

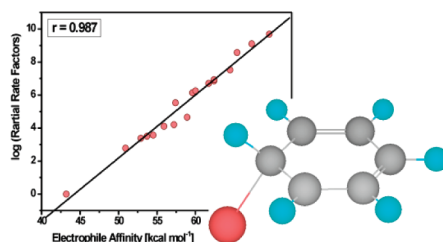
Electrophile Affinity: Quantifying Reactivity for the Bromination of Arenes

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Electrophile affinity ($E\alpha$), a recently proposed theoretical construct based on computed energies of arenium ion formation, rationalizes the substrate reactivity and regioselectivity of S_EAr bromination of three sets of available experimental arene data where closely related conditions had been employed uniformly. The $E\alpha$ parameters (computed at B3LYP/6-311+G(2d,2p)) correlated very well ($r = 0.987$) with the partial rate factors ($\log f$) for 18 regiospecific brominations of benzene and various methyl benzenes. Analysis of the bromination reactivities of 32 mono- and polysubstituted benzenes including various polar groups gave similar results ($r = 0.982$). The electrophile affinity treatment also accounted satisfactorily ($r = 0.957$) for bromination reactivities of polybenzenoid hydrocarbons. Conversely, comparisons with NBO-based charges and the electrostatic potential at nuclei (EPN) were not generally successful. The uniform effectiveness of $E\alpha$ treatments for the cases analyzed with regard both to relative substrate reactivity (e.g., benzene vs toluene) and to regioselectivity (e.g., the positional reactivity of toluene) supports the “limiting case” conventional interpretation of the electrophilic aromatic substitution mechanism as being governed by the energy of σ -complex formation. Although other mechanisms are possible under different conditions, the computed energies of arene–dibromine π -complex formation for the polysubstituted benzene set examined correlated poorly with experimental reactivity data ($r = 0.714$) and only varied from 1.8 (for benzene) to 3.5 kcal/mol, in contrast to the 10^{12} range in reactivity measured experimentally.

Introduction

A new theoretical construct, the electrophile affinity ($E\alpha$), was shown in our recent study to quantify the S_EAr reactivity for sets of chlorination, nitration, and benzylation of aromatic systems.¹ The electrophile affinity is the energy of formation of an arenium ion σ -complex at individual positions of the arene (eq 1).

$$E\alpha = [E_{\text{arene}} + E_{\text{electrophile}}] - E_{\text{arenium ion}} \quad (1)$$

Excellent correlations of electrophile affinity with the reactivity data considered¹ are in accord with the prevailing

mechanistic interpretation that the reaction rates of most S_EAr processes are governed by the transition state preceding the formation of the σ -complex intermediate.^{2–9} However,

(1) Koleva, G.; Galabov, B.; Wu, I. J.; Schaefer, H. F.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **2009**, *131*, 14722–14727.

(2) Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry, Part A, Structure and Mechanisms*, 4th ed.; Springer: New York, 2000; Chapter 10.

(3) Smith, M. B.; March, J. *March's Advanced Organic Chemistry Reactions, Mechanisms and Structure*, 6th ed.; Wiley: New York, 2006; Chapter 11.

(4) Stock, L. M.; Brown, H. C. In *Advances in Physical Organic Chemistry*; Gold, V., Ed.; Academic Press: London, 1963; Vol. 1, p 35.

(5) Taylor, R. *Electrophilic Aromatic Substitution*; John Wiley: New York, 1990.

(6) Ridd, J. H. *Acc. Chem. Res.* **1971**, *4*, 248–253.

(7) Wang, D. Z.; Streitwieser, A. *Theor. Chem. Acc.* **1999**, *102*, 78–86.

(8) Streitwieser, A. *Molecular Orbital Theory for Organic Chemists*; John Wiley and Sons: New York, 1961.

(9) Olah, G. A. *Acc. Chem. Res.* **1971**, *4*, 240–278.

Olah^{9–11} and Kochi^{12,13} have emphasized that for some electrophiles under certain conditions substrate and positional selectivity are inconsistent (e.g., low toluene/benzene reactivity ratios but high toluene ortho-para vs meta regioselectivity), indicating the existence of at least one other mechanistic pathway in which π -complexes control product formation.¹⁴ Thus, Olah et al.^{15,16} in studying the kinetics of ferric chloride catalyzed bromination of benzene and alkylbenzenes in anhydrous conditions have provided strong evidence for a low substrate selectivity in the rate-determining step, which precedes the formation of a σ -complex intermediate. High positional selectivity is governed by the transition state associated with the second step of the reaction.

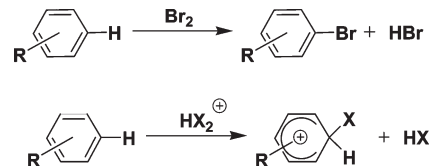
The present research analyzes three available sets of rather extensive experimental kinetic data on the reactivity and regioselectivity of the S_EAr bromination of arenes; all three sets have been obtained for catalyzed processes carried out in strongly polar acidic aqueous media. The results establish the existence of a “limiting case” mechanism where both substrate reactivities and positional selectivities appear to be determined in a single σ -complex-type transition state.

Although our main emphasis is the further evaluation of the scope and reliability of the proposed $E\alpha$ procedure, we also address the issues of substrate vs positional selectivity and comparisons of correlations of computed π - and σ -complexation energies with experimental data.

Theoretical Methods

The $E\alpha$ values were computed using the B3LYP hybrid DFT functional,^{17,18} combined with the standard 6-311+G(2d,2p) basis set.^{19,20} Cartesian coordinates and energies of all optimized structures are reported in Supporting Information. The optimized structures were characterized by harmonic vibrational frequency computations. Most of the computations were carried out with the Gaussian 03 program.²¹ Electrophile affinities were determined following eq 1. The influence of solvent was assessed by applying the IEFPCM method²² as incorporated in the Gaussian 09 program.²³

SCHEME 1. S_EAr Bromination (Top) and Model Reaction (Bottom) Employed To Compute the Electrophile Affinities ($E\alpha$) Used for the Analysis of the Experimental Reactivities and Regioselectivities



Results and Discussion

Experimental Arene Bromination Data. Our analysis of S_EAr bromination reactivity is limited by the scarcity of experimental data sets for series of reactions carried out on a representative number of substrates under identical conditions (see Scheme 1). We examined three sets of kinetic data for the S_EAr bromination, which enable good-quality comparisons with our computed $E\alpha$ values: Brown and Stock's study of a series of methyl benzenes in 85% acetic acid,²⁴ Dubois's investigation of the bromination of 28 mono- and polysubstituted benzene derivatives in water (catalyzed by perchloric acid),²⁵ and Altschuler and Berliner's²⁶ comparison of polycyclic aromatic hydrocarbons in 50% acetic acid.

Chlorination vs Bromination. The paucity of experimental data virtually precludes direct comparison of the reactivity of different S_EAr processes (e.g., our earlier study of chlorination¹ with the present bromination investigation) under identical conditions. Rate constants are available only for benzene chlorination²⁷ and bromination²⁸ in concentrated trifluoroacetic acid at 25 °C (Table 1). As a first approximation, it seemed reasonable in view of the acidic medium to model these reactions computationally (at B3LYP/6-311+G(2d,2p)) by using the HBr_2^+ and HCl_2^+ cations as the electrophiles. Similar cationic systems were established to be the halogenation agents ($COBr^+$ and $CH_3NH_2Br^+$) by Bertolini et al.²⁹ in their experimental mass spectrometric study of the bromination of gaseous aromatic compounds. The electrophile affinities ($E\alpha$, Table 1) were evaluated as the energy changes associated with the gas phase process shown in Scheme 1 (bottom).

Although the much faster rate of chlorination compared with bromination is in line with the larger exothermicity of formation of the chlorination rather than the bromination σ -complex, experimental S_EAr rates depend strongly on the conditions and the nature of the electrophile (e.g., the degree of acid catalysis). Nevertheless, the example encourages the determination of wider data sets for different electrophiles under the same reaction conditions.

Arene Bromination Reactivity. Our first analysis employing the electrophile affinity concept compares computed $E\alpha$

(10) Esteves, P. M.; Carneiro, J. E. de M.; Cardoso, S. P.; Barbosa, A. G. H.; Laali, K. K.; Rasul, G.; Prakash, G. K. S.; Olah, G. A. *J. Am. Chem. Soc.* **2003**, *125*, 4836–4849.

(11) Olah, G. A.; Malhotra, R.; Narang, S. C. *Nitration. Structure and Mechanisms*; VCH Publishers: New York, 1989.

(12) Gwaltney, S. R.; Rosokha, S. V.; Head-Gordon, M.; Kochi, J. K. *J. Am. Chem. Soc.* **2003**, *125*, 3273–3283.

(13) (a) Vasiliev, A. V.; Lindeman, S. V.; Kochi, J. K. *New J. Chem.* **2002**, *26*, 582–598. (b) Fukuzumi, S.; Kochi, J. K. *J. Am. Chem. Soc.* **1982**, *104*, 7599–7609.

(14) De la Mare has stressed the plurality of aromatic substitution mechanisms, depending on the substrate and the conditions. (a) de la Mare, P. B. D. *Electrophilic Halogenations*; Cambridge University Press: Cambridge, 1976. (b) de la Mare, P. B. D. *Acc. Chem. Res.* **1974**, *7*, 361–368.

(15) Olah, G. A.; Kuhn, S. J.; Flood, S. H.; Hardie, B. A. *J. Am. Chem. Soc.* **1964**, *86*, 1039–1044.

(16) Olah, G. A.; Kuhn, S. J.; Flood, S. H.; Hardie, B. A. *J. Am. Chem. Soc.* **1964**, *86*, 1044–1046.

(17) (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648–5652. (b) Becke, A. D. *J. Chem. Phys.* **1996**, *104*, 1040–1046.

(18) Lee, C. T.; Yang, W. T.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785–789.

(19) Curtiss, L. A.; McGrath, M. P.; Blaudeau, J. P.; Davis, N. E.; Binning, R. C., Jr.; Radom, L. *J. Chem. Phys.* **1995**, *103*, 6104–6113.

(20) Clark, T.; Chandrasekar, J.; Spitznagel, G. W.; Schleyer, P. v. R. *J. Comput. Chem.* **1983**, *4*, 294–301.

(21) Frisch, M. J. et al. *Gaussian 03* (Revision-E.01); Gaussian, Inc.: Wallingford CT, **2003**.

(22) Tomasi, J.; Mennucci, B.; Cammi, R. *Chem. Rev.* **2005**, *105*, 2999–3093.

(23) Frisch, M. J. et al. *Gaussian 09* (Revision-A.01); Gaussian, Inc.: Wallingford CT, **2009**.

(24) Brown, H. C.; Stock, L. M. *J. Am. Chem. Soc.* **1957**, *79*, 1421–1425.

(25) (a) Dubois, J. E.; Aaron, J. J.; Alcais, P.; Doucet, J. P.; Rothenberg, F.; Uzan, R. *J. Am. Chem. Soc.* **1972**, *94*, 6823–6828. (b) Rothenberg, F.; Alcais, P.; Dubois, J. E. *Bull. Soc. Chim. Fr.* **1971**, 592–597. (c) Aaron, J. J.; Dubois, J. E. *Bull. Soc. Chim. Fr.* **1971**, 603–612.

(26) Altschuler, L.; Berliner, E. *J. Am. Chem. Soc.* **1966**, *88*, 5837–5845.

(27) Andrews, L. J.; Keefer, R. M. *J. Am. Chem. Soc.* **1957**, *79*, 5169–5174.

(28) Brown, H. C.; Wirkkala, R. A. *J. Am. Chem. Soc.* **1966**, *88*, 1447–1452.

(29) Bertolini, O.; Yang, S. S.; Cooks, R. G. *Org. Mass Spectrom.* **1993**, *28*, 1313–1322.

TABLE 1. Relative Reactivity of Benzene for Chlorine and Bromine Substitution in Trifluoroacetic Acid

reaction	rate constant k_2 25 °C [L mol ⁻¹ s ⁻¹]	$\log k_2$ [kcal mol ⁻¹]	$E\alpha^c$ [kcal mol ⁻¹]	$E\alpha(\text{solv})^d$ [kcal mol ⁻¹]
chlorination ^a	7.0×10^{-3a}	-2.2	68.1	55.1
bromination ^b	7.6×10^{-7b}	-6.1	43.2	32.3

^aFrom ref 27. ^bFrom ref 28. ^cFrom computations referring to gas phase. ^dIn acetic acid medium from IEFPCM computations.

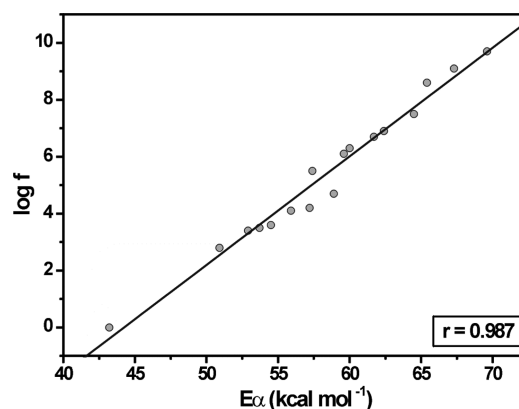
TABLE 2. Electrophile Affinities ($E\alpha$) and Logarithms of Experimental Partial Rate Factors ($\log f$) for the Acid-Catalyzed Bromination of Benzene and Methyl Benzenes (in 85% Acetic Acid)

reactant	position of bromination	$E\alpha^a$ [kcal mol ⁻¹]	$\log f^b$
benzene	1	43.2	0.0
toluene	2	50.9	2.8
	4	52.9	3.4
1,2-dimethylbenzene	3	53.7	3.5
	4	55.9	4.1
1,3-dimethylbenzene	2	57.4	5.5
	4	59.6	6.1
1,4-dimethylbenzene	2	54.5	3.6
1,2,3-trimethylbenzene	4	61.7	6.7
	5	58.9	4.7
1,2,4-trimethylbenzene	2	60.0	6.3
	5	62.4	6.9
	6	57.2	4.2
1,3,5-trimethylbenzene	2	65.4	8.6
1,2,3,4-tetramethylbenzene	4	64.5	7.5
1,2,3,5-tetramethylbenzene	4	67.3	9.1
1,2,4,5-tetramethylbenzene	3	62.4	6.9
pentamethylbenzene	6	69.6	9.7
correlation coefficient (r) ^c		0.987	

^aThe theoretical $E\alpha$ values are based on B3LYP/6-311+G(2d,2p) computations. ^bThe partial rate factors were evaluated from the experimental rate constants of ref 24. ^cCorrelation coefficient for the relationship between $\log f$ and $E\alpha$.

parameters with Brown and Stock's²⁴ experimental kinetic data for 18 regioselective brominations of benzene and 11 methyl derivatives carried out under the same reaction conditions. The partial rate factors for each aromatic ring position ($\log f$) were deduced from the kinetic data by the standard procedure^{2,30} and scaled to fit the experimental relative rates. In accord with our previous results for chlorination, nitration, and benzylation of arenes,¹ the correlation between $\log f$ and $E\alpha$ values (Table 2) is very good ($r = 0.987$; see Figure 1). This agreement underlines again the dependence of the reaction rates on the energy of σ -complex formation. Note also how well the points for benzene and toluene fall on the general correlation line in Figure 1. No difference in substrate reactivity and positional selectivity is discernible. Additional methyl substitution increases the electrophile affinities as well as the partial rate factors. This agrees with the conventional interpretations that both positive inductive and resonance (hyperconjugative) methyl group effects contribute to increased electron density in the ring, which stabilizes the electron-deficient transition state leading to the formation of the σ -complexes.

Dubois et al.'s²⁵ experimental study provides extensive data on the rates of S_EAr bromination of mono- and poly-substituted benzenes in water catalyzed by perchloric acid. The arenes considered, including those with polar methoxy-, chloro-, fluoro-, and iodo- substituents, are listed in Table 3

**FIGURE 1.** Plot of electrophile affinity ($E\alpha$) vs $\log f$ data for the bromination of benzene and methyl benzenes included in Table 2.

along with their relative rate data (vs benzene) and $E\alpha$ values for different ring positions. The good correlation ($r = 0.978$) between $E\alpha$ and $\log k_{\text{rel}}$ for this extended series of benzene derivatives (some of which are crowded with substituents) indicates that $E\alpha$ treatments are able to accommodate S_EAr reactions involving some degree of steric hindrance.

We also evaluated the influence of simulated solvation on the relationship between reaction rates and electrophile affinities theoretically by applying the IEFPCM methodology²² in Gaussian 09 to compute a modified set of $E\alpha(\text{solv})$ values. Geometries of reactants and their σ -complexes were optimized in the IEFPCM-simulated water medium at the same B3LYP/6-311+G(2d,2p) level of theory. The ZPE-corrected energy data (included in Table 3) result in an even slightly better dependence with $\log k_{\text{rel}}$ ($r = 0.982$ for $E\alpha(\text{solv})$ vs $r = 0.978$ for $E\alpha$). The plot between $E\alpha(\text{solv})$ and $\log k_{\text{rel}}$ is illustrated in Figure 2. Therefore, even though the $E\alpha(\text{solv})$ values are much reduced in magnitude from the $E\alpha$ values referring to the gas phase (see Tables 3), the medium effect does not alter the effectiveness of the $E\alpha$ analyses appreciably.

Electrophile affinities also rationalize the bromination reactivity of polycyclic aromatic hydrocarbons based on kinetic data compiled by Altschuler and Berliner in 50% acetic acid.²⁶ The correlation between the experimental partial rate factors and the theoretical $E\alpha$ values (Table 4) is quite satisfactory ($r = 0.957$). That the same is true for the relationship with the computed proton affinities ($r = 0.966$) serves to validate the level of theory employed for the present purposes. Note that the electrophile affinity treatment is quite effective both for substrate reactivity and for naphthalene regioselectivity.

We emphasize that the three good correlations with $E\alpha$ obtained in the present study document the coincidence of substrate and positional reactivity for bromination, indicating that both are governed by the transition state preceding the formation of the σ -complex under the pertinent experimental conditions examined. Nevertheless, as emphasized by Olah,^{9-11,15,16} Kochi,^{12,13} and by others,¹⁴ substrate reactivity and positional selectivity in S_EAr reactions in some other circumstances may be determined in different mechanistic steps. In such cases, good correlations between electrophile affinity and reaction rates are not to be expected. This possibility with regard to bromination is considered in more detail in the following section.

(30) Condon, F. E. *J. Am. Chem. Soc.* **1948**, *70*, 1963–1964.

TABLE 3. Electrophile Affinities ($E\alpha$) and Logarithms of Experimental Relative Rate Constants ($\log k_{rel}$) for the Perchloric Acid Catalyzed Bromination of Benzene, Methyl Benzenes, and Substituted Anisoles (in Water)

reactant	position of bromination	$E\alpha^a$ [kcal mol ⁻¹]	$E\alpha(\text{solv})^a$ [kcal mol ⁻¹] water medium	$\log k_{rel}^b$
benzene	1	43.2	30.9	0.0
toluene	2	50.9	36.0	2.8
	4	52.9	38.2	3.6
1,3-dimethylbenzene	4	59.6	42.9	6.5
1,4-dimethylbenzene	2	54.5	38.0	4.1
1,2,3-trimethylbenzene	4	61.7	43.6	7.8
1,3,5-trimethylbenzene	2	65.4	46.8	9.5
1,2,3,4-tetramethylbenzene	5	64.5	45.2	8.2
1,2,3,5-tetramethylbenzene	4	67.3	47.7	10.0
pentamethylbenzene	6	69.6	49.0	10.5
1,3,5-trimethyl-2-ethylbenzene	4	67.7	47.4	9.9
1,3,5-trimethyl-2-chlorobenzene	4	59.2	40.5	6.0
1,3,5-trimethyl-2-bromobenzene	4	59.4	40.5	6.1
methoxybenzene	4	64.5	48.1	9.5
	2	60.8	43.9	7.8
1-methoxy-2-methylbenzene	4	67.6	50.0	10.2
	6	61.7	43.2	8.4
1-methoxy-3-methylbenzene	4	70.1	51.6	11.3
1-methoxy-4-methylbenzene	2	64.3	46.1	8.5
1-methoxy-2-fluorobenzene	4	58.6	43.0	7.2
1-methoxy-3-fluorobenzene	4	61	45.1	8.7
1-methoxy-4-fluorobenzene	2	54.8	39.4	5.4
1-methoxy-2-chlorobenzene	4	59.2	42.9	7.0
1-methoxy-3-chlorobenzene	4	61.4	44.2	8.3
	6	60.7	43.0	7.1
1-methoxy-4-chlorobenzene	2	55.2	38.9	5.1
1-methoxy-2-bromobenzene	4	59.6	42.9	7.2
1-methoxy-3-bromobenzene	6	61	42.8	6.7
1-methoxy-4-bromobenzene	2	55.5	38.9	5.2
1-methoxy-3-iodobenzene ^c	6	59.7	42.9	6.7
1,4-dimethoxybenzene	2	65.7	46.0	7.9
1-methoxy-2,3-dimethylbenzene	4	72.4	53.1	11.6
1-methoxy-2,4-dimethylbenzene	6	65.4	45.6	8.4
1-methoxy-2,5-dimethylbenzene	4	73.3	54.0	11.8
1-methoxy-3,4-dimethylbenzene	6	70.8	51.2	10.7
1-methoxy-3,5-dimethylbenzene	4	75.2	55.0	12.7
	6	73.3	52.8	11.4
correlation coefficient (r)^d		0.978	0.982	

^aThe theoretical $E\alpha$ values are based on B3LYP/6-311+G(2d,2p) computations. ^bThe relative rate constants were taken from ref 25. ^cFor 1-methoxy-3-iodobenzene, separate basis sets were used for the carbon, hydrogen, and oxygen atoms (6-311+G(2d,2p)) and for the iodine atoms (DGDZVP). ^dCorrelation coefficient for the relationship between $\log k_{rel}$ and $E\alpha$.

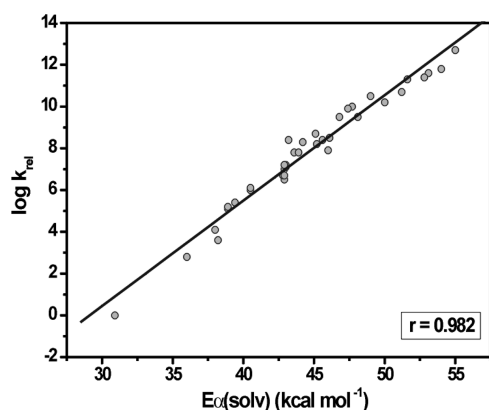


FIGURE 2. Plot of electrophile affinities $E\alpha(\text{solv})$ vs $\log k_{rel}$ for a set of 37 substitution processes in the bromination of benzene and variously substituted derivatives.

Rate-Determining Stage in S_EAr Bromination. There are diverging reports regarding the rate-limiting stage of S_EAr processes. The experimental studies of Olah et al.^{15,16} on the bromination of aromatic systems in nonaqueous conditions showed that substrate and positional selectivities are determined in different stages of the processes. Similar results

TABLE 4. Electrophile Affinities ($E\alpha$), Proton Affinities (PA), and Logarithms of Experimental Partial Rate Factors ($\log f$) for the Acid-Catalyzed Bromination of Polynuclear Aromatic Hydrocarbons (in 50% Acetic Acid)

hydrocarbon	position of reaction	$E\alpha^a$ [kcal mol ⁻¹]	PA ^a [kcal mol ⁻¹]	$\log f^b$
benzene	1	43.2	182.4	0.0
naphthalene	1	59.6	196.3	5.3
	2	56.7	193.5	3.3
phenanthrene	9	65.1	199.9	6.3
fluoranthene	3	69.2	205.2	6.8
chrysene	6	72.1	206.4	7.6
pyrene	1	76.1	211.4	10.6
1,2-benzanthracene	7	78.7	213.8	11.2
anthracene	9	77.3	212.7	12.4
acenaphthene	5	72.3	208.1	11.2
fluorene	2	67.2	203.2	7.0
correlation coefficient (r)^c		0.957	0.966	

^aThe theoretical $E\alpha$ and PA values are based on B3LYP/6-311+G(2d,2p) computations. ^bThe experimental partial rate factors were taken from ref 26. ^cCorrelation coefficients for the relationships with $\log f$.

were also obtained in studies on aromatic nitration and nitroization.^{6,9-12} Olah et al.'s¹⁰ 2003 computational investigation revealed the complexities of aromatic nitration and supported the possibility of a mechanism involving three intermediates: an electrostatically bonded π -complex, a radical-ion pair formed

TABLE 5. π Complex Formation Energies [at B3LYP/6-311+G(2d,2p)] and Logarithms of the Relative Rate Constants (Compared to Benzene) for the Interactions of Benzene, Methyl Benzenes, and Substituted Anisoles with Br₂

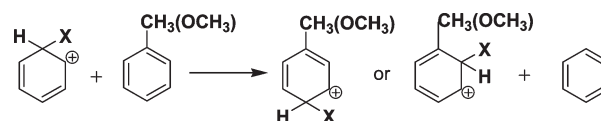
reactant	$E_{\pi\text{-complex}}$ [kcal mol ⁻¹]	rate constants ^a	log k_{rel}
benzene	-1.9	2.7×10^{-6}	0.0
toluene	-2.4	1.8×10^{-3}	3.6
1,3-dimethylbenzene	-2.9	8.0	6.5
1,4-dimethylbenzene	-2.7	3.4×10^{-2}	4.1
1,2,3-trimethylbenzene	-2.6	1.5×10^2	7.8
1,3,5-trimethylbenzene	-3.5	9.0×10^3	9.5
1,2,3,4-tetramethylbenzene	-2.8	4.6×10^2	8.2
1,2,3,5-tetramethylbenzene	-3.1	2.8×10^4	10.0
pentamethylbenzene	-3.2	9.0×10^4	10.5
1,3,5-trimethyl-2-ethylbenzene	-3.2	1.9×10^4	9.9
1,3,5-trimethyl-2-chlorobenzene	-2.7	2.8	6.0
1,3,5-trimethyl-2-bromobenzene	-2.5	3.4	6.1
methoxybenzene	-2.6	$1.7 \times 10^{+2}$	9.5
1-methoxy-2-methylbenzene	-3.2	6.9×10^2	10.2
1-methoxy-3-methylbenzene	-3.2	5.7×10^5	11.3
1-methoxy-4-methylbenzene	-2.9	8.4×10^2	8.5
1-methoxy-2-fluorobenzene	-2.1	3.9×10^1	7.2
1-methoxy-3-fluorobenzene	-2.5	1.4×10^3	8.7
1-methoxy-4-fluorobenzene	-2.0	6.7×10^{-1}	5.4
1-methoxy-2-chlorobenzene	-2.2	2.5×10^1	7.0
1-methoxy-3-chlorobenzene	-1.9	3.7×10^1	8.3
1-methoxy-4-chlorobenzene	-2.0	3.6×10^{-1}	5.1
1-methoxy-2-bromobenzene	-2.1	4.3×10^1	7.2
1-methoxy-3-bromobenzene	-1.8	1.5×10^1	6.7
1-methoxy-4-bromobenzene	-1.9	3.9×10^{-1}	5.2
1-methoxy-3-iodobenzene	-1.8	1.3×10^1	6.7
1,4-dimethoxybenzene	-3.1	2.1×10^2	7.9
1-methoxy-2,3-dimethylbenzene	-3.5	1.0×10^6	11.6
1-methoxy-2,4-dimethylbenzene	-3.0	6.5×10^2	8.4
1-methoxy-2,5-dimethylbenzene	-2.7	1.6×10^6	11.8
1-methoxy-3,4-dimethylbenzene	-3.5	1.5×10^5	10.7
1-methoxy-3,5-dimethylbenzene	-4.2	7.1×10^5	12.7
correlation coefficient (r)^b		0.714	

^aFrom ref 25. For toluene, methoxybenzene, 1-methoxy-2-methylbenzene, 1-methoxy-3-chlorobenzene, and 1-methoxy-3,5-dimethylbenzene, values of log k_{rel} which correspond to the faster process were used. ^bCorrelation coefficient for the relationship between $E_{\pi\text{-complex}}$ and log k_{rel} .

via electron transfer, and the σ -complex. Olah emphasized¹⁰ that either the conventional two-step process or the newly proposed three-step mechanism may dominate depending on the particular set of reactants, solvent, and other reaction conditions. Valuable information on the mechanisms of aromatic nitration is provided in Olah, Malhotra, and Narang's monograph.¹¹ Kochi et al.¹² applied molecular orbital computations and Marcus–Hush theory³¹ to investigate details of aromatic nitration and nitroazation processes. Their careful analyses of the reaction profiles concluded that nitration proceeds via the classic mechanism involving two intermediates (π - and σ -complexes), but the nitroazation process involves only a single intermediate (π -complex) and the Wheland σ -complex (arenium ion) is only a high energy transition state leading to the final products. All of these studies^{9–16} emphasize that the pathway of the electrophilic aromatic substitution processes may differ depending on the structure of aromatic reactant, the nature of the electrophile, and the reaction conditions. Kochi et al.'s¹³ detailed investigation of aromatic bromination emphasized the role of CT complexes and concluded, "The dative ion pair [ArH^{•+}, Br₂^{•-}] is the best (valence bond) representation of the rate-limiting transition state."

(31) (a) Marcus, R. A. *J. Chem. Phys.* **1956**, *24*, 966–979. (b) Reimers, J. R.; Hush, N. S. *Electron Transfer in Biology and the Solid State*; Oxford University Press: New York, 1989; Chapter 2, pp 27–63.

SCHEME 2. Isodesmic Reactions Involving σ Complexes of Benzene and Toluene



X = -H, -Cl, -Br, -NO₂, -CH₂C₆H₅

In contrast, we found previously¹ that the electrophile affinity index (E_{α}), based on σ -complex formation, accounts quantitatively for the experimental reactivity of several S_EAr processes, including the nitration of variously substituted benzene derivatives. Brown and Stock³² reported that the same set of σ^+ constants described the reactivity for 10 representative electrophilic aromatic substitution reactions, including nitration, quantitatively. This suggested that analogous mechanisms of all of these processes were likely. Olah's and Kochi's studies of S_EAr reactions,^{10–13,15,16} described above, prompted us to examine the quantitative dependence between reactivity and the energy of π (as well as σ) complex formation for the aromatic brominations considered in the present study.

We computed the energies of π -complex formation with Br₂ for the extended series of substituted benzenes comprising the set of bromination reactions studied by Dubois et al.²⁵ All π -complexes were fully optimized at B3LYP/6-311+G(2d,2p). The results obtained are shown in Table 5. These theoretically estimated complexation energies were then correlated with the relative rates (with respect to benzene) of the processes considered (Table 5). The results obtained showed that there is no satisfactory correlation ($r = 0.714$) between the energies of π -complex formation and log k_{rel} (Table 5), at least in this case. Considering the established strong correlation with the E_{α} values, it can safely be concluded that both substrate reactivity and positional selectivity for the three bromination processes we examined is associated with the formation of the σ -complex in the rate-limiting stage. Again, it should be emphasized that the experimental bromination data considered in this study are all obtained in acidic aqueous conditions, in which the rate-determining stage is generally associated with the formation of the σ -complex intermediate. This is the "limiting case" mechanism. We do not imply that this is the only mechanism for aromatic substitution. For brominations in nonaqueous media, alternative mechanisms of the processes are possible and need to be considered carefully in each instance.

We also searched the PES but were unable to locate a possible transition state preceding π -complex formation, which appears to be a barrierless process. The interaction of Br₂ and aromatic compounds giving strongly colored charge-transfer π -complexes is known experimentally to be very rapid.¹³ The present results are in accord with the recent study of Kochi and co-workers¹³ on electrophilic aromatic bromination. In their important contribution to the chemistry of S_EAr halogenations, these authors established the X-ray structures of the prereactive π -complexes and concluded that their transformation to arenium ions is the rate-controlling stage of the bromination reaction.

(32) Brown, H. C.; Stock, L. M. *J. Am. Chem. Soc.* **1962**, *84*, 3298–3306.

TABLE 6. Relative Isodesmic Reaction Energies (vs Benzene Analogues) for Toluene and Anisole

ipso protonated substituted benzenes		$E_{\text{isodesmic, toluene}}$ [kcal mol ⁻¹]	$E(X) - E(H)$, toluene [kcal mol ⁻¹]	$E_{\text{isodesmic, anisole}}$ [kcal mol ⁻¹]	$E(X) - E(H)$, anisole [kcal mol ⁻¹]
σ -complexes at ortho position					
C ₆ H ₆ H ⁺	H	-7.3	0	-17.0	0
C ₆ H ₆ Cl ⁺	Cl	-8.4	-1.1	-18.0	-1.0
C ₆ H ₆ Br ⁺	Br	-7.7	-0.4	-17.7	-0.7
C ₆ H ₆ NO ₂ ⁺	NO ₂	-7.0	0.3	-17.8	-0.8
C ₆ H ₆ CH ₂ C ₆ H ₅ ⁺	benzyl	-5.4	1.9	-15.3	1.7
σ -complexes at para position					
C ₆ H ₆ H ⁺	H	-8.8	0	-19.3	0
C ₆ H ₆ Cl ⁺	Cl	-9.9	-1.1	-22.0	-2.7
C ₆ H ₆ Br ⁺	Br	-9.7	-0.9	-21.3	-2.0
C ₆ H ₆ NO ₂ ⁺	NO ₂	-10.0	-1.2	-22.0	-2.7
C ₆ H ₆ CH ₂ C ₆ H ₅ ⁺	benzyl	-7.6	1.2	-17.4	1.9

In view of the available literature on the mechanism and energetics of S_EAr halogenation, the electrophile affinity concept, which relates substrate reactivity and regioselectivity to the σ -complex formation stage, appears to be a quite appropriate quantity in analyzing reactivity and positional selectivity for the bromination of arenes, carried out in highly polar media. The data from the present study provide convincing evidence supporting such an approach.

Nature of Electrophile Affinities. We have already emphasized¹ that electrophile affinity treatments characterize both the substrate reactivity and the electrophilic potential of the attacking agent. Such treatments are more specific than those involving proton affinities. E α values include interactions between aromatic substrate substituents (CH₃ or OCH₃ in Scheme 2) and the attacking electrophile (X in Scheme 2). These interactions were evaluated by isodesmic reactions involving toluene and anisole substrates at both ortho and para positions. The energies for several electrophiles are given in Table 6.

We focus on comparisons of the hydrogen-based relative energies given in columns 4 and 6. These values reflect the degree and direction of differences in E α vs PA treatments. The 4.6 kcal/mol range, from -2.7 to +1.9 kcal/mol, is appreciable and is equivalent to 10³–10⁴ in rate differences. This variation also is found among different electrophiles (vertical comparisons down columns 4 and 6). Significant individual differences also are found between toluene and anisole data (columns 4 and 6, horizontally) and in some ortho vs para comparisons. These results indicate that specific electrophile–substrate interactions may differ quite substantially and stresses the advantage of E α over PA analyses.

Electrostatic Potential at Nucleus (EPN) and Atomic Charges. Our earlier paper¹ showed that the electrostatic potential at nuclei³³ (EPN), a model-independent theoretical quantity, also provided a satisfactory treatment of S_EAr chlorination and nitration reactivity. EPN values reflect the variation of electron density, the dominant contributions

coming from the local densities around each atomic site. We have shown that the EPN index describes a number of charge-controlled organic reactions as well as hydrogen bonding excellently.³⁴ Other work has demonstrated the applicability of molecular surface electrostatic potential minima and maxima for the theoretical assessment of reactivity.³⁵ However, the EPN index did not correlate with experimental partial rate factors for S_EAr benzylation.¹ Although steric influences of the bulky benzyl moiety on the reaction rates may have been responsible, the effectiveness of EPN in describing the reactivity and regioselectivity of arene bromination also is limited. While the EPN values correlate satisfactorily with the partial rate factors for the bromination of methyl benzenes (Table S1 in Supporting Information), there is no correlation between the EPN index and reactivity for the series of substituted benzenes examined kinetically by Dubois et al.²⁵ NBO atomic charges,³⁶ evaluated at the same DFT level, do not correlate with reactivity (see Tables S1 and S2 in Supporting Information).

Both EPN values and NBO charges reflect the electronic structure of the initial arene reactants rather than the rate-controlling transition states when these are associated with σ -complex formation. Hence, simple correlations between the EPN and NBO charge indices and the rates of S_EAr reactions cannot be expected generally. There may be more favorable cases for the application of these indices than those we have analyzed here. As discussed by Olah,^{9–11,15,16} Kochi,^{12,13} and others¹⁴ the rate-limiting stages of S_EAr processes with other mechanisms may involve different types of intermediate complexes preceding arenium ion formation. The role of π -complexes in such reactions was reviewed by Lenoir recently.³⁷

Conclusions

Both S_EAr reactivity and regioselectivity data for the bromination of mono- and polysubstituted benzene derivatives^{24,25}

(33) (a) Wilson, E. B. *J. Chem. Phys.* **1962**, *36*, 2232–2233. (b) Politzer, P. In *Chemical Applications of Atomic and Molecular Electrostatic Potentials*; Politzer, P., Truhlar, D. G., Eds.; Plenum Press: New York, 1981; p 7.

(34) (a) Bobadova-Parvanova, P.; Galabov, B. *J. Phys. Chem. A* **1998**, *102*, 1815–1819. (b) Galabov, B.; Bobadova-Parvanova, P. *J. Phys. Chem. A* **1999**, *103*, 6793–6799. (c) Dimitrova, V.; Ilieva, S.; Galabov, B. *J. Phys. Chem. A* **2002**, *106*, 11801–11805. (d) Galabov, B.; Cheshmedzhieva, D.; Ilieva, S.; Hadjieva, B. *J. Phys. Chem. A* **2004**, *108*, 11457–11462. (e) Galabov, B.; Ilieva, S.; Hadjieva, B.; Atanasov, Y.; Schaefer, H. F. *J. Phys. Chem. A* **2008**, *112*, 6700–6707. (f) Galabov, B.; Nikolova, V.; Wilke, J. J.; Schaefer, H. F.; Allen, W. D. *J. Am. Chem. Soc.* **2008**, *130*, 9887–9896. (g) Galabov, B.; Ilieva, S.; Schaefer, H. F. *J. Org. Chem.* **2006**, *71*, 6382–6387.

(35) (a) Scrocco, E.; Tomasi, J. *Topics in Current Chemistry*; Springer-Verlag: Berlin, 1973, p 95. (b) *Molecular Electrostatic Potentials*; Murray, J. S., Sen, K., Eds.; Elsevier: Amsterdam, 1996. (c) Murray, J. S.; Politzer, P. *Chem. Phys. Lett.* **1988**, *152*, 364. (d) Murray, J. S.; Lane, P.; Brinck, T.; Politzer, P. *J. Phys. Chem.* **1991**, *95*, 844–848. (e) Suresh, C. H.; Gadre, S. R. *J. Org. Chem.* **1997**, *62*, 2625–2627. (f) Suresh, C. H.; Gadre, S. R. *J. Am. Chem. Soc.* **1998**, *120*, 7049–7055. (g) Suresh, C. H.; Gadre, S. R. *J. Phys. Chem. A* **2007**, *111*, 710–714.

(36) Reed, A. E.; Weinstock, R. B.; Weinhold, F. *J. Chem. Phys.* **1985**, *83*, 735–746. (b) Reed, A. E.; Curtiss, L. A.; Weinhold, F. *Chem. Rev.* **1988**, *88*, 899–926.

(37) Lenoir, D. *Angew. Chem., Int. Ed.* **2003**, *42*, 854–857.

and polycyclic aromatic hydrocarbons²⁶ correlate quantitatively with electrophile affinities ($E\alpha$), a recently proposed theoretical quantity. These three sets of data analyzed quantitatively here reveal no indication of the intervention of aromatic electrophilic substitution mechanisms^{9–16} under these conditions other than those involving Wheland σ -complex formation in the rate-determining steps. The effect of simulated solvation by the IEFPCM method (Gaussian 09) on the electrophile affinities (Table 3) confirmed the results of the gas-phase computations. No correlation between the energies of π -complex formation and reaction rates for a series of 32 S_{EAr} bromination substitutions reported by Dubois et al.²⁵ was found (Table 5). The rates of these bromination reactions appear, therefore, to be governed by Wheland σ -complex-like transition states. Computations on model isodesmic reactions reveal that electrophile affinities reflect the specific interaction

between aromatic substrate and electrophile. These results do not exclude the possibility that other aromatic substitution mechanisms are followed under other conditions, but they do establish further the limiting case.

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Supporting Information Available: Complete references; energies and Cartesian coordinates of all optimized geometric structures; Tables S1 and S2. This material is available free of charge via the Internet at <http://pubs.acs.org>.