Investigation of the Early Steps in Electrophilic Bromination through the Study of the Reaction with Sterically Encumbered Olefins

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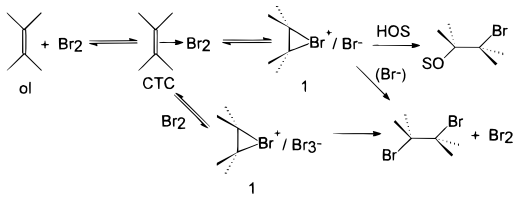
Introduction

The electrophilic bromination of an alkene is probably the quintessential reaction of the double bond and is portrayed in undergraduate textbooks as being a well-understood process adhering to the generalized mechanism depicted in Scheme 1.[1,2] For alkenes that do not form a highly stabilized β-bromocarbocation, the reaction invariably proceeds with the initial instantaneous formation of an olefin−Br_2 charge transfer complex[3] (CTC) which has been shown to be on the reaction pathway.[4,5]

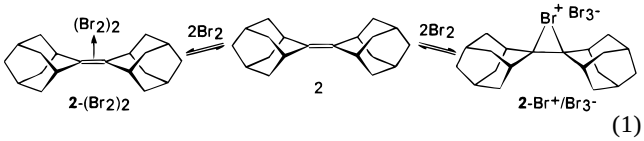
Central to any rationalization of the stereochemical and structure/reactivity characteristics of this deceptively simple reaction is the postulate of the three-membered bromonium ion intermediate (**1**) first proposed by Roberts and Kimball in 1937 to account for the *trans* mode of addition.[6] Generally, these species are too short lived to be detected during the electrophilic addition reaction, and although widely accepted as intermediates, until the late 1960s, virtually no information about their structures or physicochemical properties was available. Olah and co-workers subsequently demonstrated that the these species can be generated under stable ion conditions (SbF_5, SO_2) and their NMR spectra determined.[7]

A major breakthrough in the field occurred in 1969−70 when Wynberg and co-workers reported[8] that adamantylideneadamantane (Ad═Ad, **2**), when treated with Br_2 in chlorinated hydrocarbons, produced a yellow precipitate, then formulated as the world's first isolable three-membered bromonium/Br_3^- salt. Subsequent studies[9] led to the opinion that several atypical properties of the precipitate, such as the ability to release Br_2 and reform Ad═Ad, were more consistent with the behavior of a molecular π-complex, (**2**−$(Br_2)_2$). The identity of the yellow precipitate finally was resolved in 1985 when

Scheme 1



we reported the crystal structure of **2**−Br^+/Br_3^-.[10]



(1)

The structure of **2**−Br^+ absolutely precludes any *trans* attack so that the electrophilic addition stops at the bromonium ion. Although this is a unique case, it begged the question of whether one could learn something about the early stages of electrophilic bromination up to the ion formation and perhaps beyond by studying this olefin, and others where the product-forming steps were abnormally slow because of steric hindrance to nucleophilic opening of the ion. Over the last 10 years, this goal has been realized and a wealth of information has been generated about the behavior of the ionic and charge-transfer intermediates generated during Br_2 addition to the double bond. In what follows we will deal with many of the important findings.

CTC

When a reactive olefin and Br_2 are mixed, a transient species (the CTC) having a λ_{max} of 260−280 nm is instantly

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(1) For reviews of the general literature see: (a) DeLaMare, P. B. D.; Bolton, R. *Electrophilic Additions to Unsaturated Systems*, 2nd ed.; Elsevier: New York, 1982; pp 136−197. (b) V'yunov, K. A.; Ginak, A. I. *Russ. Chem. Rev. (Engl. Transl.)* ***1981***, *50*, 151. (c) Schmid, G. H.; Garrat, D. G. In *The Chemistry of Double Bonded Functional Groups*; Patai, S., Ed.; Wiley: New York, 1977; Suppl. A, Part 2, p 725. (d) Schmid, G. H. In *The Chemistry of Double-Bonded Functional Groups*; Patai, S., Ed.; Wiley: New York, 1989; Suppl. A, Vol. 3, Part 1, p 699. (e) Ruasse, M.-F. *Adv. Phys. Org. Chem.* **1993**, *28*, 207.

(2) For reviews of specific aspects of electrophilic bromination such as nucleophilic solvent assistance and open vs closed ionic intermediates see: (a) Ruasse, M.-F.; Motallebi, S. *J. Phys. Org. Chem.* **1991**, *4*, 527. (b) Ruasse, M.-F. *Acc. Chem. Res.* **1990**, *23*, 87.

(3) (a) Dubois, J. E.; Garnier, F. *Spectrochim. Acta* **1967**, *A23*, 2279. (b) Fukuzumi, S.; Kochi, J. K. *J. Am. Chem. Soc.* **1981**, *103*, 2783; **1982**, *104*, 7599. (c) Holroyd, S.; Barnes, A. J.; Suzuki, S.; Orville-Thomas, W. J. *J. Raman Spectrosc.* **1982**, *12*, 162 and references therein. (d) Bobrov, A. V.; Kimel'fel'd, Ya. M.; Mostovoy, A. B. *J. Raman Spectrosc.* **1978**, *7*, 88 and references therein.

(4) Gebelein, C. G.; Frederick, G. D. *J. Org. Chem.* **1972**, *37*, 2211.

(5) (a) Bellucci, G.; Bianchini, R.; Ambrosetti, R. *J. Am. Chem. Soc.* **1985**, *107*, 2464. (b) Bellucci, G.; Bianchini, R.; Chiappe, C.; Lenoir, D.; Attar, A. *J. Am. Chem. Soc.* **1995**, *117*, 6243.

(6) Roberts, I.; Kimball, G. E. . *J. Am. Chem. Soc.* **1937**, *59*, 947.

(7) (a) Olah, G. A.; Bollinger, J. M.; Brinich, J. . *J. Am. Chem. Soc.* **1968**, *90*, 2587. (b) Olah, G. A. *Halonium Ions*; Wiley-Interscience: New York, 1975.

(8) (a) Strating, J. Wierenga, J. H.; Wynberg, H. *J. Chem. Soc., Chem. Commun.* **1969**, 3581. (b) Wierenga, J. H.; Strating, J.; Wynberg, H. *Tetrahedron Lett.* **1970**, 4579.

(9) Olah, G. A.; Schilling, P. A.; Westerman, P. W.; Lin, H. C. *J. Am. Chem. Soc.* **1974**, *96*, 3581.

(10) Slebocka-Tilk, H.; Ball, R. G.; Brown, R. S. *J. Am. Chem. Soc.* **1985**, *107*, 4505.

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Scheme 2

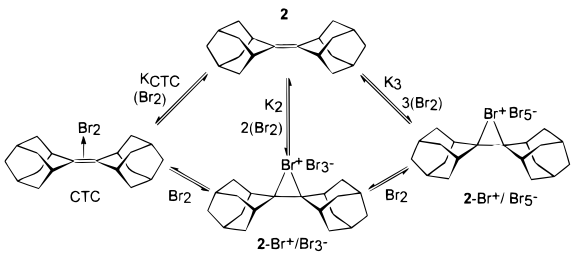
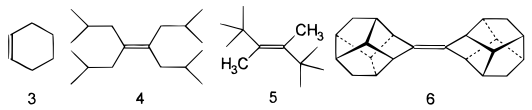


Table 1. Formation Constants (K_{CTC}) for Olefin−Br_2 Charge Transfer Complexes in Dichloroethane, T = 25 °C

olefin	K_{CTC} (M^{-1}) (25 °C)	ref
2	289(4)	12
3 (cyclohexene)	0.47	5a
4 (tetraisobutylethylene)	9.7	14
5 (2,2,3,4,5,5-hexamethylhex-3-ene)	84	5b
6 (*d,l*-trishomocubylidene-d_3-trishomocubane-d_3)	768	15
7 ((*E*)-2,2,5,5-tetramethyl-3,4-diphenylhex-3-ene)	1.2	18

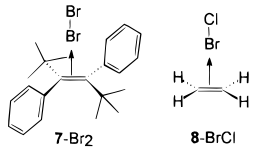
formed. Although these charge-transfer complexes between an olefin and Br_2 were widely known[11] and supposed intermediates in the electophilic addition,[1,4] it was not until 1985 that clear evidence of their being on the reaction pathway was uncovered.[5a] The main problem in ascertaining the role of the CTC during the reaction kinetics stems from the fact that, for most systems, the complex is very reactive and quickly forms bromonium bromide or tribromide ion pairs even in solvents of low polarity. Following the identification of the structure of **2**−Br^+, our group, in collaboration with that of Professor Giuseppe Bellucci (University of Pisa), undertook a study of the solution behavior of Ad═Ad and Br_2 in 1,2-dichloroethane.[12] From nonlinear least squares (NLLSQ) fitting of the UV−vis spectra of solutions containing varying [Ad═Ad] and [Br_2], it was found that the equilibrium shown in Scheme 2 was established, the value for the formation constant of the CTC (K_{CTC}) being 289 M^{-1}. Further NMR studies on this system[13] showed that the spectra of the mixtures in $ClCH_2CH_2Cl$ were highly variable as expected for a rapidly exchanging system in which the equilibrium concentrations of the various components were dependent on the exact concentrations of the reagents.

Given in Table 1 are the formation constants for complexes formed from olefins **2**−**7** and Br_2 in 1,2-dichloroethane. The K_{CTC} values vary by roughly 10^3-fold depending on the substitution pattern and electron-donating ability of the alkene as well as the steric crowding around the double bond which may preclude an optimum interaction in the CTC.[14] Of the olefins in the table, only Ad═Ad cannot proceed beyond the stage of the bromonium ion; **3** and **6** produce the normal dibromide addition products while **4** and **5** give double bond rearranged allylic



bromides (*vide infra*). This indicates that Ad═Ad is not an atypical olefin[16] with respect to its generation of a CTC with a high formation constant, and suggests that many of the things learned from studies of this olefin might be directly applicable to the bromination of reactive alkenes.

The data in Table 1 show the relationship between alkene structure and K_{CTC}, but provide no information about the structure of the CTC. Theoretical calculations indicate that little charge is transferred from the olefin to the halogen and that dispersion energy is the main driving force for complexation.[17] Bellucci and co-workers[18] have studied the first reported example[19] of an olefin (**7**)−Br_2 complex that cannot, for reasons of very severe steric compression, proceed beyond the stage of the CTC, the formation constant being 1.2 M^{-1}. The available thermodynamic parameters for the formation of the CTCs of **3**,[5a] **4**,[14] **5**,[5b] and **7**[18] (ΔH = −4.6 ± 0.2, −4.1 ± 0.4, −5.7 ± 0.4, and −3.3 ± 0.1 kcal/mol; ΔS = −17.0 ± 0.6, −9.2 ± 0.1, −10.3 ± 1.3, and −10.6 ± 0.5 cal/(K/mol), respectively) in 1,2-dichloroethane indicate a favorable enthalpy which is offset by an unfavorable entropy as expected for a process creating a complex from two reactants. Calculations of the structure of **7**−Br_2 at the MP2/6-31G* level[18] indicated that the optimum structure is a C_{2v} "T"-shape with a relatively unperturbed electron distribution and structure, the distance from the midpoint of the double bond and the first Br being 2.92 Å. This can be compared with an experimental value of 2.98 Å determined for the similar Br−double bond distance in **8**−BrCl using gas phase rotational spectroscopy where it was also found that the ethylene geometry is scarcely perturbed.[20]



Bromonium Ion

When the Ad═Ad/Br_2 equilibrium mixture (see Scheme 2) is sonicated in the presence of methyl triflate (MeOTf)

(11) (a) Dubois, J. E.; Garnier, F. *Spectrochim. Acta* **1967**, *A23*, 2279. (b) Bobrov, A. V.; Kimel'fel'd, Ya. M.; Mostovaya, L. M.; Mostovoy, A. B. *J. Raman Spectrosc.* **1978**, *7*, 88 and references therein. (c) Holroyd, S.; Barnes, A. J.; Suzuki, S.; Orville-Thomas, W. J. *J. Raman Spectrosc.* **1982**, *12*, 162 and references therein. (d) Fukuzumi, S.; Kochi, J. K. *J. Am. Chem. Soc.* **1981**, *103*, 2783; **1982**, *104*, 7599.

(12) Bellucci, G.; Bianchini, R.; Chiappe, C.; Marioni, F; Ambrosett, R.; Brown, R. S.; Slebocka-Tilk, H. *J. Am. Chem. Soc.* **1989**, *111*, 2640.

(13) Bellucci, G.; Bianchini, R.; Chiappe, C.; Ambrosetti, R.; Catalano, D.; Bennet, A. J.; Slebocka-Tilk, H.; Aarts, G. H. R.; Brown, R. S. *J. Org. Chem.* **1993**, *58*, 3401−3406.

(14) Brown, R. S.; Slebocka-Tilk, H.; Bennet, A. J.; Bellucci, G.; Bianchini, R.; Ambrosetti, R. *J. Am. Chem. Soc.* **1990**, *112*, 6310.

(15) Bellucci, G.; Bianchini, R.; Chiappe, C.; Gadgil, V. R.; Marchand, A. P. *J. Org. Chem.* **1993**, *58*, 3575.

(16) Up until the demonstration that **6** had a high formation constant for the olefin−Br_2 CTC, the highest value known for such complexes was that of Ad═Ad at 289 M^{-1} (ref 13). It was reasonably suggested (ref 2b, footnote 17b) that since Ad═Ad cannot proceed to products, its behavior and perhaps physicochemical properties were not representative of those of more normal olefins.

(17) (a) Prissette, J.; Seger, G.; Kochanski, E. *J. Am. Chem. Soc.* **1978**, *100*, 6941. (b) Kochanski, E. *Quantum Theory Chem. React. 1980−82*. **1981**, *2*, 177.

(18) Bellucci, G.; Chiappe, C.; Bianchini, R.; Lenoir, D.; Herges, R. *J. Am. Chem. Soc.* **1995**, *117*, 12001.

(19) Olah and Prakash (Olah, G. A.; Prakash, G. K. *J. Org. Chem.* **1977**, *42*, 580) have reported an apparent unreactivity of tetraneopentylethylene toward Br_2. Examination of molecular models indicates that this olefin may also form a CTC which is prevented, by steric compression, from proceeding to the bromonium ion.

(20) Bleomink, H. L.; Hind, K.; Legon, J. C. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1512.

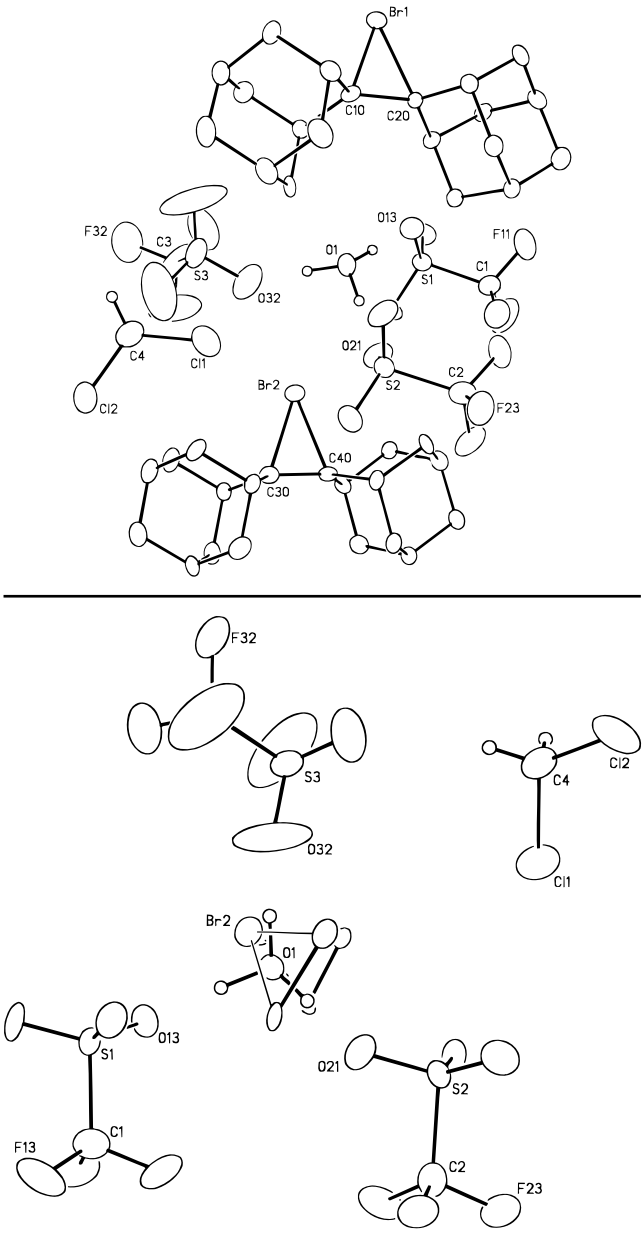


FIGURE 1. Two ORTEP views of the asymmetric unit in the structure of 2−BR$^+$/OTf$^-$. In (b) (bottom) is a view of the asymmetric unit down the Br_2-Br_1 axis highlighting the $CF_3SO_3^-$, H_3O^+, and dichloromethane molecule. All carbon atoms in the Ad═Ad groups except those bonded to the bromines are omitted for clarity.

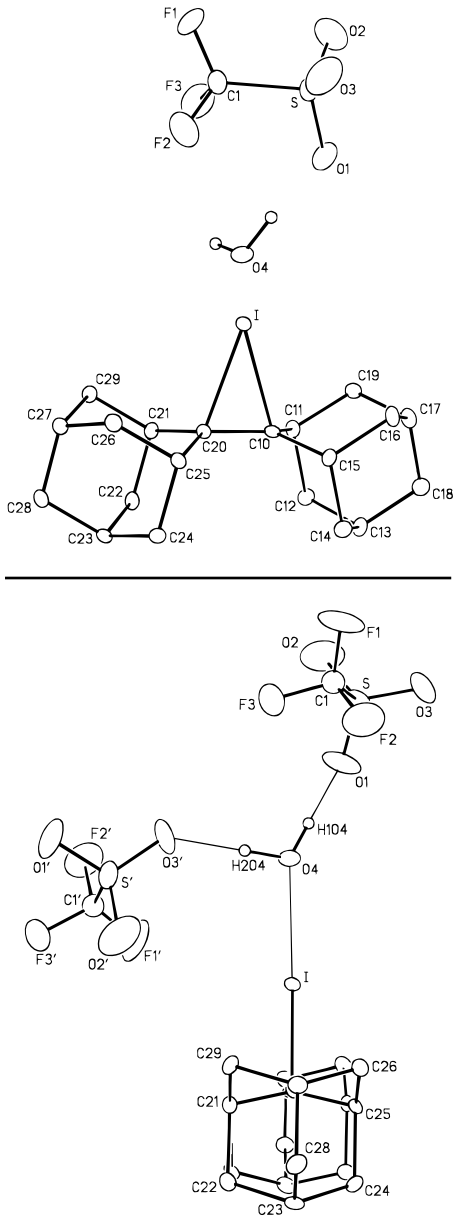
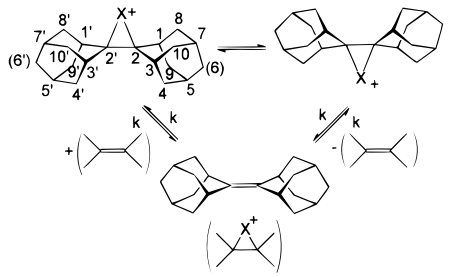


FIGURE 2. Two ORTEP views of the asymmetric unit of 2−I$^+$/OTf$^-$. (b) (bottom) shows an alternative view down the $C_{10}-C_{20}$ bond illustrating the interaction of the water molecule with the I and the symmetry-related triflates.

and the volatiles (CH_3Br, Br_2) are removed, a white solid remains which is characterized by ^{1}H NMR, ^{13}C NMR, and X-ray diffraction as the bromonium ion/$CF_3SO_3^-$ salt, **2**−Br$^+$/OTf$^-$.[21] Shown in Figure 1 is the ORTEP view of the bromonium triflate which indicates that the unit cell contains two bromonium ions held together by a layer consisting of three triflates, H_3O^+, and CH_2Cl_2, the latter two species coming from adventitious water and the solvent of crystallization. The corresponding iodonium ion can be synthesized by treating Ad═Ad with I_2 and AgOTf followed by removal of the AgI precipitate. The ORTEP view of the X-ray structure of **2**−I$^+$/OTf$^-$/monohydrate is shown in Figure 2. These two halonium ions have C_{2v} symmetry, and the carbon skeletons are nearly superimposable, the essential differences in structure being the central $C_{10}-C_{20}$ (Figures 1 and 2) bond lengths of 1.49 and 1.45 Å (0.15 and 0.11 Å longer than in the parent olefin) and C−X bond lengths which are 2.11 ± 0.02 and 2.35 ± 0.01 Å for the bromonium and iodonium ions, respectively.[21b]

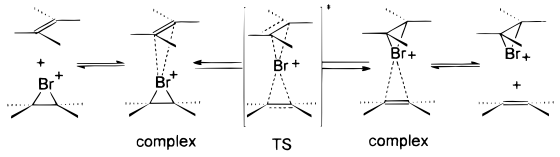
^{13}C NMR spectroscopy proves to be an effective tool for studying these ions in solution. The ^{13}C resonances for the carbons on the top side of the molecule ($C_{8,8',10,10'}$ adjacent to the X$^+$ in the left-hand structure in eq 2) are downfield of their counterparts ($C_{4,4',9,9'}$) on the bottom side. At −80 °C the ions each possess two perpendicular planes of symmetry, one containing the two central carbons and the halonium ion, and the other containing the X$^+$ and bisecting the central $C_2-C_{2'}$ bond. Addition of small amounts of Ad═Ad to the mixtures at −80 °C

(21) (a)Bennet, A. J.; Brown, R. S.; McClung, R. E. D.; Klobukowski, M.; Aarts, G. H. M.; Santarsiero, B. D.; Bellucci, G.; Bianchini, R. *J. Am. Chem. Soc.*, **1991,** *113*, 8532. (b) Brown, R. S.; Nagorski, R. W.; Bennet, A. J.; McClung, R. E. D.; Aarts, G. H. M.; Klobukowski, M.; McDonald, R.; Santarsiero, B. D. *J. Am. Chem. Soc.* **1994**, *116*, 2448.



(2)

broadens the resonances to ultimately give a single narrow line for $C_{4,4',8,8',9,9',10,10'}$ and one for $C_{5,5',7,7'}$. At coalescence the apparent structure has three perpendicular planes of symmetry. This indicates that there is a fast two-step exchange process which translocates the X^+ from the top to the bottom side of the molecule through the intervention of a second Ad═Ad molecule. The second-order rate constants for this site exchange between Ad═Ad and **2**−Br^+ or **2**−I^+ are 2×10^6 and $(7.6 \pm 0.8) \times 10^6$ M^{-1} s^{-1}, respectively, at −80 °C. The activation parameters for the site exchange of Br^+ in **2**−Br^+ are $\Delta H^{\ddagger} = 1.8 \pm 0.2$ kcal/mol and $\Delta S^{\ddagger} = -21 \pm 1$ cal/(K·mol).[21b] This low an enthalpy for Br^+ transfer between two Ad═Ad molecules indicates that the barrier for the reaction is largely determined by that of viscous flow through the solvent (CH_2Cl_2) and a stringent orientation requirement for the reactive encounters. Detailed *ab initio* multiconfiguration SCF calculations of the Br^+ transfer between two ethylenes[21] give a comprehensive picture of the changes in bonding accompanying the transfer. They indicate that the reaction coordinate consists of the three intermediate states shown in eq 3, with the two degenerate olefin−



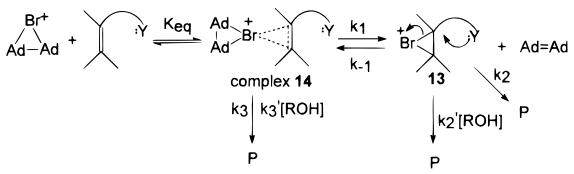
(3)

bromonium complexes being −4.2 kcal/mol lower in energy than the respective starting materials and the D_{2d} transition state being 9.3 kcal/mol above the free reactants. For the corresponding iodonium ion, the energies of the complexes and transition state for transfer are −4.7 and 1.9 kcal/mol relative to the free components.

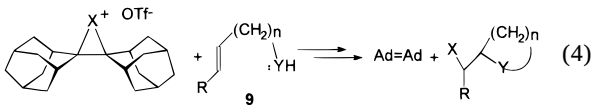
It should be pointed out that observation of the amazingly facile Br^+ or I^+ transfer between alkenes[21] was, up until 1991, completely unprecedented. Under normal conditions during bromination of reactive olefins in nonnucleophilic solvents, this process undoubtedly is occurring, but cannot be observed since there is no way to probe the Br^+ transfer between the olefins in competition with the product-forming steps. Nevertheless, the facility of the transfer in such a sterically encumbered system as Ad═Ad suggests that Br^+ transfer from **2**−Br^+ to other acceptor alkenes should occur readily.

We have verified this expectation for the halocyclization reactions depicted in eq 4.[22] Halocyclizations are particularly appropriate choices for reaction with **2**−X^+/OTf^- since, in the presence of the poorly nucleophilic triflate

Scheme 3

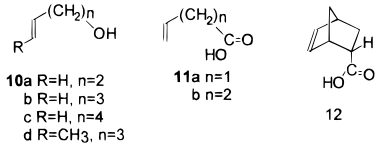


counterion, the nascent halonium ions from **9** can be trapped by an internal nucleophile. The kinetics of these



(4)

processes are monitored conveniently by observing the decrease in absorbance of the bromonium or iodonium ion triflates at 250 or 260 nm, respectively, in dichloroethane containing an excess of the acceptor olefin. There are several observations of note. Iodocyclization initiated by **2**−I^+ for a given case occurs 30−100-fold faster than bromocyclization. X^+ transfer and cyclization of the alcohols are fastest for formation of the five-membered ring, explicable[23] by invoking a complex mixture of OH inductively withdrawing effects superimposed upon an anchimeric assistance by Y: of the X^+ addition to the π-bond which is optimized when a five-membered ring can be formed. Comparison of the rate data for **10b,d** shows that a more highly substituted double bond reacts faster and, for a given ring size, lactonization is slower than ether cyclization (e.g., **10b** vs **11b**) which is a



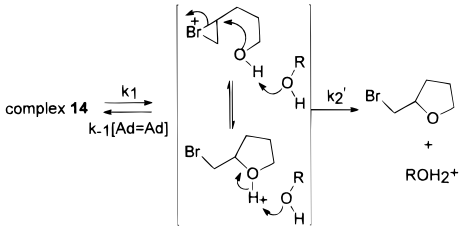
consequence of the greater inductive withdrawing ability of the COOH group relative to the OH. Oddly, in most of the bromocyclizations, added Ad═Ad markedly suppresses the reaction rate. In the cases of **10b** and **11b**, the reaction is completely suppressed at high [Ad═Ad]. In other cases added Ad═Ad suppresses the reaction rate to a certain point, but no further. Finally, in some of the cases, e.g., **10b**−**d**, the reaction exhibits kinetic terms which are second order in [alkenol]. In fact, for these cases, added propanol or pentanol will catalyze the reaction. None of the above behavior is seen for any of the reactions with **2**−I^+.

This seemingly complex behavior can be rationalized by the general mechanism given in Scheme 3 which includes two reversibly formed intermediates along the reaction pathway. The common species rate suppression exhibited by added Ad═Ad requires that there be at least one intermediate that can be captured by free olefin at a rate that competes with product formation. This intermediate is probably the nascent bromonium ion **13**. The rate with which the thermodynamically favorable transfer from **13** to Ad═Ad must be at least as fast or faster than the rate that Br^+ is transferred from **2**−Br^+ to Ad═Ad, e.g.,

(22) (a) Neverov, A. A.; Brown, R. S. *Can. J. Chem.* **1994**, *72*, 2540. (b) Neverov, A. A.; Brown, R. S. *J. Org. Chem.* **1996**, *61*, 962.

(23) Williams, D. L. H.; Bienvenue-Goetz, E.; Dubois, J. E. *J. Chem. Soc. B* **1969**, 517.

2×10^7 M^{-1} s^{-1} at 25 °C.[21] In the cases where added Ad=Ad suppresses the reaction to a certain point and no further, there must be another channel for formation of the product which we suggest involves direct cyclization within complex **14**. In Scheme 3 there are four channels for breakdown of these intermediates to products. Two of these, k_2 and k_3, involve spontaneous cyclization of **13** and complex **14**, while the remaining two involve a second alkene (in the case of the alkenols) or a molecule of alcohol, k_2'[ROH] and k_3'[ROH]. The suggested mechanism for this catalysis is shown in eq 5 where the second



(5)

ROH acts as a base to remove the proton from the intramolecular OH and assists cyclization of the nascent bromonium ion. For the ROH-promoted cyclization directly from the complex **14**, a similar general base removal of the proton from the attacking intramolecular OH group can be envisioned, but proton removal, ring closure, and dissociation of the Ad=Ad must be coupled processes.

As a final point, when a bromonium ion such as **2**−Br^+ is denied any route for product formation, it has only one reaction possibility. This is transfer of the Br^+ to an acceptor of some sort such as a reactive alkene (*vide supra*) or, less commonly considered, to Br^-, thereby regenerating the alkene and Br_2. The latter process would be formally equivalent to reversal of bromonium ion formation. To gain some information about the rate of Br^- reaction with the Br^+ of **2**−Br^+, we have undertaken stopped-flow experiments wherein **2**−Br^+/OTf^- is rapidly mixed with tetrabutylammonium bromide in $ClCH_2CH_2Cl$.[24] The reaction is monitored by observing the rate of formation of Br_3^- at 270 nm, this being formed by a diffusion-limited[25] reaction of Br_2 and Br^- (eq 6). At

$$(n\text{-Bu})_4N^+/Br^- + \mathbf{2}\text{-}Br^+/OTf^- \rightarrow (n\text{-Bu})_4N^+/OTf^- + Br_2 \xrightarrow[\text{fast}]{Br^-} Br_3^- \quad (6)$$

concentrations of 2.5×10^{-6} M **2**−Br^+ and 1×10^{-5} M tetrabutylammonium bromide, the reaction is completely over within the "dead time" of the instrument (~2 ms), giving a lower limit to the rate constant for the removal of Br^+ from the bromonium ion of 1×10^8 M^{-1} s^{-1}. The rapidity of this reaction undoubtedly means that reversal of bromonium ion formation can easily compete with product formation during the course of electrophilic bromination of reactive olefins (*vide infra*).

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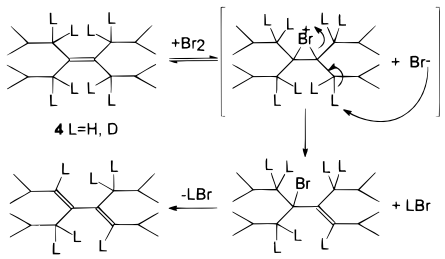
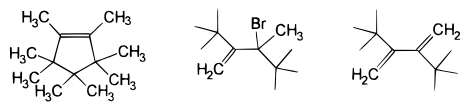
Scheme 4



Beyond the Bromonium Ion: Hindered but Reactive Olefins

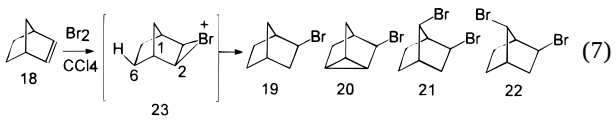
When a sterically congested olefin forms a bromonium ion for which the normal product-forming steps of addition are retarded, other reaction pathways will be chosen to produce atypical products. Among these are molecular rearrangements and elimination of an allylic H to form a double bond rearranged allylic bromide. Tetraisobutylethylene (**4**, TIBE) was originally reported[26] to form brightly colored solutions during bromination which suggested the formation of extensively conjugated products arising from a series of addition/eliminations. Subsequent work in our labs[14] showed that the reaction followed the course given in Scheme 4 with the production of a rearranged allylic bromide that decomposed to the diene which underwent further bromination/HBr elimination. This sort of rearrangement is mechanistically similar to that reported by Wynberg et al.[28a] where the reaction of NCS, NBS, or *tert*-butyl hypochlorite with tetrasubstituted ethylenes gives double bond rearranged allylic halides. Similarly, the bromination of sterically demanding olefins **5**[5b,27] and **15**[28b] has been reported to yield dienes and double bond rearranged allylic bromides. Particularly informative is the study of hindered systems that are perdeuterated at the allylic positions. For example, **4**-d_8 (Scheme 4, L = D) shows a significant primary deuterium kinetic isotope effect (DKIE) of 2.3 for bromination in acetic acid at 25 °C which can only be accommodated by the mechanism given in the scheme if the rate-determining step is the removal of one of the allylic C−L bonds.[14] This requires that all steps leading up to the proton removal, including the formation of the CTC and bromonium ion, be reversible. In the case of bromination of **4**, L = H, D, added acetate does not accelerate the reaction in acetic acid so the elimination of L−Br must occur from a bromonium/bromide ion pair and intermolecular bases such as acetate are incapable of effecting the proton removal. Primary DKIEs of 2.05 and 2.17 are seen for the bromination of **5**-d_6 at 25 °C in acetic acid and 1,2-dichloroethane, respectively,[5b] signifying that, in this bromination too, the rate-limiting step is removal of the allylic C−L to generate **16** which subsequently eliminates L−Br to yield **17**.



15 16 17

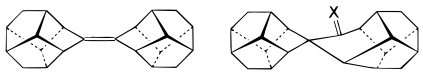
For other olefins the reaction can give large amounts of Wagner−Meerwein rearrangement. One of the most

notorious examples of this is bromination of norbornene (**18**)[29] which, after careful scrutiny,[30] was shown to give two monobromides (**19, 20**) and at least five dibromides, the ones formed in largest amounts being **21** and **22** (eq 7). Apparently **20**−**22** arise from a common intermediate,



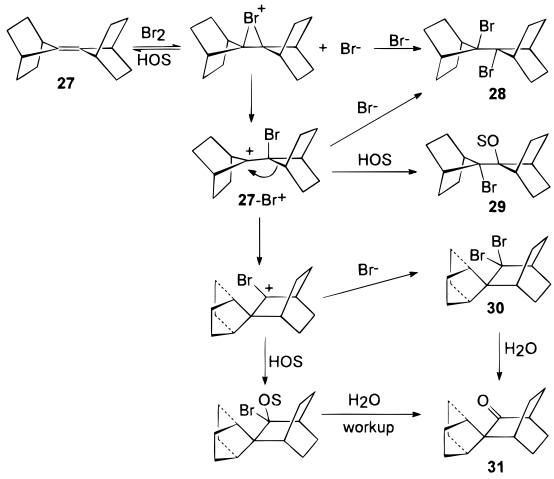
(7)

the *exo*-bromonium ion **23,** via removal of the C_6−H and C_6−C_2 bond formation or rearrangement of the norbornyl cation, respectively, while **19** arises from simple ionic addition of HBr to norbornene. Although the norbornyl system possesses a number of rearrangement pathways, including 6−2 hydride migration which can give rise to small amounts of the other dibromides alluded to above, more heavily substituted olefins appear to have less modes for rearrangement and therefore are somewhat easier to study. For example, Marchand and co-workers[31] have shown that *meso*-trishomocubylidene-d_3-homocubane-d_3 (**24**), when brominated in CCl_4 for 24 h gives, after workup, the rearranged ketone **25** which must have arisen from hydrolysis of the dibromide **26**.

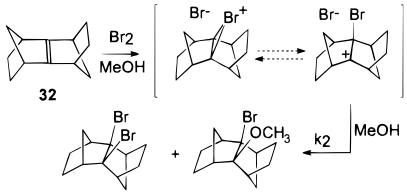


The mechanism for this sort of rearrangement can be understood by considering the situation for Br_2 addition to 7-norbornylidene-7′-norbornane (**27**)[32] which, in acetic acid, gives rise to four products as shown in Scheme 5.[33] The key step in producing the rearranged products (**30**, **31**) is the rearrangement that takes the β-bromocarbocation, **27**−Br^+, into the α-bromocation which then can be captured by Br^- to yield the rearranged dibromide (**30**). This was shown to produce the ketone on aqueous workup.[33b] Olefin **27** also provides direct kinetic evidence that the intermediate bromonium ion must be reversibly formed. As a function of increasing [Br^-], the rate constant for bromination in acetic acid drops dramatically: a variation in the [Br^-] from 0 to 0.04 M cuts the rate by 100-fold, suggesting a common ion rate depression which signifies the presence of an intermediate, the bromonium ion, which is driven back to starting materials in the presence of excess Br^-.[33,34]

Scheme 5



Scheme 6



Finally, we consider the bromination of *anti*-sesquinorbornene (**32**), which originally was reported[35] to react instantly in chlorinated hydrocarbons to yield the corresponding *cis*-dibromide. This olefin is an interesting one since it lacks the proclivity of its parent, norbornene (**20**), to undergo extensive rearrangement, and its structure allows only the formation of *cis* adducts. We have studied[36] its bromination in methanol as a function of added Br^-, and after accounting for the $Br_2 + Br^- \rightleftharpoons Br_3^-$ equilibrium,[34] there is no common ion rate depression, meaning that there is no intermediate that can be captured by external Br^- to re-form starting material. Furthermore, product analysis indicates that the dibromide/methoxybromide ratio is ∼9/91 and invariant to changes in added Br^-. This is accommodated by the mechanistic sequence given in Scheme 6 where the products are formed exclusively by collapse of the intimate ion pair. In view of the improbability of a frontside attack on the bromonium ion intermediate, the ion must open to a β-bromocarbocation which then collapses to products. On the basis of the likely rate constant for trapping of the ions by external Br^- (10^9−10^{10} M^{-1} s^{-1}), and the observed lack of such, a lifetime of 10^{-11} s for the ionic forms was suggested.[36] This value is slightly less than the experimentally determined lifetimes of 10^{-9}−10^{-10} s for the bromonium ions of cyclohexene, cyclopentene, tetramethylethylene, and styrene in methanol.[37]

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(32) Olefin **27** was originally reported to brominate to give **28** by Bartlett and Ho (Bartlett, P. D.; Ho, M. S. *J. Am. Chem. Soc.* **1974**, *96*, 627).
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(34) Addition of Br^- to a solution of Br_2 causes the instantaneous formation of an equilibrium amount of Br_3^-. Both Br_2 and Br_3^- are brominating agents, but the latter is much poorer which causes a deceleration of the bromination rate in the presence of Br^-. The deceleration seen in the case of **27** greatly exceeds what can be accounted for on the basis of the tribromide equilibrium, and therefore demands that there be a common ion rate retardation.[33]
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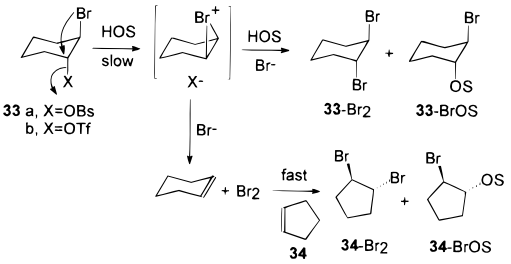
Scheme 7



Normal Bromonium Ions and Reversal of Their Formation

Prior to the 1990s it was generally considered that reversal of bromonium ion formation during the course of Br_2 addition to a double bond was an unimportant, although not unknown,[38] process. For the reaction of a normal, reactive olefin, it is a major problem to determine whether the ions are reversibly formed because of the short lifetime and the fact that once Br_2 and the olefin are re-formed, they ultimately give addition products. Therefore, most of the systems in which reversibility is implicated involve special features, such as benzylic carbons or isomerization of a double bond (e.g., stilbenes[38c,39]), or severe hindrance so that the product-forming steps are retarded by steric congestion.[38a,b,40] Reversibility of ion formation in the case of Ad═Ad (**2**),[8,10,12,21] TIBE (**4**),[14] 2,2,3,4,5,5-hexamethylhex-3-ene (**5**),[5b] and 7-norbornylidene-7′-norbornane (**27**)[32] is well established on kinetic or other grounds, but these too are hindered olefins in which reversal may be artificially promoted by the high barriers to the forward reaction.

The first indication that reversal might be more prevalent for normal olefins than was previously believed came from a series of experiments in which the *trans*-bromobrosylates of cyclohexene (**33a**) and cyclopentane (**34a**) were solvolyzed at 75 °C in acetic acid containing Br^- and an acceptor olefin, namely, cyclopentene and cyclohexene, respectively.[41] The experiments were confirmed in 1993 using the trifluoromethanesulfonate (OTf) of cyclohexene (**33b**), which was reactive at room temperature in both methanol and acetic acid.[42] The idea, outlined in Scheme 7 for **33**, was that the solvolyses of bromobrosylates or triflates of cyclohexene or cyclopentene should be subject to internal neighboring group assistance and produce the corresponding bromonium ions **33**−Br^+ and **34**−Br^+ which can be captured by Br^- to give Br_2 and the free olefin. The so-produced Br_2 then reacts with the excess scavenger olefin to produce its normal addition products. For **33b**, solvolysis in acetic acid containing 0.5 M cyclopentene and varying [Br^-] showed that there was more than twice as much of the cyclopentenyl addition products (**34**−Br_2 + **34**−BrOS) than dibromocyclohexane (**33**−Br_2).[42] Importantly, control experiments established that no direct attack of Br^- on **33b** which leads to elimination is occurring, and that *free* Br_2 is formed during the course of the reaction. Thus, during solvolysis of **33b,** the ratio of the transfer products (**34**−Br_2/**34**−BrOS) was 12.3, exactly the same as the ratio observed when Br_2 is added to cyclopentene in acetic acid under the same conditions. Furthermore, in the absence of Br^-, no cyclopentyl products were observed during solvolysis so that, under the reaction conditions, no direct transfer of the Br^+ from the bromonium ion of cyclohexane to cyclopentene can occur. Therefore, the only way that cyclopentyl products can be produced during the solvolysis is from the Br_2 produced from Br^- capture on Br^+ of the cyclohexenyl bromonium ion. The ratio of (**34**−Br_2 + **34**−BrOS)/**33**−Br_2 gives the relative amount of Br^- capture on Br^+ relative to C. In acetic acid and methanol the ratios are roughly 2.2 and 12, independent of the [Br^-], signifying surprisingly that Br^- in fact prefers to capture the ion on Br^+ rather than on carbon.

Conclusions

The indirect showing that a bromonium ion intermediate produced during solvolysis (which presumably has similar characteristics to the one produced during electrophilic Br_2 addition to an alkene) can be captured by Br^- on the Br^+ provides solid evidence that reversal is competitive with product formation arising from opening the bromonium ion even in the case of nonsterically congested olefins. This, coupled with the direct kinetic measurements[24] showing that **2**−Br^+ reacts with Br^- with a rate constant greater than 10^8 M^{-1} s^{-1}, indicates that reversal must now be accepted as the norm, and not an unusual occurrence relegated to a special class of hindered olefins where the product-forming steps are retarded. In the above we have presented recent work showing that the bromination of variously hindered alkenes can be stopped at the CTC (**7**[18]) or bromonium ion (Ad═Ad[10,21]) stage. Other hindered olefins can proceed beyond these steps, but usually give atypical, rearranged products. The study of hindered olefins also exposes a new phenomenon, the rapid transfer of Br^+ between olefins. This reaction likely occurs during normal brominations but cannot be observed because of the rapidity of the product-forming steps.

This Account is dedicated to the memory of the late Professor Giuseppi Bellucci of the University of Pisa with whom the author shared a collaboration dealing with the bromination of sterically hindered olefins for many years. In addition, the author thanks the talented researchers who are listed as co-authors of the publications emanating from his laboratories, and the Natural and Engineering Research Council of Canada for ongoing financial support.

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