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Mode of Electronic Effect Transmission via the Amide Bond

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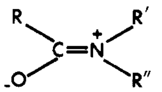
The directional characteristics of electronic effect transmission via the amide bond have been tested by way of studies on a variety of amide bond systems. pK_a's are reported for series of 3′- and 4′-substituted 4-carboxybenzanilides, 3- and 4-substituted 4′-carboxybenzanilides, and 3- and 4-substituted oxanilic acids and compared with previously reported pK_a data on series of 3′- and 4′-substituted 4-carboxybiphenyls, 4′-substituted 4-aminobenzanilides, 4-substituted 4′-aminobenzanilides, 4′-substituted 4-aminobiphenyls, and 3- and 4-substituted benzoic acids. Also reported are ^{1}H NMR substituent chemical shift data for the acyl methyl protons of series of 4′-substituted 4-acetylbenzanilides, 4-substituted 4′-acetylbenzanilides, 4′-substituted 4-acetylbiphenyls, and *N*-methyl amides (GCONHMe, G = alkyl group or substituted alkyl group). These studies confirm the conjugative effect transmission ability of the amide bond and the directional independence of this effect with respect to the position of variable substitution on either the nitrogen or carbonyl side of the bond. The transmission of inductive effects via a π-inductive mechanism is, however, directionally dependent. The latter dependence is reflected in less efficient transmission from the carbonyl side of the bond.



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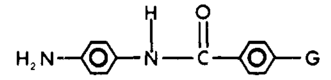

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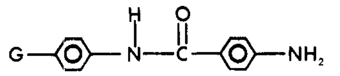

III

The question of the nature and mode of electronic effect transmission via the amide bond is of considerable interest and impact relative to the study of relationships between the structure of amide bond systems and their physical, chemical, or biological properties. For example, the importance of a resonance contributor such as I has been invoked to explain the planarity and restricted rotation which has been observed about amide bonds and also to provide the basis for the assumption that the amide bond can function as an effective transmitter of electronic effects.[1] The latter assumption has, however, been questioned by Menger and his co-workers[2] whose data on 4-substituted 4′-aminobenzanilides (II) indicate that the various substituents have virtually no effect on the pK_a of the amino group. On the other hand, similar data on the isomeric 4′-substituted 4-aminobenzanilides (III) indicate an ordering of the pK_a's based on classical electronic effect considerations.[3] The results of studies on other amide bond systems confirm[4-7] that the amide bond can indeed function as a transmitter of electronic effects, and some workers,[3,6] in order to explain the differences between II and III, have suggested a unidirectional transmission effect for the amide bond. Specifically, the suggestion has been that the amide bond can function as a transmitter of electronic effects but can do so effectively only from the nitrogen side of the bond. However, if such were the case, the importance of contributing structure I would seem to be questionable for amide bond systems. What appears to be the more important consideration is not simply the position of various substituents relative to the amide nitrogen but rather the nature of both the substituents and the reaction center and their positions relative to the amide bond. For example, for series II, where the reaction center is an unequivocally resonance electron-donating group positioned on the nitrogen side of the amide bond, there are no important isovalent, interaction-contributing resonance structures possible which simultaneously involve the amino group, the amide bond, and any of the substituent G groups. That is, there is no direct conjugative interaction from (or to) the reaction center via the amide bond to (or from) the variable substituents. The result is a leveling of the substituent effects and thus of the pK_a's. On the other hand, for the isomeric series III, where the amine reaction center is positioned on the carbonyl carbon side of the amide bond, direct conjugative interaction is possible between the amine reaction center and electron-withdrawing G groups via the amide bond. The ΔpK_a (ΔpK_a = pK_a of parent compound minus pK_a of substituted compound) data in Table I for series II and III, when compared to similar data for a series of 4′-substituted 4-aminobiphenyls (IV),[8,9] clearly demonstrate the leveled substituent effects in II and the comparable effects in III and IV for G = Cl and NO_2.

Table I. ΔpK_a's for Series II, III, and IV

G	ΔpK_a [a]		
	II [b]	III [c]	IV [d]
OMe	−0.07	−0.05	−0.02 [g]
Me	0.03	−0.02	−0.07
H	*e*	*f*	*h*
Cl	0.01	0.19	0.16
NO_2	0.07	0.60	0.57,[i] 0.68[j]

[a] ΔpK_a = pK_a of parent compound (G = H) minus pK_a of substituted compound. [b] Reference 2. [c] Reference 3. [d] References 8 and 9. [e] pK_a of 4′-aminobenzanilide is 4.55. [f] pK_a of 4-aminobenzanilide is 2.94. [g] ΔpK_a for 4′-OH compound. [h] pK_a of 4-aminobiphenyl is 4.27 in 10% EtOH[8] and 4.05 in 50% EtOH.[9] [i] ΔpK_a in 50% EtOH. [j] ΔpK_a in 10% EtOH.

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(1) Zabicky, J., Ed.; "The Chemistry of Amides"; Wiley-Interscience: New York, 1970.

(2) Donohue, J. A.; Scott, R. M.; Menger, F. M. *J. Org. Chem.* **1970**, *35*, 2035.

(3) Idoux, J. P.; Zarrillo, R. *J. Org. Chem.* **1975**, *40*, 1519.

(4) Peters, F. B.; Johnson, Jr., H. W. *J. Org. Chem.* **1975**, *40*, 1517 and references cited therein.

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(6) Kadin, S. B. *J. Org. Chem.* **1971**, *36*, 1160.

(7) Bennett, J.; Delmas, M.; Maire, J. C. *Org. Magn. Reson.* **1969**, *1*, 319.

(8) Idoux, J. P.; Cantwell, V. S.; Hinton, J.; Nelson, S. O.; Hollier, P.; Zarrillo, R. *J. Org. Chem.* **1974**, *39*, 3946.

(9) Byron, D. J.; Gray, G. W.; Wilson, R. C. *J. Chem. Soc. C* **1966**, 831.

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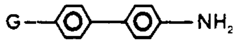
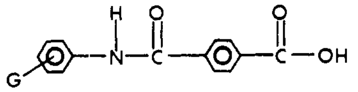


IV

Thus, if a unidirectional transmission effect does not in fact operate for the amide bond, then a study for related series of benzanilides, where the reaction center is an unequivocally resonance electron-withdrawing group, should illustrate effects opposite to those reported for II and III. We report here studies on a number of amide bond systems which are designed to demonstrate these electronic transmission effects. These studies include comparisons of (i) pK_a data for series of 3′- and 4′-substituted 4-carboxybenzanilides (V), 3- and 4-substituted 4′-carboxybenzanilides (VI), and 3′- and 4′-substituted 4-carboxybiphenyls (VII) and (ii) NMR chemical shift data for series



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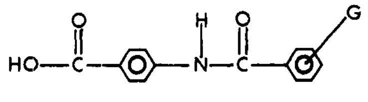

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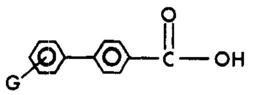
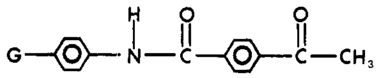


VII

of 4′-substituted 4-acetylbenzanilides (VIII), 4-substituted 4′-acetylbenzanilides (IX), and 4′-substituted 4-acetylbiphenyls (X). In addition, in order to demonstrate in a



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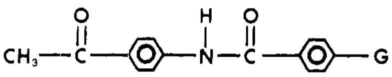

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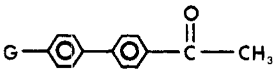
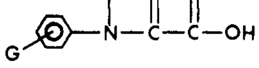
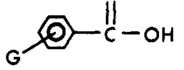


X

more direct manner the influence of a perturbing amide bond, we have also determined and report here the pK_a's for a series of 3- and 4-substituted oxanilic acids (XI). The latter data are compared with existing data for correspondingly substituted benzoic acids (XII).[10a]



XI



XII

Table II. pK_a Data for Series V, VI, and VII

G	pK_a			ΔpK_a^{a}		
	V^b	VI^b	VII^c	V	VI	VII
H	5.70	6.51	5.62			
4-Me	5.71	6.58	5.67	−0.01	−0.07	−0.05
3-Me		6.51	5.69		0	−0.07
4-Cl	5.73	6.41	5.42	−0.03	0.10	0.20
3-Cl	5.68	6.40	5.43	0.02	0.11	0.19
4-OMe	5.76	6.69	5.76	−0.06	−0.18	−0.14
3-OMe	5.68		5.66	0.02		−0.04
4-NO_2	5.63	6.35	5.20	0.07	0.16	0.42

[a] ΔpK_a = pK_a of parent compound (G = H) minus pK_a of substituted compound. [b] Determined potentiometrically in 50% tetrahydrofuran-water at 24 °C. The values represent the average of at least two determinations. [c] From ref 9.

Table III. Substituent Chemical Shift Data for Acetyl-Group Protons in Series VIII, IX and X

G	SCS,^{a} Hz			ΔSCS^b		
	VIII	IX	X	VIII	IX	X
NO_2	158.7	154.0	157.5	−0.4	0.2	−2.0
Cl	158.3	153.5	155.6	0	0.7	−0.1
H	158.3	154.2	155.5			
Me	157.7	152.3		0.6	1.9	
MeO	158.0	152.8	154.3	0.3	1.4	1.2

[a] Determined vs. Me_4Si at 37 °C in 10% (w/v) Me_2SO-d_6. The values represent the average of at least three determinations. [b] ΔSCS = the chemical shift of the acetyl methyl protons of the parent compound (G = H) minus the chemical shift of the acetyl methyl protons of the substituted compound.

Table IV. Results of Correlation Analysis for the pK_a's of Series III, IV, VI, and VII

series	$-\rho_{m/p}$^{a}	$-\rho_I$^{b}	$-\rho_R$^{c,d}
III	0.64	0.56	0.46
IV	0.67	0.63	0.60
VI	0.29	0.25	0.34
VII	0.54	0.55	0.46

[a] $\sigma_{m/p}$ constants from: McDaniel, D. H.; Brown, H. C. *J. Org. Chem.* **1958**, *23*, 420. Statistical parameters (footnote *e*) for these correlations are given as series no., *r* (correlation coefficient), *s* (standard deviation from regression): III, 0.984, 0.06; IV, 0.930, 0.12; VI, 0.901, 0.05; VII, 0.983, 0.04. [b] σ_I constants from ref 14. [c] σ_R (for series III and IV) and $\sigma_{R(BA)}$ (for series VI and VII) from ref 14. [d] Statistical parameters (footnote *e*) for the correlations used to determine ρ_I and ρ_R are given as series no., *R* (multiple correlation coefficient), *s* (standard deviation from regression): III, 0.995, 0.04; IV, 0.995, 0.04; VI, 0.941, 0.06; VII, 0.993, 0.04. [e] Snedecor, G. W. "Statistical Methods", 5th ed.; The Iowa State University Press: Ames, Iowa, 1956.

Results and Discussion

The pK_a's and ΔpK_a's for V and VI as well as those reported previously[9] for VII are given in Table II. Substituent chemical shift (SCS) data for the acetyl-group protons of VIII, IX, and X are reported in Table III. The pK_a's for XI as well as those reported previously[10a] for XII are shown in Table V.

Inspection of the data in Table II for V, VI, and VII indicates results opposite to that described above for II, III, and IV. That is, for series V (variable substitution on the nitrogen side of the amide bond), the ΔpK_a data indicate a leveling of the substituent effects in the same manner as that for II (variable substitution on the carbonyl side of the amide bond). However, comparable effects are observed in VI (variable substitution on the carbonyl side of the amide bond) and VII for G = 4-Me and 4-OMe in the same manner as that in III (variable substitution on the nitrogen side of the amide bond) and IV for G = 4-Cl and 4-NO_2. In effect then, the normal conjugative transmitting ability of the 1,1′-bond in IV and in VII is

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(10) (a) Albert, A.; Serjeant, E. P. "Ionization Constants of Acids and Bases"; Methuen: London, 1962; p 127. (b) *Ibid.*, Chapter 2. (c) *Ibid.*, Chapter 5.

Table V. pK_a Data for Series XI and XII

	pK_a		ΔpK_a[c]	
	XI[a]	XII[b]	XI	XIII
H	2.18	4.17		
3-Me	2.42	4.27	−0.24	−0.10
4-Me	2.45	4.37	−0.27	−0.20
3-OMe	2.11	4.09	+0.07	+0.08
4-OMe	2.65	4.47	−0.47	−0.30
4-F	2.43	4.14	−0.25	+0.03
3-Cl	1.91	3.83	+0.27	+0.34
4-Cl	2.00	3.98	+0.18	+0.19
$4\text{-}NO_2$	1.62	3.43	+0.56	+0.74

[a] Determined potentiometrically in water at 25 °C. The values represent the average of at least two determinations. [b] From ref 10a (determined in water at 25 °C). [c] $\Delta pK_a = pK_a$ of parent compound (G = H) minus pK_a of substituted compound.

not impeded when perturbed by the amide bond in either III or VI even though the direction of that transmission occurs from opposite sides of the amide bond in III and in VI. In addition, similar results are obtained when a nonreaction property is used as a probe of any directional electronic effect transmission via the amide bond. For example, the ΔSCS data (^{1}H NMR substituent chemical shifts of the acyl methyl protons) in Table III for VIII, IX, and X indicate a leveling of the substituent effects for VIII (which is directionally substituted like V) but the same effect for IX (which is directionally substituted like VI) and X for G = 4-Me and 4-OMe.

Thus, while it seems to be clearly established that the amide bond can function as an efficient transmitter of electronic effects and that the transmission is not unidirectional in character,[11] the quantitative assessment of the nature of the transmission does provide an interesting insight as to its origin. For example, the $\rho_{m/p}$ values reported in Table IV, which are obtained by subjecting the pK_a's for III, IV, VI, and VII to correlation analysis[13] via the simple Hammett equation, offer a measure of the susceptibility of the reaction center to changes in electron density as caused by the various substituents and thus provide a comparative indication of the electronic effect transmission in one system relative to that in another. The essential identity of the $\rho_{m/p}$ values for III and IV indicates that the efficiency of electronic effect transmission is essentially identical for these two systems, while a similar comparison for VI and VII would indicate a less efficient transmission of electronic effects in VI relative to VII. In an attempt to identify the origin of the differences between III and IV as compared to VI and VII, the pK_a's were subjected to further analysis via the dual substituent parameter equation treatment (Table IV).[13,14] The latter approach indicates that the differences in electronic effect transmission lie not in the resonance component of that transmission but in the inductive component. That is, the relative resonance transmission coefficient for III and IV, $\rho_R(\text{III})/\rho_R(\text{IV}) = 0.76$, is essentially identical with that for VI and VII, $\rho_{R(BA)}(\text{VI})/\rho_{R(BA)}(\text{VII}) = 0.74$. However, the corresponding inductive transmission coefficient for VI and VII, $\rho_I(\text{VI})/\rho_I(\text{VII}) = 0.45$, is only approximately half that for III and IV, $\rho_I(\text{III})/\rho_I(\text{IV}) = 0.89$. This difference in inductive transmission coefficient between VI/VII and III/IV may reflect a directional difference in the ability of the amide bond to transmit electronic effects via a π-inductive mechanism since, as demonstrated previously by Taft and his co-workers,[14b] such effects are included in and follow the σ_I scale of substituent constants. An additional indication of this possibility is provided by analyzing the perturbing influence of the amide bond in XI compared to XII.[15] Inspection of the data in Table V indicates a similar and consistent ordering of the pK_a's for XI and XII (except for G = 4-F)[16] based on the expected electron-withdrawing and -donating abilities of the various substituents. Further, the efficiency of electronic effect transmission for XI and XII is essentially identical. That is, correlation analysis of the pK_a's for XI yields a $\rho_{m/p}$ value of 0.97 compared to that of unity as originally defined by Hammett for the pK_a's of XII in water at 25 °C and an inductive transmission coefficient of 0.80 which compares favorably (0.89) with that determined for III/IV.

The results of this study confirm the amide bond's conjugative effect transmission ability and demonstrate that this transmission is directionally independent of the position of variable substitution relative to either the nitrogen or the carbonyl side of the bond. The transmission of electronic effects via a π-inductive mechanism does, however, appear to be directionally dependent on the position of substitution relative to the amide bond center. The latter dependence results in less efficient transmission of π-inductive effects from the carbonyl side of the bond.

Experimental Section

Series V, VI, VIII, IX, X, and XI and the *N*-methyl amide series listed in ref 11 were all prepared by methods previously reported in the literature.[17] All of the compounds were recrystallized to constant melting points from appropriate solvents or were vacuum distilled.

The pK_a's for series V and VI were determined potentiometrically by measuring the pH of a solution containing equivalent amounts of the carboxylic acid and its salt. Approximately 2×10^{-4} mol of the carboxylic acid was dissolved in the minimum amount of tetrahydrofuran (10–50 mL), and an equal volume of boiled, deionized water was added to obtain a 50% tetrahydrofuran–water solvent mixture. The calculated amount of 0.0101 N NaOH needed to half-neutralize the carboxylic acid was added from a 5-mL microburet and the pH (sample electrode, Ag/AgCl glass; reference electrode, liquid junction; digital display research pH meter) of the resulting solution was then read. The pK_a's

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(11) For simple amide bond systems not capable of conjugative interactions, the influence of some substituents is a function of their substitution position relative to the amide nitrogen. For example, previously reported[12] data for an extensive series of N-monosubstituted acetamides (MeCONHG) indicate that the effect of any G on the ^{1}H NMR SCS of Me is primarily conformational in nature. On the other hand, for the isomeric series GCONHMe, the effect of G on the ^{1}H NMR SCS of Me appears to be conformational for alkyl groups and inductive and/or field for polarizable groups. For example, the ^{1}H substituent chemical shifts (in 10% CCl_4 vs. Me_4Si) for the *N*-methyl protons of GCONHMe are as follows [G, SCS (Hz)]: Me, 162.6; Et, 162.6; *n*-Pr, 163.8; *i*-Pr, 160.2; *i*-Bu, 162.0; *t*-Bu, 163.2; neopentyl, 161.4; $CH_2{=}CHCH_2$, 165.6; $ClCH_2$, 168.6.

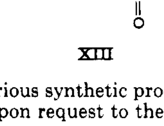
(12) Idoux, J. P.; Scandrett, J. M.; Sikorski, J. A. *J. Am. Chem. Soc.* **1977**, *99*, 4577.

(13) Chapman, N. B., Shorter, J., Eds.; "Correlation Analysis in Chemistry"; Plenum Press: New York, 1978.

(14) (a) Ehrenson, S.; Brownlee, R. T. C.; Taft, R. W. *Prog. Phys. Org. Chem.* **1973**, *10*, 1. (b) Dayal, S. K.; Ehrenson, S.; Taft, R. W. *J. Am. Chem. Soc.* **1972**, *94*, 9113.

(15) Unfortunately, a complete comparison cannot be made since the series isomeric with XI (i.e., *N*-benzoyl-substituted carbamic acids) are not known.

(16) For G = 4-F in series XI, (the possibility of) a contributing structure such as XIII would cause an acid-weakening effect. A similar type of contributing structure is not possible for G = 4-F in series XII. We thank one of the referees for bringing this to our attention.



XIII

(17) Details of the various synthetic procedures and literature references can be obtained upon request to the corresponding author.

reported in Table II for series V and VI represent the average of at least two determinations. The maximum deviation from the mean of replicate pK_a values did not exceed 1.5% except for the 3-Cl compound of series VI (2.2%).

The pK_a's of series XI (Table V) were determined in water at 25 °C either by potentiometric titration[10b] of the sodium salt of the acid (for G = H, 3-Me, 4-Me, 4-OMe, and 4-F) or by conductimetry[10c] (for G = 3-OMe, 3-Cl, 4-Cl, and 4-NO_2). The pK_a's determined by potentiometry are the average of three determinations and those determined by conductimetry are the average of two determinations. The maximum deviation from the mean of replicate pK_a values did not exceed 0.9% for any of the compounds studied.

The substituent chemical shifts (SCS) in hertz for series VIII, IX, and X (Table III) and the *N*-methyl amide series listed in ref 11 were measured on a Varian T-60 spectrometer vs. Me_4Si at 37 °C either in 10% (w/v) Me_2SO-d_6 or in 10% (w/v) CCl_4 solutions. All of the values reported represent the average of at least three determinations. The maximum deviation from the mean of replicate SCS values did not exceed 0.7% for any of the compounds in any of the series studied.

Acknowledgment. This work was supported in part by the Office of Research and by the Foundation of The University of Central Florida.

Registry No. V (G = H), 16777-78-9; V (G = 4-Me), 72269-13-7; V (G = 4-Cl), 59291-79-1; V (G = 3-Cl), 59291-77-9; V (G = 4-OMe), 72269-14-8; V (G = 3-OMe), 72269-15-9; V (G = 4-NO_2), 72269-16-0; VI (G = H), 582-80-9; VI (G = 4-Me), 72269-17-1; VI (G = 3-Me), 72269-18-2; VI (G = 4-Cl), 70204-56-7; VI (G = 3-Cl), 70204-55-6; VI (G = 4-OMe), 28547-12-8; VI (G = 4-NO_2), 19717-14-7; VIII (G = NO_2), 50440-54-5; VIII (G = Cl), 72269-19-3; VIII (G = H), 72269-20-6; VIII (G = Me), 72269-21-7; VIII (G = MeO), 72269-22-8; IX (G = NO_2), 62507-48-6; IX (G = Cl), 72269-23-9; IX (G = H), 5411-13-2; IX (G = Me), 72269-24-0; IX (G = MeO), 72269-25-1; X (G = NO_2), 135-69-3; X (G = Cl), 5002-07-3; X (G = H), 92-91-1; X (G = MeO), 13021-18-6; XI (G = H), 500-72-1; XI (G = 3-Me), 17738-78-2; XI (G = 4-Me), 42868-89-3; XI (G = 3-OMe), 72269-26-2; XI (G = 4-OMe), 41374-62-3; XI (G = 4-F), 69066-43-9; XI (G = 3-Cl), 17709-99-8; XI (G = 4-Cl), 17738-71-5; XI (G = 4-NO_2), 103-94-6.

Substituent Effects in Hydrogen Abstraction from 10-Substituted-9-methylanthracenes. Correspondence with Ring Substitution[1]

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Hydrogen abstraction from a series of eight 10-substituted-9-methylanthracenes at 70 °C has been examined by means of photoinduced reaction with bromotrichloromethane. An excellent Hammett correlation could be obtained with σ^+ parameters. The ρ value of -0.78 ± 0.05 showed a correlation coefficient of 0.99 and a standard regression from the mean of 0.06. This corresponds well to the value of -0.83 ± 0.04 previously determined for the trichloromethylation of 9-substituted anthracenes. These results extend to polycyclic systems the relationship recently proposed by Pryor of correspondence between ρ values for hydrogen abstraction from toluenes and substitution into benzenes.

In benzenoid systems, there exists a decided similarity in Hammett correlations between studies in which the reaction site occurs in conjugation with the ring system and those examples of attack upon the ring itself. This is especially true for electrophilic aromatic substitution at the para position where correlations with σ^+ are obtained. This observation is clarified and rationalized by a consideration of resonance structures for the respective transition states.[3] Where analogous radical processes are concerned, the above should at least also be qualitatively true and most pertinent in situations where a relatively high degree of charge separation is present in the transition state. More explicitly, the anticipation is that the transition states for hydrogen abstraction from a series of substituted toluenes and ring substitution into a series of substituted benzenes by a common radical should be markedly similar.

Noting the above correspondence in transition-state models, Pryor and co-workers have postulated a quantitative relationship between the respective reactions.[4] It is held that the ρ value for hydrogen abstraction by a given radical from substituted toluenes is, within experimental tolerances, identical with that obtained for substitution by the same radical in corresponding benzenes. Supportive experimental data have been summarized by these workers.[4]

Some concern must be expressed about the data utilized to generate the relationship. The most compelling shortcoming arises from the fact that few radicals will both abstract hydrogen from a series of toluene substrates and also undergo substitution to the corresponding benzenes at the same temperature. None of the common, typically electrophilic radicals employed for benzylic hydrogen abstraction studies, e.g., chlorine, bromine, trichloromethyl, and *tert*-butoxy radicals, etc., will ring substitute in benzene under comparable reaction conditions. Pryor has been obliged to base his relationship on generally nonselective carbon radicals with rather small ρ values. At this extreme of nonselectivity, comparisons are more tenuous.

Polycyclic aromatic compounds undergo radical ring substitution much more readily than simple benzene de-

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[1] Presented at the 34th Northwest Regional Meeting of the American Chemical Society, June 15, 1979.

[2] (a) Oregon State University. (b) College of Idaho.

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