-Grisdale equation (2), in which F^+ is a

$$(\sigma_{ij}^+)_{\text{x}} = \frac{F_{\text{x}}^+}{r_{ij}} + \Delta q_{ij} M_{\text{x}}^+ \quad (2)$$

measure of the field set up by the substituent, M^+ is a measure of the capacity for resonance interaction of the substituent, and r_{ij} is the distance between atoms i and j . F^+ and M^+ constants are established for each substituent by the use of Brown's σ_{p}^+ and σ_{m}^+ constants in conjunction with $1/r_{ij}$ and Δq_{ij} values appropriate to the toluene-benzyl cation pair. Effective substituent constants, σ_{ij}^+ , can then be calculated for any aromatic system from equation (2).

In practice the Δq_{ij} terms are obtained from molecular orbital calculations. The charge distributions of neutral compounds are computed with use of a methyl group as a side chain model; replacement of the methyl group with a planar methylene provides the computational model for the carbonium ion. The availability of standard programs for CNDO/2 and INDO all valence electron molecular orbital models¹⁰ make it feasible to compute Δq_{ij} values for a wide variety of heterocyclic systems. Such methods, by virtue of their uniquely defined heteroatom parameters and overall superiority to Huckel molecular orbital theory are well-suited to this application.

Two particular features of this approach are to be noted. The F_{INDO}^+ and M_{INDO}^+ values for typical substituents¹¹ show nearly complete separation into field (\mathcal{F}) and resonance (\mathcal{R}) terms when analyzed in terms of the Swain and Lupton model¹²; ($F_{\text{INDO}}^+ = 91\% \mathcal{F}$, $M_{\text{INDO}}^+ = 95\% \mathcal{R}$). In addition, this approach is particularly suitable for predictions for new systems.

Applications and Predictions: For thiophene, the very close similarity of the $(\Delta q_{ij})_{\text{CNDO}}$ terms to those of benzene explains the excellent correlations observed for electrophilic^{13,14} and solvolytic¹⁵ reactions with σ_{m}^+ and σ_{p}^+ . It follows from the close correspondence of the \mathcal{R} for 5-substituted-2-furyl systems (Table I) that correlation with σ_{p}^+ should be excellent; in fact it is¹⁶. The high Δq for 5-substituted-3-furyl systems rationalizes the high $k_{5\text{-Me}}/k_{\text{H}}$ rate ratios observed^{17,18}. The high percentage resonance predicted for 5-substituted-2-benzofuryl systems has been tested, and we find that the percentage resonance is 44 ± 4 . The predicted high resonance component for 2-substituted-5-benzofuryl systems is notable, and intentions are to test this shortly. For one or two additional situations, these methods give predictions well in accord with experiment. The near identity of Δq values for two substituent positions in the 3-benzofuryl system is reflected in our experimentally determined rates.

TABLE I

Field and Resonance Sensitivities for Solvolysis Reactions.

Ring System	i ^a	j ^b	r _{i,j} ^c	Δq (INDO)	Δq (CNDO)	ΔR ^d Pred.	ΔR ^e found
benzene	3	1	1.732	0.0353	0.0368	30	
	4	1	2.000	0.2109	0.2115	65	
furan	5	2	1.571	0.2726	0.2763	66	66±2
	4	2	1.605	0.0696	0.0642	39	41
	5	3	1.605	0.1150	0.1076	49	44
thiophene	5	2	1.768	-	0.2051	-	
	4	2	1.672	-	0.0395	-	
benzofuran	6	2	3.271	0.1363	0.1377	66	66±3
	5	2	3.293	0.0497	0.0473	47	44±1
	2	5	3.293	0.0727	-	54	
	6	3	3.045	0.0659	0.0666	49	
	5	3	2.782	0.0670	0.0669	51	

a) Substituent position; b) Side chain position; c) In units of benzene bond lengths; d) Calculated for a typical group of substituents (footnote 11) using F_{INDO}^+ and M_{INDO}^+ with Δ as defined by Swain and Lupton, Ref. 12; e) Determined by using the observed relative rates in the Swain and Lupton treatment, Ref. 12.

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