Mechanism in Electrophilic Aliphatic Substitution: A Kinetic and Stereochemical Study of Bromodemercuration with Bromide Ion Catalysis[1]

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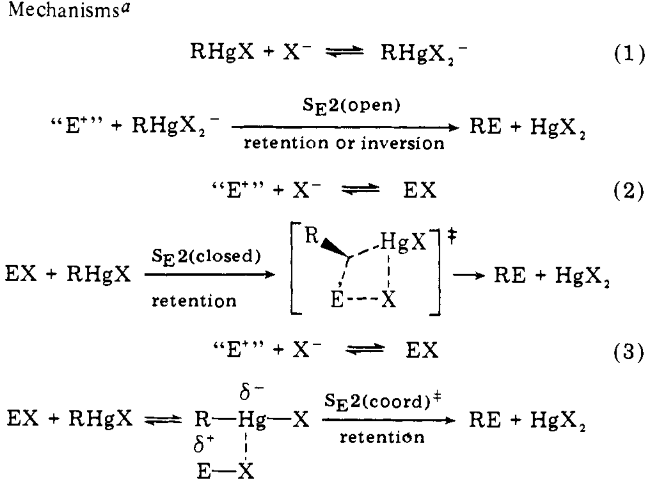
Abstract: The bromide ion catalyzed bromolysis of alkylmercuric bromides in methanol (S_E2) has been found to occur with retention of configuration with the investigated secondary and primary substrates. A structure-reactivity study of successive methyl-for-hydrogen replacement in the substrate revealed that a rate-accelerating inductive (electronic) effect works in opposition to a rate-retarding steric effect. Whereas the former dominates for α substitution, the latter dominates for β substitution. The results are nicely correlated for primary substrates by $\log k_R/k_{Me} = -10.9\sigma^* + 1.5E_s$ and for secondary substrates by $-17.9\sigma^* + 1.054E_s$, wherein σ^* and E_s are the well-known Taft inductive and steric parameters, respectively.

In contrast to the well-defined inversion stereochemistry observed for S_N2 reactions,[2] both retention and inversion stereochemistries have been observed for demonstrable S_E2 reactions.[3] Whereas the structure-reactivity characterization of S_N2 is handled adequately by a straightforward rate-retarding steric effect associated with branching at both the α- and β-carbon atoms,[2] no simple analogous framework exists for S_E2 reactions. The mechanistic picture is more complicated for S_E2 than for S_N2 because the substrates which undergo electrophilic aliphatic substitution are inevitably organometals which can possess quite diverse electronic architectures. Most importantly is the wide variety then possible concerning the identity and electronegativity of leaving and entering groups, as well as the complex steric consequences thereof.

All known simple electrophilic cleavages of the carbon-mercury bond occur with retention of configuration at carbon. For alkylmercuric halides, stereochemical as well as kinetic studies have been carried out utilizing both metal electrophiles and halogen electrophiles. Both reactions exhibit marked catalysis by added halide ion, which can be understood in terms of a preequilibrium complexing of the organomercurial substrate, resulting in improved leaving group ability and enhanced C-Hg bond nucleophilicity (eq 1). Catalysis can alternatively be rationalized by a preequilibrium halide complexing of the electrophile, if the halide ion is transferred to mercury during the course of reaction; the bond between the catalytic halide ion and mercury can form either (i) simultaneously with (or nearly so) electrophilic cleavage, defining the cyclic S_E2 (closed) mechanism (eq 2) or (ii) prior to electrophilic cleavage, defining the S_E2 (coord) mechanism (eq 3), where "coord" refers to a pre-transition state donor-acceptor coordination. The variety of reactions possible is outlined in Scheme I.

Scheme I. The S_E2(open), S_E2(closed), and S_E2(coord) Mechanisms[a]



[a] "E⁺"/EX = "X⁺"/X_2, X_2/X_3^-, $MX_n^{+m}/MX_{n+1}^{+m-1}$. An additional set of reactions is generated by substituting $RHgX_2^-$, $RHgX_3^{2-}$, and HgX_3^- for RHgX, $RHgX_2^-$ and HgX_2, respectively, in eq 1-3.

For the reaction of RHgX with halogens, the presence of added halide is often a prerequisite for a study of electrophilic cleavage, since a free-radical cleavage, which normally competes, is thereby suppressed.[4,5]

Hughes, Ingold, and co-workers[6] employed a radioactive label to measure the rates of one-alkyl mercury-for-mercury exchange reactions (eq 4) with various levels of anion catalysis.

$$^{203}HgX_2 + RHgX \rightleftharpoons HgX_2 + R^{203}HgX \qquad (4)$$

Although only limited data were obtained, the effect of α substitution appeared to be simply one of steric rate retardation, which one might expect for a frontside displacement (van der Waals repulsion). Interestingly, for the one- and especially two-anion catalyzed reactions, there were indications that β branching also had a rate-retarding effect.

In contrast to electrophilic attack by mercury(II), where the two electrons at the transition state should be fairly evenly distributed among the three "reacting" atoms (C, Hg, Hg), in the case of attack by the much more electronegative halogen, these same two electrons would be localized mainly on the electrophile, leaving the carbon center severely electron deficient. A large *electronic* substituent effect might then be expected. Some early evidence for such was obtained by Keller[4] for the iodinolysis of alkylmercuric iodides and by Reutov and co-workers[7] for halogenolysis of substituted benzylmercuric halides. However, the former study reported rates for only three alkyl groups, and in the latter study the interpretation of substituent effects is uncertain because of the possibility of competing reaction sites.[8]

In order to obtain a reliable S_E2 (retention) structure-reactivity framework for the halogenolysis of RHgX, the reactions of a series of (saturated) alkylmercuric bromides with bromine in methanol was studied, wherein (i) the effects of branching in the alkyl moiety at the α, β, and γ positions could be independently assessed and (ii) the degree of catalysis could be measured as a function of added bromide ion concentration (at constant ionic strength).

Results: Stereochemistry

Jensen and co-workers established that retention of configuration is the normal course of *electrophilic* (as opposed to radical) cleavage of the carbon–mercury bond by bromine.[9] Complete stereospecificity was observed for bromination in pyridine at low temperature, but in methanol (with oxygen present to reduce the competing radical component of the reaction) the best result was 85% net retention.

In the current study, optically active ((−) as well as (+)) *sec*-butylmercuric bromide (at least 70% resolved) and *erythro*-1,2-dideuterio-3,3-dimethylbutylmercuric bromide, synthesized according to Scheme II,[10] were cleaved by bromine in methanol (open to the air) *containing bromide ion* under a variety of conditions. The result from all experiments was 90 ± 6% net retention of configuration, with no apparent correlation between the percent retention and the bromide ion concentration in any single experiment.

Results: Kinetics

The rate of reaction of alkylmercuric bromides with bromine in methanol containing NaBr and $NaClO_4$ (to maintain a constant ionic strength of 0.30 M) was followed spectrophotometrically (monitoring the disappearance of the bromine color) at 25.00 ± 0.01 °C. Observed second-order rate constants were calculated for the stoichiometry

$$RHgBr + Br_2 \rightarrow RBr + HgBr_2 \tag{5}$$

according to

$$\text{rate} = \frac{-d[Br_2]_t}{dt} = k_{obsd}[Br_2]_t[RHgBr]_t$$
$$= k_{obsd}[Br_2]_t([Br_2]_t + [RHgBr]_0 - [Br_2]_0) \tag{6}$$

where the subscripts 0 and t refer respectively to *initial* concentrations and *total* concentrations of active reagent, present in the various forms indicated by the following equilibria:[11]

$$Br_2 + Br^- \overset{K_1}{\rightleftharpoons} Br_3^- \tag{7}$$

$$RHgBr + Br^- \overset{K_2}{\rightleftharpoons} RHgBr_2^- \tag{8}$$

$$RHgBr_2^- + Br^- \overset{K_3}{\rightleftharpoons} RHgBr_3^{2-} \tag{9}$$

Thus

$$[Br_2]_t = [Br_2] + [Br_3^-] \tag{10}$$

and

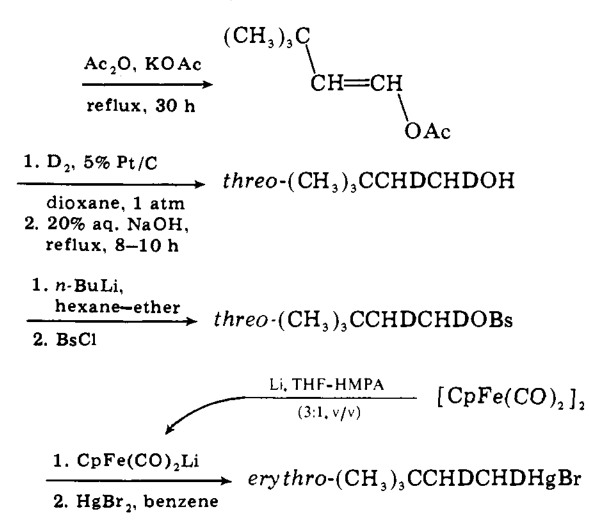
$$[RHgBr]_t = [RHgBr] + [RHgBr_2^-] + [RHgBr_3^{2-}] \tag{11}$$

The value of K_1 (MeOH, 25 °C, μ = 0.2 M) has been determined to be 177 M^{-1} by Dubois and Herzog.[13] No systematic measurements of mercurial equilibria constants (K_2 and K_3) have been conducted in methanol. However, a handful of values (spanning a variety of R groups and anionic ligands) has been obtained in 50% aqueous methanol,[14] ethanol,[15] and water.[16] From these data it appears that K_2 is on the order of 1 M^{-1} (25 °C) and K_3 is smaller; both are more or less insensitive to structural variation of the R group.

First-order dependence in each reactant was checked for several organomercurial substrates by varying independently the initial concentration of one or the other reactant and verifying the constancy of the calculated k_{obsd}.

The bromodemercurations studied herein exhibited marked catalysis by added bromide ion, consistent with the findings of previous RHgX cleavage studies. Unfortunately, direct measurement of the very slow uncatalyzed rates was not reproducible, due in part to the occurrence of a competing radical reaction and in part to a competing oxidation of the solvent by bromine,[17] both of which are suppressed in the presence of bromide ion.[18]

Scheme II. Synthesis of *erythro*-1,2-Dideuterio-3,3-dimethylbutylmercuric Bromide



Scheme III. Kinetic Scheme for Bromodemercuration with Bromide Ion Catalysis

uncatalyzed: $Br_2 + RHgBr \xrightarrow{k_2}$ products

one-anion catalysis: $Br_2 + RHgBr_2^- \xrightarrow{k_{3A}}$ pdts *or*
$Br_3^- + RHgBr \xrightarrow{k_{3B}}$ pdts

two-anion catalysis: $Br_3^- + RHgBr_2^- \xrightarrow{k_{4B}}$ pdts
$Br_2 + RHgBr_3^{2-} \xrightarrow{k_{4A}}$ pdts *or*

The representation of bromide ion catalysis in terms of the observed second-order kinetics is given in Scheme III. This treatment presumes (i) that anion catalysis of greater than second-order is negligible and (ii) that separate action of the catalytic bromide ion(s) via a termolecular (or quadrimolecular) mechanism is unlikely. The alternate expressions within each of the two classes of anion catalysis are kinetically indistinguishable, and, in order to present the rate data without implying any particular mechanism, the "dummy" rate coefficients k_3 are k_4 are utilized to represent one- and two-anion catalysis, respectively:

$$\text{rate} = k_2[Br_2][RHgBr] + k_3[Br_2][RHgBr][Br^-] + k_4[Br_2][RHgBr][Br^-]^2 \tag{12}$$

where

$$k_3 = k_{3A}K_2 + k_{3B}K_1 \tag{13}$$

and

$$k_4 = k_{4A}K_2K_3 + k_{4B}K_1K_2 \tag{14}$$

are derived from eq 7–9 and Scheme III. Then, k_{obsd} can be solved as a function of rate coefficients, equilibrium constants, and the bromide ion concentration, utilizing eq 6–12 and Scheme III:

$$k_{obsd} = \frac{k_2 + k_3[Br^-] + k_4[Br^-]^2}{(1 + K_1[Br^-])(1 + K_2[Br^-] + K_2K_3[Br^-]^2)} \tag{15}$$

At low $[Br^-]$, the contribution of the k_4 term is small, and $(1 + K_2[Br^-] + K_2K_3[Br^-]^2)$ is approximately unity.

Table I. Rate Coefficients (s^{-1} M^{-1}) for Bromodemercuration in Methanol at 25.00 ± 0.01 °C at 0.30 M Ionic Strength

RHgBr	k_{3A}	k_{3B}	k_{4A}	k_{4B}
α branching				
CH_3-	1.68	0.0095	88.5	0.15
CH_3CH_2-	18.1	0.102	124	0.21
$(CH_3)_2CH$-	1310	7.4	3540	6.0
$(CH_3)_3C$-	5660	32	4720	8
β branching (primary R)				
CH_3CH_2-	18.1	0.102	124	0.21
$CH_3CH_2CH_2$-	7.43	0.042	41.3	0.07
$(CH_3)_2CHCH_2$-	2.09	0.01182	5.49	0.0093
$(CH_3)_3CCH_2$-	0.2903	0.00164	0.177	0.0003
β branching (secondary R)				
$CH_3CH(Me)$-	1310	7.4	3540	6.0
$MeCH_2CH(Me)$-	1016	5.74	708	1.2
$Me_2CHCH(Me)$-				
$Me_3CCH(Me)$-	53.3	0.301	70.8	0.120
γ branching (primary R)				
$CH_3CH_2CH_2$-	7.43	0.042	41.3	0.07
$MeCH_2CH_2CH_2$-	8.32	0.047	43.7	0.074
$Me_2CHCH_2CH_2$-				
$Me_3CCH_2CH_2$-	12.5	0.0707	50.0	0.0847

Therefore a plot of k_{obsd} $(1 + K_1[Br^-])$ vs. $[Br^-]$ should approach a straight line at low $[Br^-]$, with slope k_3 and intercept k_2. The low $[Br^-]$ used for these plots is approximated by $[Br^-]_t$, as long as the added [NaBr] is considerably greater than the initial concentration of reactants (RHgBr and Br_2). However, at very low $[Br^-]_t$, the bromide ion concentration must be calculated as a function of $[Br^-]_t$, $[Br_2]_t$, and $[RHgBr]_t$, and in this case only initial rates are valid since $[Br_2]_t$ and $[RHgBr]_t$ decrease with time and a significant fraction of bromide ion is tied up by the product $HgBr_2$. Because of this difficulty and the fact that the uncatalyzed rates are very slow compared with the anion-catalyzed rates,[19] only k_3 values obtained from these plots are given (an example is shown in Figure 1). The intercept of such a plot occurs so near the origin that the error associated with its extrapolated value varies over several orders of magnitude for any reasonable error associated with the slope.

At higher concentrations of bromide ion, that fraction of the total reactant pairs present in the form of *two*-anion catalysis (k_{4A} or k_{4B}) becomes significant. The importance of the k_4 term relative to the k_3 term for a given mercurial can be assessed by observing the behavior of the k_{obsd} $(1 + K_1[Br^-])$ vs. $[Br^-]$ plot on going to high concentrations of bromide ion. A fall-off of the slope, a constant slope, or a rise in slope can be interpreted to imply that two-anion catalysis is respectively of lesser, of similar, or of greater importance than is one-anion catalysis. A graphical determination of k_4 requires the values of the mercurial-bromide equilibrium constants (K_2 and K_3). Since these are known only approximately, a useful method for obtaining k_4 is a trial-and-error simulation of the k_{obsd} vs. $[Br^-]$ data utilizing eq 15. Assuming the values $K_2 = 1.0\ M^{-1}$ and $K_3 = 0.30\ M^{-1}$, the value of k_4 was chosen which allowed the calculated k_{obsd} vs. $[Br^-]$ function[20] to most closely fit the experimental data. Furthermore, this simulation method (i) served as a check on the k_3 values obtained by the graphical technique and (ii) allowed an appraisal of the error associated with both the rate constants and the assumed equilibrium constants. In Table I are listed the values of k_3 and k_4, calculated according to the graphical and/or computer simulated techniques, expressed in terms of the rate coefficients for the two levels of anion catalysis (using eq 13 and 14 and the assumed values of K_2 and K_3).

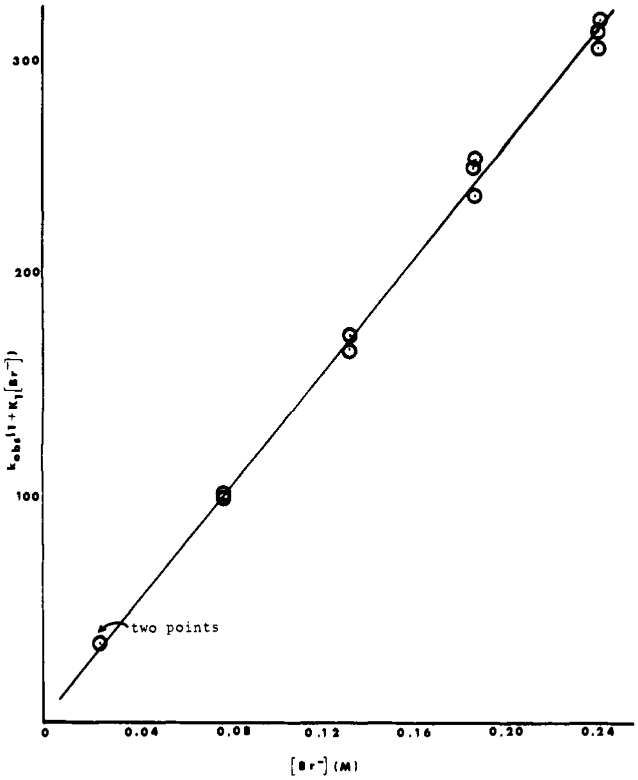


Figure 1. A plot of k_{obsd} $(1 + K_1[Br^-])$ vs. $[Br^-]$ for the bromine cleavage of isopropylmercuric bromide in methanol at 25 °C, $\mu = 0.30$ M.

Discussion

Stereochemistry. One of the goals of the present study was to aid in our understanding of the factors which together control the stereochemical outcome of S_E2 reactions. It is generally believed that whenever (i) the electrophile is attached to a nucleophilic fragment and (ii) the metal is coordinatively unsaturated, the coordination of the electrophile to the metal can occur prior to, or simultaneous[21] with, C-M cleavage (Scheme I), favoring retention. If (i) the metal is coordinatively saturated and/or (ii) frontside attack is sterically disfavored due to either a bulky metal ligand system and/or a bulky electrophile, then *inversion* may be favored.

Although only retention has been observed for normal C-Hg bond cleavage, it would be interesting to achieve a switch in stereochemistry, taking the above generalities into account. For the compounds for which predominant stereochemical retention was demonstrated (R = *sec*-butyl and 3,3-dimethylbutyl), the kinetic term involving one-anion catalysis is almost wholly responsible for the observed reaction.[22] Thus, at least the k_3 term must correspond to a retention process, but it is not at this time possible to say which of the two kinetically indistinguishable reacting pairs (k_{3A} or k_{3B}) is responsible for observed reaction—indeed, they may operate simultaneously. If inversion were to occur at all in this system, the k_{4A} term would be the "best bet" for such observation. This reaction (eq 16) would involve a coordinatively saturated and relatively

$$Br\text{-}Br + R\text{-}HgBr_3^{2-} \xrightarrow[\text{inversion}]{k_{4A}} Br^- + BrR + HgBr_3^- \quad (16)$$

bulky metal (which would be an excellent leaving group) and a reactive "open" electrophile (bromine but not tribromide ion has been shown to be an effective electrophile in a demonstrated S_E2 inversion reaction).[3c] In order to establish the steric

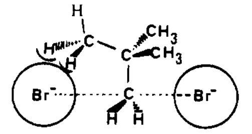


Figure 2. Steric model for the bromide exchange reaction of neopentyl bromide.

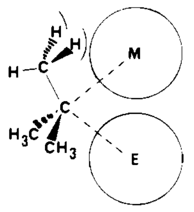


Figure 3. α-steric effect model for electrophilic attack on a *tert*-butyl organometal.

outcome of the k_4 (two-anion catalyzed) term with certainty, one would need to measure stereochemistry when this kinetic term made the major contribution to the overall cleavage. Unfortunately, such condition could not be achieved in this study. In passing, it should be noted that two-anion catalysis could also occur via k_{4B} retention (open or closed) or k_{4A} retention (open).

It is acknowledged that the possibility of electron transfer must be taken into account when discussing electrophilic cleavage by halogens.[23,24] In fact some reactions involving transition metals which originally appeared to represent S_E2 inversion have since been shown to be nonconcerted, the first step being oxidation of the metal center by halogen.[24] Subsequent S_N2 attack by halide ion is responsible for the observed carbon–metal bond cleavage.

In the case of organomercurials (and other nontransition organometals) the electrons most susceptible to oxidation are in the C–M σ bond, such that one- and two-electron oxidation would lead to alkyl radicals (eq 17) and carbonium ions (eq 18), respectively.[25] In the present study, it would be highly unlikely that either of these two reactions could produce alkyl bromide with 90% retained configuration. However, the transition state for the herein-studied cleavage is characterized by a significant development of charge separation, which is equivalent to partial electron transfer.

$$\mathrm{Br_2 + RHgBr_n{}^{1-n} \rightarrow [Br_2]^{-\cdot} + R\cdot + HgBr_n{}^{2-n} \rightarrow pdts} \qquad (17)$$

$$\mathrm{Br_2 + RHgBr_n{}^{1-n} \rightarrow 2\,Br^- + R^+ + HgBr_n{}^{2-n} \rightarrow pdts} \qquad (18)$$

A Separation of Polar and Steric Effects for the Substrate.[1] On considering the one-anion catalysis rate data in Table I, two opposite trends are observed. Successive methyl-for-hydrogen replacement at the α carbon results in a marked rate acceleration ($k_{t\text{-Bu}}/k_{\text{Me}} = 3 \times 10^3$), whereas such substitution at the β carbon is accompanied by a decrease in rate ($k_{\text{Np}}/k_{\text{Et}} = 0.016$) (Np = neopentyl). The former trend is consistent with the expected electronic effect associated with cleavage by the electronegative electrophile bromine: The development of electron deficiency at the reaction center in the transition state is relieved by electron-donating alkyl substituents. This same rate trend should be paralleled for β substitution as well if only electronic forces are operative, though here rate differences should be smaller by an amount proportional to the inductive attenuation factor of the interposed methylene group (a factor of about 5 for hydrocarbons[26]). However, successive β substitution results in a *rate decrease*, apparently indicating that a steric effect is circumventing the expected electronic effect.

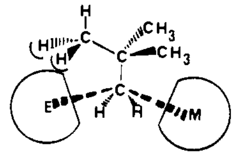


Figure 4. β-steric effect model for electrophilic attack on a neopentyl organometal.

A priori, two types of steric rate retardation must be considered for the substitution reaction being examined here. The first is the classical case of steric compression (van der Waals repulsion) encountered at the transition state that is not present in the ground state, a situation created by the required partial bonding of *both* entering and leaving groups to the α carbon (as in, for example, S_N2 reactions[27]). A second potential rate-retarding effect is steric inhibition of solvation of a localized charge developed at the transition state.[28] As indicated in this study by the large α-substituent (polar) effect, the α carbon becomes electron deficient at the bromodemercuration transition state, and alkyl substitution could sterically be interfering with the reorientation of solvent (methanol) molecules required for stabilizing this positive charge. The "steric compression" effect should depend fairly critically on precise molecular geometry. For example, in the S_N2 reaction, the rate-retarding influence of β substitution (particularly in the case of neopentyl substrates) as well as α substitution is understood in terms of a precise transition-state geometrical description,[27] e.g., as shown in Figure 2 for neopentyl bromide undergoing bromide exchange. On the other hand, steric inhibition of solvation should depend rather *loosely* on exact atomic configuration, primarily because (i) charge–donor and charge–dipole interactions are energetically more spatially "flexible" than is covalent bonding and (ii) a "bad" repulsive interaction can be distributed over many atomic pairs, utilizing a large array of motional degrees of freedom.

Successive methyl-for-hydrogen substitution at the γ carbon can be seen (Table I) to result in a slight rate increase. Such can be rationalized in terms of an (attenuated) inductive effect operating in the absence of a significant steric effect. This "*sharp* cut-off" of the steric effect experienced by moving the position of alkyl branching a distance of only one C–C bond length (from the β to the γ carbon) is unlikely in terms of inhibition of solvation (for which rate retardation should *gradually* attenuate with continued displacement of steric bulk away from the reaction center).

The data in Table I suggest that, on going from one- to two-anion catalysis, the magnitude of the β steric effect is increased (compare $k_{\text{Np}}/k_{\text{Et}}$), while the electronic effect simultaneously diminishes (compare $k_{t\text{-Bu}}/k_{\text{Me}}$). This is additional evidence against steric inhibition of solvation, since one would expect the diminished requirement for solvation of the k_4 transition state to correlate with a less severe steric effect.

It appears that steric compression at the transition state is responsible for the experimentally obtained rate trends. In contrast to S_N2 inversion, a retention mechanism might be expected to exhibit severe steric rate retardation for branching at the α carbon (as shown in Figure 3 for a *tert*-butyl substrate), but it is not obvious (nor previously documented) that such should be the case for branching at the β carbon as well. However, for bromodemercuration and other electrophilic demetallations, a situation exists in which entering groups (E) and/or leaving groups (M) (i) are large (e.g., a metal atom plus its ligand system) and (ii) are attached to the carbon center through long covalent bonds; in this case, a β-steric effect may be of common occurrence. It is qualitatively apparent from the construction of molecular models that steric compression for β branching (as shown in Figure 4 for a neopentyl substrate)

Table II. The Correlation of One-Bromide Ion-Catalyzed Bromodemercuration with σ^* and E_s

group	σ^*	E_s	$\rho^*\sigma^*$	δE_s	sum	$\log k_R/k_{Me}$
primary			$-10.9\sigma^*$	$1.5E_s$		
CH_3-	0	0	0	0	0	0
CH_3CH_2-	−0.10	−0.07	1.090	−0.105	0.985	1.032
$CH_3CH_2CH_2$-	−0.115	−0.36	1.254	−0.540	0.714	0.646
$CH_3CH_2CH_2CH_2$-	−0.122[a]	−0.41[a]	1.330	−0.615	0.715	0.695
$(CH_3)_2CHCH_2$-	−0.135[a]	−0.91[a]	1.472	−1.365	0.107	0.095
$(CH_3)_3CCH_2$-	−0.165	−1.74	1.799	−2.610	−0.812	−0.762
secondary			$-17.9\sigma^*$	$1.054E_s$		
$(CH_3)_2CH$-	−0.19	−0.47	3.401	−0.495	2.906	2.892
$CH_3CH_2CH(CH_3)$-	−0.22[a]	−1.11[a]	3.938	−1.170	2.768	2.782
$(CH_3)_3CCH(CH_3)$-	−0.28	−3.33	5.012	−3.510	1.502	1.501

[a] The original values $\sigma^*_{n\text{-Bu}} = -0.130$, $\sigma^*_{i\text{-Bu}} = -0.125$, and $\sigma^*_{s\text{-Bu}} = -0.21$ have been noted to be "too low" or "too high" in relation to the other groups.[32,35] In keeping with LFE requirements and the suggestions from ionization potential data, the σ^* values are here reassigned and the respective E_s values are corrected according to $E_s' = E_s - 2.48(\sigma^{*\prime} - \sigma^*)$ in order to retain internal consistency with regard to the rates of alkaline ester hydrolysis.[26]

may be as severe as for α branching. Consistent with this hypothesis is the observation (Table I) that the β-steric effect is more severe for two- than for one-anion catalysis (indirect evidence for such phenomena was previously obtained[6b] from the halide ion dependence of the one-alkyl Hg-for-Hg exchange rates): the greater number of anions involved, the larger is the effective size of the leaving/entering groups.

Finally, a mechanistic description for bromodemercuration with bromide ion catalysis, that is consistent with both the observed retention stereochemistry and the rate trends apparent over the full range of substitution explored, must involve a superposition of a large electronic effect and a large steric effect (viz. of the type depicted in Figures 3 and 4, where no statement regarding the question of open vs. closed mechanisms is intended).

For successive α substitution, a huge electronic effect predominates over the large steric effect, yielding a *net polar* sequence (though spanning a much reduced range of relative rates than would be observed if no steric effect were operating). For successive β substitution, the now smaller electronic effect is overshadowed by the continued large steric effect, yielding a *net steric* sequence (though again the range of relative rates would be much larger if here the polar effect were absent). For successive γ substitution, any steric effect must be small, and the residual polar effect is manifested in the net rate sequence observed.

It has been common practice for aliphatic reactions to attempt a separation of polar and steric effects in terms of σ^* and E_s, respectively (eq 19).[20,29] Although the σ^* values were

$$\log k/k_0 = \sigma^*\rho^* + \delta E_s \qquad (19)$$

originally calculated for substituents attached to a carbonyl group, R—C(=O)—OX, these values have been applied to a systems of the type RCH_2X for correlating the polar effect of substitution reactions at saturated carbon.[30] In this case, however, σ^* values are not available for secondary (R_2CHX) or tertiary (R_3CX) systems. In order to correlate all substrates, σ^* values can be applied directly to RX systems, if it is realized that the reaction parameter which now correlates the data (ρ^*_X) will be larger than the one that would be obtained above ($\rho^*_{CH_2X}$) by a factor of $1/\alpha^*_{CH_2}$ (where $\alpha^*_{CH_2}$ is the "relay" factor, given by $\rho^*_{CH_2X} = \alpha^*_{CH_2}\rho^*_X$).

Although the validity of σ^* as a measure of *alkyl* inductive effects has been questioned,[31] there is no doubt that alkyl groups are capable of assuaging an electron deficiency by other than a hyperconjugative effect (e.g., as evidenced by gas-phase ionization potentials[32]). Since the σ^* scale does obey the "additivity" and "attenuation" requirements of linear free-energy (LFE), it is utilized here in order to permit the indicated magnitude of the polar effect to be compared with that of other well-known reactions.

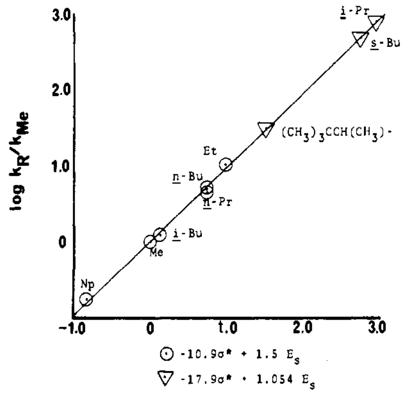


Figure 5. The correlation of one-bromide ion-catalyzed bromodemercuration with σ^* and E_s.

Unlike polar substituent constants, no simple LFE function interrelates *steric* substituent parameters, since these will depend fairly precisely on a given transition state geometry. Steric substituent parameters are available for backside displacement (the α scales of Streitwieser[33] and Okamoto[34]) but not for frontside attack. Although the E_s scale developed by Taft[26] from ester hydrolysis data pertains to a geometry different from either frontside or backside attack at tetrahedral carbon, it is expected to correlate the here-studied retention reaction much better than will the α scale. The E_s value for R in R—C(=O)—OX is used here for R in $RHgBr_n^{1-n}$ rather than for R in $RCH_2HgBr_n^{1-n}$, since electrophilic attack occurs not on carbon but on the rather long C-Hg bond.

The correlation for primary substrates of the one-bromide ion-catalyzed rates by the two-variable-parameter Taft equation yields an excellent fit (Table II and Figure 5) to eq 20. It is not expected that secondary and tertiary compounds

$$\log k_R/k_{Me} = -10.9\sigma^* + 1.5E_s \qquad (20)$$

will be correlated by this same equation: The transmission of the electronic effect for a remote substituent to the reaction center is proportional to the electron density on the intervening carbon atom(s).[31a] For the here-studied bromodemercuration reaction, the electronic effect of the β (and γ) substituents is expected to be increasingly "felt" at the reaction center upon successive methyl-for-hydrogen replacement at the α carbon; viz., the magnitude of ρ^* which correlates the various series

Table III. Relative Rates (with Respect to $k_{\text{methyl}} \equiv 1$) for Several S_E2 Reactions

	reactants:	$RHgBr + Br_2 + Br^-$ [a]	$RHgX + HgX_2$ [b]	$RB(OH)_2 + HOO^-$ [c]	$RHgR' + HOAc$ [e]	$RSn(neopentyl)_3 + Br_2$ [g]
	solvent:	MeOH	EtOH	H_2O	HOAc	MeOH
	temp (°C):	25	60, 100	25	37.5	45
	stereochemistry:	retention	retention	retention [d]	retention [f]	inversion
R	methyl	[1]	[1]	[1]	[1]	[1]
	ethyl	10.8	0.42		2.0	0.144
	n-propyl	4.42				0.041
	n-butyl	4.95		38.		0.029
	isobutyl	1.24				0.024
	neopentyl	0.173	0.33			0.0006
	isopropyl	780.			1.6	0.0075
	sec-butyl	605.	0.06	180.		0.0027
	tert-butyl	3370.		560.	very small	

[a] This study. [b] Reference 6. [c] Reference 37. [d] A. G. Davies and B. P. Roberts, *J. Chem. Soc. C*, 1474 (1968); G. W. Kalbalka and N. S. Bowman, *J. Org. Chem.*, **38,** 1607 (1973); D. E. Bergbreiter and D. P. Rainville, *J. Org. Chem.*, **41,** 3031 (1976). [e] Reference 38. [f] Reference 3a, p 64. [g] Reference 40.

of compounds is expected to increase in the order

$$X_3C\text{—}\boxed{CH_2}\text{—}HgBr$$

$$X_3C\text{—}\boxed{CH(CH_3)}\text{—}HgBr$$

$$X_3C\text{—}\boxed{C(CH_3)_2}\text{—}HgBr$$

The one-anion catalyzed rates for cleavage of the three secondary compounds are best correlated (Table II and Figure 5) by eq 21. This ρ^* is larger than for primary compounds, and

$$\log k_R/k_{Me} = -17.9\sigma^* + 1.054E_s \qquad (21)$$

the smaller steric effect ($\delta = 1.054$ vs. 1.5) is consistent with an earlier transition state reached for the more exothermic cleavage of the secondary substrates. A series of tertiary substrates would be expected to be correlated by an even larger ρ^* and an even smaller δ.

By using the relay factor $\alpha^*_{CH_2} = 0.2$ suggested by Taft[26] for the attenuation of the alkyl electronic effect, the values $\rho^*_{CH_2X} = -2.2$ and $\rho^*_{CH(CH_3)X} = -3.58$ are calculated for one-anion catalyzed bromodemercuration. These values can directly be compared with $\rho^*_{CH_2X} = -0.742$ reported for ethanolysis of primary alkyl tosylates at 100 °C,[30a] $\rho^*_{C(CH_3)_2X} = -3.29$ reported for ethanolysis of tertiary alkyl chlorides at 25 °C,[30a] and $\rho = -4.54$ for solvolysis of aryldimethylcarbinyl chlorides in 90% aqueous acetone at 25 °C.[36] The values $\delta = 1.5$ and 1.054 can be compared with $\delta = 1$ for aliphatic ester hydrolysis (though the geometrical differences of the transition states should be kept in mind). In summary, the present LFE correlation confirms that both electronic and steric effects for bromodemercuration are large.

Only limited and usually incomplete structure-activity studies have thus far appeared in the literature for S_E2 reactions that have been demonstrated to involve retention of configuration at carbon. Most have examined only the effect of *α branching* on reaction rate, and given in Table III are rate sequences which indicate the operation of predominantly steric effects (column 2)[6] and predominantly electronic effects (column 3)[37] as well as a "mixed" sequence indicating both effects are important (column 4).[38] The results presented herein (column 1) suggest that the interplay of steric and electronic effects may not be revealed unless the examination of the effect of branching is extended to the β and γ carbons.

For those S_E2 reactions that have been shown to occur with *inversion* of configuration at carbon, only steric rate sequences have so far been observed, but different sequences, indicating different structural dependencies of the steric effect, have been reported.[3c,f,g,39] A rather complete structure-activity study for a reaction which exhibits the S_N2-like rate-retarding effect for branching at both the α and β carbons is recorded in the last column of Table III. It is believed that with the proper selection of system, an S_E2 inversion reaction which exhibits predominant electronic control could be observed.

The structure-activity analysis performed here for one-bromide ion-catalyzed bromodemercuration has both recognized the indistinguishability between two mechanistic options (Scheme III) and assumed the operation of a single mechanism for all substrates. With due respect to these assumptions, it remains noteworthy that the present report provides the first documented case both (i) that an S_E2 reaction may be governed by superposed and opposing large steric and large electronic effects and (ii) that frontside displacement may be sterically retarded by β branching as well as by α branching, a notion generally acknowledged previously only for backside displacement mechanisms.

Experimental Section

General. Unless otherwise specified, all materials were utilized as obtained commercially, except for routine distillation of solvents from drying agents and recrystallizations of solids. Routine ^1H NMR spectra were obtained on a Varian T-60 instrument and deuterium-decoupled spectra on a modified Varian HA-100 instrument. Optical rotations at the sodium D line (589 nm) were obtained directly by using a Bendix polarimeter (for small rotations) and also by extrapolation from readings at 546 and 578 nm using a Zeiss polarimeter (for larger rotations). Gas chromatographic analyses were performed utilizing a flame ionization Varian Aerograph Series 120 instrument.

Sodium bromide and sodium perchlorate were recrystallized from methanol containing a trace of HBr and $HClO_4$, respectively, and dried in vacuo.

Bromine (Mallinckrodt, AR) was washed with concentrated H_2SO_4 and distilled from KBr, the center cut being used for kinetic studies. Methanol (AR) was refluxed over and distilled from first $Mg(OMe)_2$ and then Br_2 (about 0.1% v/v) under a dry nitrogen atmosphere.

Alkyl halides were freshly distilled from P_2O_5 under dry N_2 for Grignard syntheses.

Alkylmercuric bromides were generally prepared by dropwise addition of the appropriate Grignard reagent, RMgBr (in dry Et_2O or THF), to a mechanically stirred slurry of an excess of $HgBr_2$ (dried in vacuo) in Et_2O at 0 °C under dry N_2. After stirring at room temperature for several hours, water was added and the ether was removed by rotary evaporation. The resulting sludge was partitioned between $CHCl_3$ and dilute aqueous HBr. The combined $CHCl_3$ extracts were washed with dilute aqueous HBr and then distilled water, and dried over $MgSO_4$. The crude residue obtained upon removal of solvent was recrystallized three times from absolute ethanol (under N_2, in the dark for secondary and tertiary materials) for use in kinetic studies.

Neopentylmercuric bromide was obtained by adding the Grignard reagent prepared from neopentyl chloride (Columbia) to $HgBr_2$. In order to ensure the absence of any RHgCl contaminant, the crude mercurial obtained was stirred with a large excess of NaBr in ethanol.

Methylmercuric bromide was obtained by anion exchange from methylmercuric iodide (which results when methyl iodide is used as Grignard precursor, regardless of which mercuric salt is utilized) by treatment with a slight excess of $AgNO_3$ in methanol (in the dark), separating off the precipitated AgI, and then pouring the CH_3HgNO_3 solution into an excess of NaBr in 50% aqueous ethanol.

3,3-Dimethyl-2-butylmercuric Bromide. It was first necessary to prepare 3,3-dimethyl-2-bromobutane from the corresponding commercially available alcohol (Aldrich) via a Wiley synthesis,[41] due to the extreme propensity for rearrangement in this system. Use of the standard DMF or higher temperatures still resulted in substantial amounts of the rearranged material (2,3-dimethyl-2-bromobutane) and olefin(s). Utilization of triphenylphosphine dibromide, prepared in situ, in tetraglyme at 0 °C minimized the byproducts. Further purification of the desired alkyl bromide was accomplished by selective solvolysis of the rearranged tertiary alkyl bromide in 80% aqueous methanol buffered with $NaHCO_3$.[42] Neopentyl halides are known to react sluggishly in Grignard syntheses—in the present case, entrainment with $BrCH_2CH_2Br$, refluxing THF, and a 50% excess of Mg were required to achieve conversion. Synthesis of the mercurial was carried out as usual.

Resolution of *sec*-butylmercuric bromide was accomplished by selective crystallization of the diastereomeric mandelate salts (obtained by treating RHgBr with silver mandelate). Shaking the resolved *sec*-butylmercuric mandelates (in $CHCl_3$) with an excess of aqueous NaBr afforded optically active *sec*-butylmercuric bromide.[9]

***trans*-3,3-Dimethyl-1-butenyl Acetate.** 3,3-Dimethylbutyric acid was reduced to the aldehyde by lithium-in-methylamine according to Whitesides et al.[10] One-half mole of $(CH_3)_3CCH_2CHO$, 0.67 mol of Ac_2O, and 0.085 mol of KOAc were heated together at reflux (115 °C) for 30 h.[43] The mixture was allowed to cool and cold water was added. The aqueous layer was separated off, and the organic layer was freed of acid by washing several times with aqueous Na_2CO_3. Drying over Na_2SO_4 and vacuum distillation yielded first 3 mL of recovered $(CH_3)_3CCH_2CHO$ (low boiling) and then 25 mL of 3,3-dimethyl-1-butenyl acetate (bp 48 °C at 14mm Hg), predominantly trans by ^1H NMR.

***threo*-1,2-Dideuterio-3,3-dimethyl-1-butanol.** Hydrogenation of the enol acetate in dioxane using only a small amount of 5% Pt/C as catalyst (0.01 g per 8 mL of enol acetate), so that the uptake of hydrogen was slow, afforded the threo alcohol without detectable scrambling of label (as determined by ^1H NMR). Utilizing greater amounts of or different metal catalysts resulted in significant intramolecular label scrambling.

***erythro*-1,2-Dideuterio-3,3-dimethylbutylmercuric bromide** was prepared by a modified method of Whitesides et al.[10] The threo alcohol in ether (under dry N_2 at 0 °C) was titrated with *n*-BuLi (in hexane), using 2,2′-biquinoline as indicator. After stirring for 15-20 min, a slight excess of freshly recrystallized *p*-bromobenzenesulfonyl chloride was added as the solid in portions. After stirring for 1 h, the resulting suspension was centrifuged, and the supernatant (containing the alkyl brosylate) was added to a 15% excess of $CpFe(CO)_2Li$ (Cp = cyclopentadienyl), previously prepared in THF-HMPA (3:1 v/v) by reduction of the iron dimer with finely chopped Li wire. The resulting mixture was stirred for 5 h and then concentrated by rotary evaporation at room temperature. The HMPA concentrate was diluted with degassed benzene, a slight excess of $HgBr_2$ was added, and the mixture was stirred for 6 h under dry N_2. Most of the benzene was then evaporated, and addition of aqueous ethanol precipitated the mercurial as a tannish solid. Decoloration was effected by boiling in ethanol with Nuchar. A small amount of the product was converted to the alkylmercuric acetate (with AgOAc in methanol), which, because of its improved solubility, permitted good resolution of a deuterium decoupled ^1H NMR spectra of the -CHD-CHD- resonances. In this way, the diastereomeric purity was established to be ≥78% (≤11% threo).

Kinetic Method. The disappearance of the Br_2/Br_3^- color was monitored with a Beckman DU spectrophotometer equipped with a Gilford thermostated cell compartment. For slower kinetics, reaction was initiated by mixing standard bromine and mercurial solutions (containing the appropriate salt concentrations) which had previously reached temperature equilibrium in the same circulating bath used to feed the cell compartment. For the faster kinetics, reaction was initiated by adding 2 drops of a preadjusted Br_2/CCl_4 solution directly to the spectrophotometric cell filled with the mercurial (and salt) solution. In the latter case, the initial bromine concentration was obtained from the extrapolated (to time = 0) OD (optical density).

The observed extinction coefficient at a particular wavelength is given by

$$\epsilon_{\text{obsd}} = \frac{\epsilon_{\text{Br}_2}[\text{Br}_2] + \epsilon_{\text{Br}_3^-}[\text{Br}_3^-] + \epsilon_{\text{Br}_5^-}[\text{Br}_5^-]}{[\text{Br}_2]_\text{t}}$$

and, in the case $[\text{Br}^-]_\text{t} \gg [\text{Br}_2]$, reduces to

$$\epsilon_{\text{obsd}} = \frac{\epsilon_{\text{Br}_3^-}K_1[\text{Br}^-] + \epsilon_{\text{Br}_2}}{1 + K_1[\text{Br}^-]}$$

Beer's Law plots were performed at various $[\text{Br}^-]_\text{t}$ at 386 nm and 25 °C to obtain ϵ_{obsd} as a function of $[\text{Br}^-]_\text{t}$. The slope and intercept of such function yielded the values $\epsilon_{\text{Br}_3^-} = 758$ and $\epsilon_{\text{Br}_2} = 150$.

For kinetics run at low $[\text{Br}^-]_\text{t}$, the free $[\text{Br}^-]$ is no longer equal to $[\text{Br}^-]_\text{t}$ (a substantial portion is tied up as Br_3^-) and changes during the course of the reaction. Since the fraction of bromine present as either Br_2, Br_3^-, or Br_5^- also changes during the course of the reaction, the extinction coefficient would be time variant, since no isobestic point exists for all three species. In these cases, the kinetics were monitored at or near the isobestic point of Br_2 and Br_3^-, and the extinction coefficient used was an average value calculated as $(OD_0 - OD_\infty)/[RHgBr]_0$. (Such value was best determined from the faster kinetics, since a good infinity value of optical density could be obtained.)

Integration of the rate expression

$$\text{“Br}_2\text{”} + \text{“RHgBr”} \xrightarrow[k_{\text{obsd}}]{} \text{pdts}$$

(reactants present
in various forms)

$$dx/dt = k_{\text{obsd}}([\text{Br}_2]_0 - x)([\text{RHgBr}]_0 - x)$$

where x is the product concentration at time t yields

$$\frac{1}{[\text{Br}_2]_0 - [\text{RHgBr}]_0} \ln \frac{[\text{RHgBr}]_0[\text{Br}_2]_\text{t}}{[\text{Br}_2]_0[\text{RHgBr}]_\text{t}} = k_{\text{obsd}}t$$

Rearrangement and utilization of the reaction stoichiometry allows the second-order rate constants k_{obsd} to be obtained as $(1/D) \times$ slope of a plot of $\ln [\text{Br}_2]_\text{t}/([\text{Br}_2]_\text{t} - D)$ vs. t, where $D = [\text{Br}_2]_0 - [\text{RHgBr}]_0$.

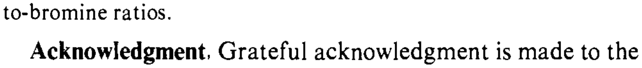
For slower reactions at low $[\text{Br}^-]$, it was necessary to correct the OD readings for the reaction-independent decay of the bromine titer (presumably due to oxidation of the solvent methanol).

Product Analyses. The determination of reaction product(s) under kinetic conditions (low reactant concentrations), for purposes of evaluating reaction yield and stereochemistry, was carried out in two fashions:

(i) On a convenient scale, a reaction was run for a period of time corresponding to 4-5 half-lives (from the measured rate constant). Dilution with water and extraction of the organic material(s) into a measured quantity of trichlorobenzene allowed for a gas chromatographic or NMR determination of product identity and yield. The alkyl halide could be obtained from the extract by distillation at reduced pressure.

(ii) The alkyl halide was removed as formed, as an azeotrope with methanol (at reduced pressure), for a duration of 4-5 reactions half-lives. Dilution of the azeotrope with water and extraction of the organic material(s) into trichlorobenzene permitted a product analysis as in (i).

Reactions were also monitored under nonkinetic conditions (high reactant concentrations) in NMR tubes, using CD_3OD as solvent. In these experiments, the yield and purity of product obtained were identical with those obtained under kinetic conditions (>95%) in all cases except for the substrate 3,3-dimethyl-2-butylmercuric bromide, which at *low* bromide-to-bromine ratios led to direct byproduction of rearranged alkyl bromide and the corresponding methyl ether, as well as olefin. This is conceivably due to a carbonium ion forming oxidation reaction:



$$Br_2 + (CH_3)_3C\text{—}\underset{\displaystyle CH_3}{\underset{|}{CH}}\text{—}HgBr \rightarrow (CH_3)_3C\text{—}\underset{\displaystyle CH_3}{\underset{|}{CH^+}} + HgBr_2 + Br^-$$

No such byproduct was obtained for any substrate at *high* bromide-to-bromine ratios.

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(19) An upper limit of k_2 can be obtained (i) by extrapolating the k_{obsd} vs. $[Br^-]$ function at low $[Br^-]$ to $[Br^-] = 0$ or (ii) from the extrapolated (to time = 0) slope of a second-order kinetic analysis performed with *no added* bromide ion. In this way, a rough estimate of the rate enhancement associated with one-anion catalysis (k_3/k_2) is found to be at least 1000 M^{-1}.

(20) Using k_2 as obtained according to note 19 and k_3 as obtained from plots (as in Figure 1).

(21) Although D. A. Slack and M. C. Baird, *J. Am. Chem. Soc.* **98**, 5539 (1976), claim that concerted S_E2 (closed) is symmetry forbidden, such is only true in the case of a four-electron transition state. With additional utilization of an empty metal orbital and a halogen lone pair, a concerted, symmetry-allowed six-electron process is possible.

(22) Substitution of the rate coefficients of Table I into eq 13–15 shows how the overall rate is distributed among the three degrees (0, 1, and 2) of bromide-ion catalysis.

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