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Stereoelectronic Control of Aromatic Electrophilic Substitution. Importance of Independent Resonance Form Energies

Lawrence I. Kruse*[a] and Jin K. Cha[b]

[a] *Department of Medicinal Chemistry, Smith Kline & French Laboratories, 1500 Spring Garden Street, Philadelphia, Pennsylvania 19101, U.S.A.*

[b] *Department of Chemistry, Harvard University, 12 Oxford Street, Cambridge, Massachusetts 02138, U.S.A.*

Unexpected regiochemistry observed in the electrophilic substitution of polarized aromatic compounds is explained as occurring *via* a transition state which most closely resembles the valence-bond aromatic resonance form of lowest energy; electrophilic attack *ortho* to an aryl ether or ester is suggested to occur *trans*-antiperiplanar to the nonbonding, coplanar oxygen orbital, and therefore s-*cis* to the substituent to give the observed low *ortho/para* ratios because of the directed bulk of the group.

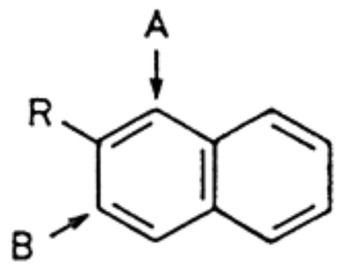
Electrophilic aromatic substitution is a reaction which is fundamental to organic chemistry, and resonance, steric, and inductive effects combine to determine the mixtures of positional isomers often obtained. This communication suggests that stereoelectronic effects can become the factor which controls the positional reactivity of certain aromatic compounds. Consideration of relative resonance energies for potential transition states (approximated here as σ-complexes) provides a useful method for predicting the regiochemistry of aromatic substitution reactions. Functional groups which control reactivity by changing transition-state energies should also perturb ground-state π-electron densities; with suitably substituted compounds this has already been confirmed spectroscopically.[1]

The carbon–carbon bond length (*ca.* 1.4 Å) in aromatic systems provides steric compression to electrophiles approach-

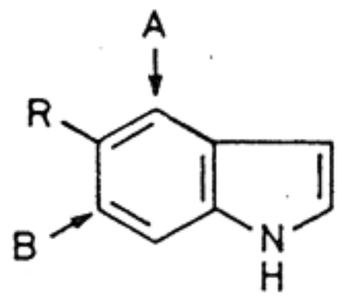
Table 1. Electrophilic and Claisen substitution reactions of aromatic systems.

Compound	Heat or electrophile	Position of attack[a]	Compound	Heat or electrophile	Position of attack[a]
(1a)	Heat[b]	A	**(6b)**	HNO_3[p]	A → B[r]
(1b)	'$Me_2\overset{+}{N}=CH_2$'[c]	A	**(6c)**	HNO_3[p]	A
(2a)	Heat[d]	A	**(7a)**	HNO_3[s]	A
(2b)	'$Me_2\overset{+}{N}=CH_2$'[e]	A	**(7b)**	Br_2[t]	A
(3)	Heat[f]	5A : 1B	**(8)**	HNO_3[u]	2A : 1B
			(8)	Cl_2[v]	4A : 1B
(4a)	Bu^tOCl[g]	A			
(4b)	Bu^tOCl[g]	B			
(4c)	Cl_2,[h] Br_2[i]	A	**(9)**	HNO_3[w]	2A : 1B
(4c)	HNO_3[j]	*ca.* 2A : 3B			
(4d)	HNO_3[k]	A	**(10a)**,[x] **(10b)**[q]	HNO_3	A
(4d)	Br_2[l]	B			
(4e)	HNO_3[m]	A	**(11a)**	Heat[y]	6A : 1B
(4e)	Br_2[m]	B	**(11b)**	Heat[y]	11A : 6B
			(11c), **(11d)**	Heat[y]	A
(5a),[n] **(5b)**[o]	HNO_3	A	**(11e)**	Heat[y]	2A : 1B
			(11f)	Heat[z]	A
(6a)	HNO_3[p]	3A : 4B	**(11g)**	Heat[z]	B
(6a)	Br_2[q]	A			

[a] In each example isomer A is the predicted product. [b] L. Claisen, *Chem. Ber.*, 1912, **45**, 3157. [c] J. Decombe, *C. R. Acad. Sci.*, 1933, **197**, 258. [d] M. Julia and J.-Y. Lallemand, *Bull. Soc. Chim. Fr.*, 1973, 2046. [e] S. A. Monti, W. O. Johnson, and D. White, *Tetrahedron Lett.*, 1966, 4459. [f] D. G. Clark, L. Crombie, and D. A. Whiting, *J. Chem. Soc., Perkin Trans.* 1, 1974, 1007. [g] D. Ginsburg, *J. Am. Chem. Soc.*, 1951, **73**, 702. [h] J. K. Faulkner and D. Woodcock, *J. Chem. Soc.*, 1962, 4437. [i] S. F. Hazlet and R. J. Brotherton, *J. Org. Chem.*, 1962, **27**, 3253. [j] R. Pschorr and W. Stohrer, *Chem. Ber.*, 1902, **35**, 4393. [k] S. F. MacDonald, *J. Chem. Soc.*, 1948, 376. [l] L. C. Raiford and W. C. Stoesser, *J. Am. Chem. Soc.*, 1927, **49**, 1077. [m] L. C. Raiford and J. E. Milbery, *J. Am. Chem. Soc.*, 1934, **56**, 2727. [n] L. C. Raiford and W. C. Stoesser, *J. Am. Chem. Soc.*, 1928, **50**, 2556. [o] L. C. Raiford and E. H. Wells, *J. Am. Chem. Soc.*, 1935, **57**, 2500. [p] F. Pollecroft and R. Robinson, *J. Chem. Soc.*, 1918, **113**, 645. [q] T. G. H. Jones and R. Robinson, *J. Chem. Soc.*, 1917, **111**, 903. [r] Isomer A is the kinetic product (HNO_3/Et_2O; 0 °C; 2 min) which rearranges to B(0 °C; 15 min), J. Cha, unpublished observation. [s] L. Rubenstein, *J. Chem. Soc.*, 1925, **127**, 1998. [t] J. Cha, unpublished observation. [u] H. E. Dadswell and J. Kenner, *J. Chem. Soc.*, 1927, 580. [v] M. E. Flaugh, T. A. Crowell, J. A. Clemens, and B. D. Sawyer, *J. Med. Chem.*, 1979, **22**, 63. [w] D. A. Evans, C. E. Sacks, W. A. Kleschick, and T. R. Taber, *J. Am. Chem. Soc.*, 1979, **101**, 5789; P. A. Grieco, K. Kanai, and E. Williams, *Heterocycles*, 1979, **12**, 1623. [x] W. H. Perkin, Jr., and R. Robinson, *J. Chem. Soc.*, 1914, **105**, 2376. The regiochemical outcomes with compounds (**10a**, **b**) may derive in part from the noncoplanar, and therefore, nonconjugated 2-methoxy-group. [y] J .M. Bruce and Y. Roshan-Ali, *J. Chem. Soc., Perkin Trans.* 1, 1981, 2677. [z] W. Baker and O. M. Lothian, *J. Chem. Soc.*, 1935, 628.



(1) **a**; R = CH_2=$CHCH_2O$
b; R = O^-



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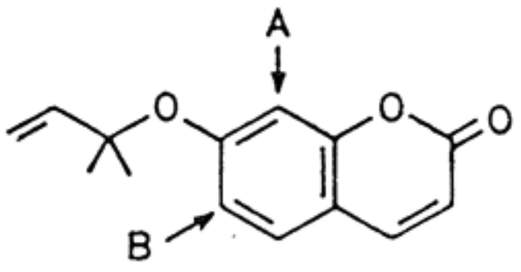

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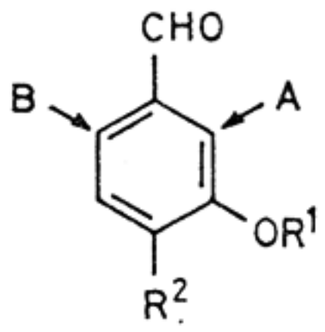
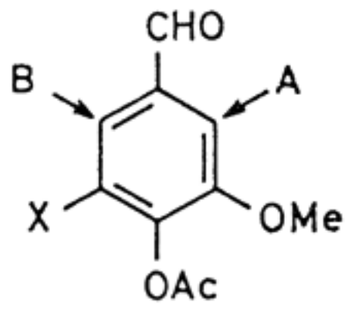


(4)

	R^1	R^2
a;	H	H
b;	Me	H
c;	H	MeO
d;	Me	AcO
e;	Me	$PhCO_2$



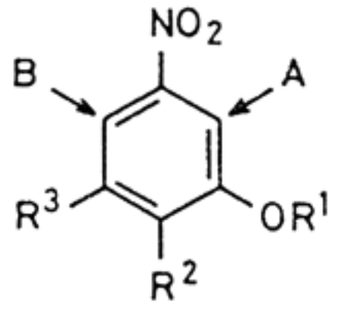
(5) **a**; X = Br
b; X = I

ing *ortho* to an existing substituent to make attack between two *meta*-substituents extremely unfavourable because of the two developing *ortho*-interactions in the transition state. However, certain substituted aromatic compounds contrast this principle by reacting to give as a major, or sole, product the isomer resulting from substitution between two *meta*-groups. Table 1 provides a number of these and related substitutions, and although these examples are not comprehensive, they present a compelling argument for electronic control of positional reactivity which originates in small but significant energy differences for the major aromatic resonance forms.† These energy differences increase and ultimately become product-determining as the molecule moves along the reaction co-ordinate towards the transition state.‡

We propose the following principle: in the absence of overwhelming steric constraints, aromatic substitution will occur *via* a transition state which most closely resembles the valence-

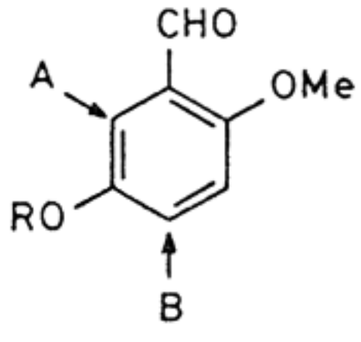
† Although Table 1 contains examples of nitration, these examples must be interpreted with care, since the nitration of aromatic compounds more reactive than toluene has been suggested to occur by an electron-transfer mechanism: C. L. Perrin, *J. Am. Chem. Soc.*, 1977, **99**, 5516.

‡ Since this effect is due to differences in transition-state energies, a careful distinction must be made between *kinetic* and *thermodynamic* product distributions. Reactions which equilibrate products and starting materials under the reaction conditions will provide apparent 'exceptions' as the kinetic products here are seldom thermodynamically preferred. Compound (**6b**) provides an example of this.

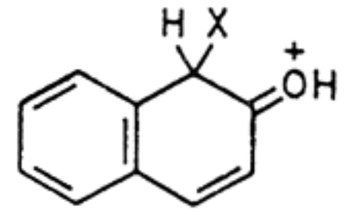


(6)

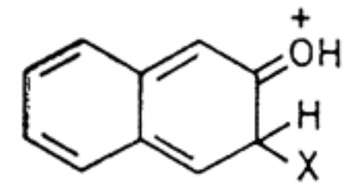
	R^1	R^2	R^3
a	H	MeO	H
b	Me	AcO	H
c	H	MeO	NO_2



(7) a; R = H
b; R = Me



(A)



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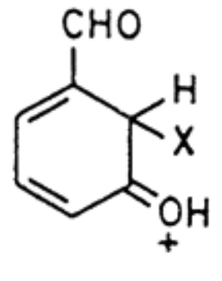
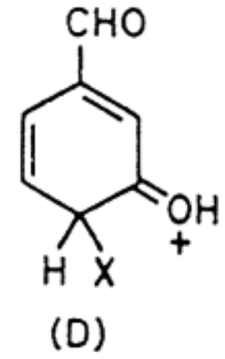
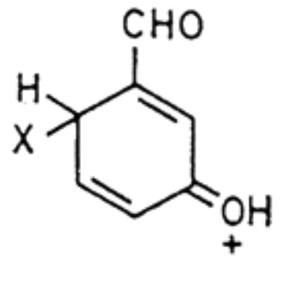


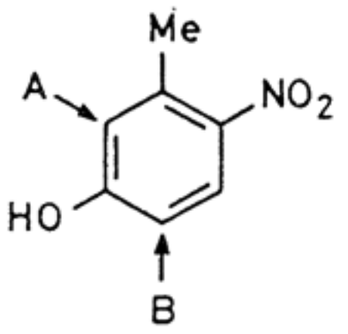
(C)



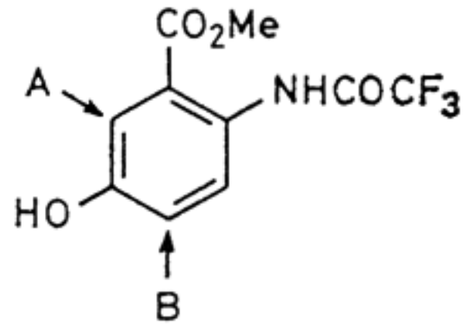
(D)



(E)



(8)



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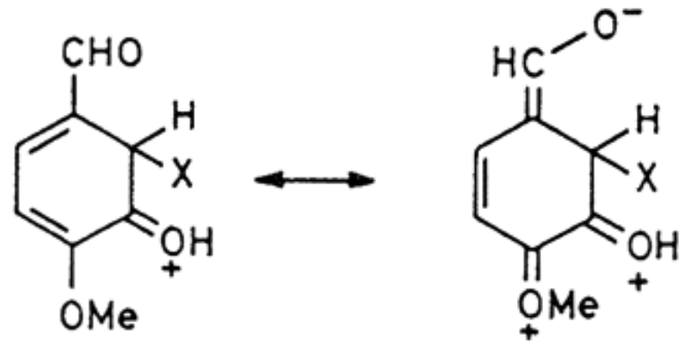
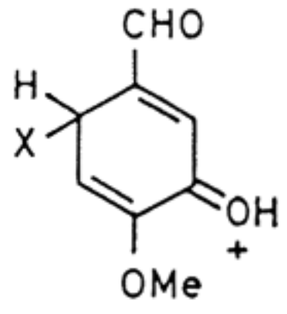
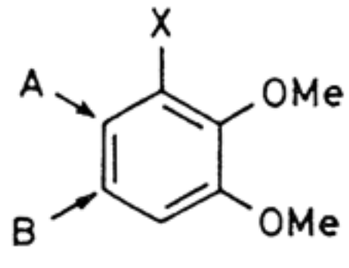


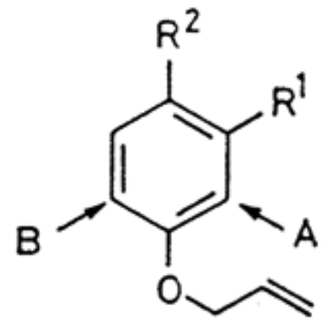
(F) (G)



(H)

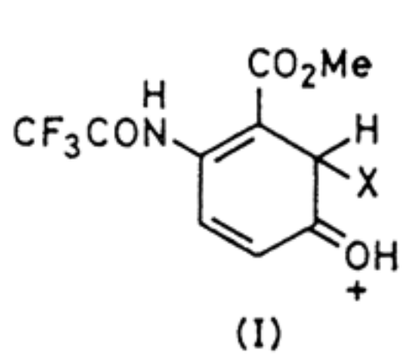


(10) a; X = CHO
b; X = NO_2

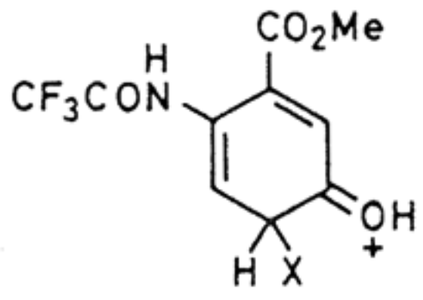


(11)

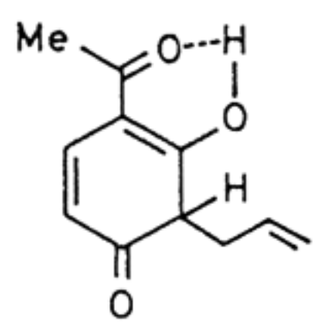
	R^1	R^2
a	CO_2Me	H
b	CO_2Me	OH
c	Ac	H
d	Ac	OH
e	CHO	OH
f	OH	Ac
g	OMe	Ac



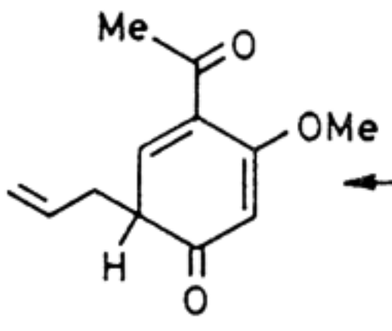
(I) (J)



(K)



(L)



(M) (N)

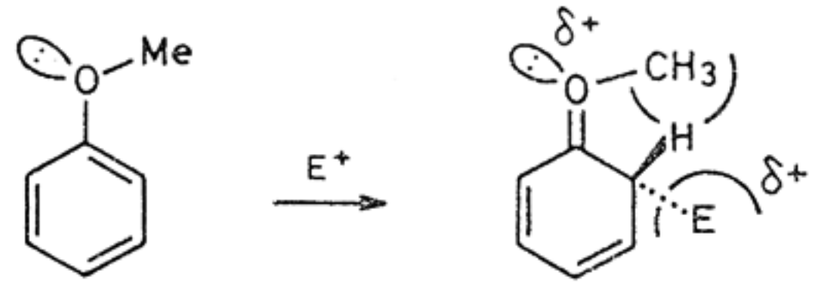
bond-resonance form of lowest energy.§ Compounds (**1a, b**) provide a known and well established illustration of this principle. 2-Naphthol derivatives react preferentially by a transition state resembling the σ-complex (A) which maintains resonance stabilization in one aromatic ring, rather than (B), where resonance for both rings is disturbed. A simple extension of the well established results for closely related compounds (**2a, b**) and (**3**) to the other compounds in Table 1 is not readily apparent, however. With compound (**4a**) it is necessary to consider the σ-complexes (C)—(E). Of these, (C) is preferred, since (D) and (E) are 'cross-conjugated' and the two carbonyl groups are separated by only one double bond, whereas in (C) the unfavourable α-dicarbonyl interaction is doubly vinylogous. (We have deliberately used this very qualitative level for discussion of the examples for ease of application and prediction.) Resonance-enhancing functional groups may further stabilize a preferred σ-complex; compounds (**4c**) and (**9**) have electron-donating groups which stabilize (F) ⟷ (G) *vs.* (H) and (I) ⟷ (J) *vs.* (K). Application of these considerations to aromatic Claisen reactions [compounds (**11a—e**)] allows the prediction of what will be the major or exclusive product. Compounds (**11f, g**) suggest that hydrogen bonding may also help to stabilize a transition state, since (**11f**) reacts *via* structure (L) whereas (**11g**) prefers the resonance-stabilized structure (M) ⟷ (N).¶ The energy difference between the

§ An MO description suggests that attack occurs at the position of highest π-electron density. Several of the reactions in Table 1 have been known for some time, and early attempts to explain regiochemistry were primarily descriptive, usually invoking aromaic 'bond fixation' or 'mesomeric effects.' However, one theoretical treatment did correctly identify partial resonance effects as influencing reactivity: M. J. S. Dewar, *J. Chem. Soc.*, 1949, 463.

¶ The importance of hydrogen bonding in the reactions of compounds (**11f, g**) was noted in the original paper (Table 1, footnote z). The resonance contributions determined from the nuclear Overhauser effect [see compounds (**8c, d**) in Table 1 in ref. 1] precisely parallel the chemical reactivity of compounds (**11f, g**).

σ-complexes for compound (**8**) is expected to be much smaller, making the origin of regiochemical control for this example uncertain.**

With a change from phenol to a methyl ether [*cf.* compounds (**4b**, **d**, **e**)], the attack of large electrophiles (*e.g.* bromine) appears to be based solely on steric preference. However, compounds (**5a**, **b**) in which there is comparable steric hindrance to attack at both positions A and B, and compound (**7b**), which has no free *para*-position, react exactly as predicted. The ratios of the partial rate factors for chlorination (*para/ortho ca.* 7.4) or bromination (*para/ortho ca.* 126) of anisole (X) in acetic acid[2] are similar to the ratios observed for the chlorination (*para/ortho ca.* 7.08) and bromination (*para/ortho ca.* 171) of t-butylbenzene,[3] and much larger than those observed for the structural congener ethylbenzene.[4] We propose that electronic control of reactivity directs the *O*-alkyl group toward the electrophile with an increase in apparent bulk. It has already been suggested that the methoxy-group and the ring are coplanar during electrophilic attack on anisole.[5] Calculations have shown that the π-electron density at the *ortho*-position in anisole which is s-*cis* to the methoxy-group is higher than that at the s-*trans*-position.[6] We suggest that the *trans*-antiperiplanar lone pair of electrons on oxygen [structure (X)] distinguishes between the two *ortho*-positions, making the position s-*cis* to the methoxy-group the more susceptible to electrophilic attack. As anisole progresses along the reaction co-ordinate [(X) → (Y)], loss of aromatic resonance causes nonbonding interactions to become more important and the lone pair of electrons on oxygen causes a lengthening of the *trans*-antiperiplanar carbon–carbon bond by an n → σ* interaction to assist substitution.[7] As a result, in the case of *ortho*-substitution, an electrophile will prefer to approach s-*cis* to the increasingly rigid methoxy-group with a consequent decrease in rate for *ortho*-substitution compared with the unencumbered *para*-position.



(X) (Y)

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2 L. M. Stock and H. C. Brown, *J. Am. Chem. Soc.*, 1960, **82**, 1942.
3 L. M. Stock and H. C. Brown, *J. Am. Chem. Soc.*, 1959, **81**, 5615.
4 For partial rate data, see R. O. C. Norman and R. Taylor, 'Electrophilic Substitution in Benzenoid Compounds,' Elsevier, Amsterdam, 1965.
5 G. Illuminati, *J. Am. Chem. Soc.*, 1958, **80**, 4945.
6 G. M. Anderson III, P. A. Kollman, L. N. Domelsmith, and K. N. Houk, *J. Am. Chem. Soc.*, 1979, **101**, 2344.
7 Selectivity in substitutions of quinone *O*-methyloximes has been attributed to n → σ* interactions. See J. E. Baldwin and R. K. Norris, *J. Org. Chem.*, 1981, **46**, 967.

** The methyl ether corresponding to the phenol (**8**) [compound (**9a**) in Table 1 in ref. 1] shows no detectable conformational preference.