

Noncatalytic Bromination of Benzene: A Combined Computational and Experimental Study

Andrey V. Shernyukov,^[a] Alexander M. Genaev,^{*[a]} George E. Salnikov,^[a,b] Henry S. Rzepa,^{*[c]} and Vyacheslav G. Shubin^[a]

The noncatalytic bromination of benzene is shown experimentally to require high 5–14 M concentrations of bromine to proceed at ambient temperatures to form predominantly bromobenzene, along with detectable (<2%) amounts of addition products such as tetra and hexabromocyclohexanes. The kinetic order in bromine at these high concentrations is 4.8 ± 0.06 at 298 K and 5.6 ± 0.11 at 273 K with a small measured inverse deuterium isotope effect using D₆-benzene of 0.97 ± 0.03 at 298 K. These results are rationalized using computed transition states models at the B3LYP+D3/6-311++G(2d,2p) level with an essential continuum solvent field for benzene applied. The model with the lowest predicted activation free energies agrees with the high experimental kinetic order in bromine and involves formation of an ionic, concerted, and asynchronous transition state with a Br₈ cluster

resembling the structure of the known Br_9^- . This cluster plays three roles; as a Br^+ donor, as a proton base, and as a stabilizing arm forming weak interactions with two adjacent benzene C—H hydrogens, these aspects together combining to overcome the lack of reactivity of benzene induced by its aromaticity. The computed inverse kinetic isotope effect of 0.95 agrees with experiment, and arises because C—Br bond formation is essentially complete, whereas C—H cleavage has not yet commenced. The computed free energy barriers for the reaction with $4Br_2$ and $5Br_2$ for a standard state of 14.3 M in bromine are reasonable for an ambient temperature reaction, unlike previously reported theoretical models involving only one or two bromines. © 2015 Wiley Periodicals, Inc.

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Introduction

Electrophilic substitution of aromatic compounds, including halogenation, is typically described by a two-stage mechanism with formation of a Wheland (arenium cation) intermediate at the first stage of the reaction.^[1] However, in a recent paper,^[2] an alternative addition-elimination (A_F) mechanism for electrophilic substitution, first proposed about a 100 years ago,^[3] has been firmly established for the chlorination of anisole by Cl₂ in CCl₄. It is of interest to reveal if such a mechanism takes place in the case of noncatalytic bromination of benzene itself. This reaction is unusual, as bromination of aromatic compounds with bromine is usually performed in the presence of a catalyst.^[4] The apparent inability of benzene to be involved in a noncatalytic reaction with bromine is noted in numerous textbooks^[5] (see also the Supporting Information for more examples) and is regarded as a dogma of aromaticity. To the best of our knowledge, there is only one article in which information on the noncatalytic bromination of benzene under mild (i.e., at ambient rather than reflux^[6]) conditions is presented.^[7] In a more recent paper,^[8] the uncatalyzed electrophilic bromination of aromatics in supercritical CO₂ has been described, with the suggestion that the efficiency of the CO₂ in this reaction is due to its high quadruple moment, Lewis acid character and low basicity. A recent theoretical study^[9] of the interaction of benzene and other aromatic compounds with bromine in the nonpolar solvent CCl₄ or in isolation concluded that the energetic barriers for benzene bromination under such conditions are too high for practicable mechanistic studies and that polar acidic media and/or Lewis acid catalysis are essential to accelerate the reaction to an observable rate. The main purpose of the present report is to explore further low energy mechanistic pathways for the uncatalyzed reaction between benzene and bromine and to establish if the computational models are supported by experiment.

Experimental Results for Reaction Between Bromine and Benzene

The kinetics of the reaction were studied at a large excess of bromine and/or at low benzene conversion, so that the change in the concentration of bromine could be neglected. It was found that under these conditions, the order of the reaction in benzene was pseudo first order, but that the rate of

[b] G. E. Salnikov

[c] H. S. Rzepa

We dedicate this article to Paul Schleyer, who was a passionate advocate of the fertile interplay between computation and experiment.

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[[]a] A. V. Shernyukov, A. M. Genaev, G. E. Salnikov, V. G. Shubin N.N. Vorozhtsov Novosibirsk Institute of Organic Chemistry, Siberian Branch of the Russian Academy of Sciences, 9, Acad. Lavrentiev Ave., Novosibirsk, 630090, Russian Federation E-mail: genaev@nioch.nsc.ru

Novosibirsk State University, Pirogova, 2, Novosibirsk 630090, Russian Federation

Department of Chemistry, Imperial College London, Exhibition Road, South Kensington Campus, London SW7 2AZ, United Kingdom. E-mail: rzepa@imperial.ac.uk



Table 1. Dependence of pseudo first order rate constant on Br_2 concentration (at 298 K, with 0.2 volume fraction of CD_2Cl_2).			
Volume fraction of Br_2	Concentration of Br_2 (M)	k_{1}, s^{-1}	
0.74	14.3	2.3×10^{-4}	
0.60	11.5	$7.4 imes 10^{-5}$	
0.43	8.3	1.5×10^{-5}	
0.29	5.7	$2.6 imes10^{-6}$	
0.18	3.5	1.9×10^{-7}	
0.084	1.6	$6.9 imes 10^{-9}$	

the reaction increased dramatically with increasing Br_2 concentration (Table 1, Scheme 1; full experimental details can be found in the Supporting Information).

The order of the reaction in bromine was determined by a differential method^[10] using the kinetic eqs. (1) and (2) relating a pseudo first order reaction to a formal reaction of order n+1, respectively. From these equations, we obtained eq. (3).

$$-d[\mathsf{PhH}]/d\mathsf{t} = k_1[\mathsf{PhH}] \tag{1}$$

$$-d[\mathsf{PhH}]/d\mathsf{t} = k_{n+1}[\mathsf{PhH}][\mathsf{Br}_2]^n \tag{2}$$

$$\log k_1 = n \log[\operatorname{Br}_2] + \log k_{n+1} \tag{3}$$

From the kinetic data inserted into eq. (3), we infer a reaction order in bromine of 4.8 ± 0.06 at 298 K and 5.6 ± 0.11 at 273 K (Fig. 1). According to these data, the rate of benzene bromination proceeding under mild conditions without any solvent or catalyst is high enough to be measured if a large concentration of bromine is used, the order of the reaction in bromine being about 5. We have excluded the following factors as contributing significantly to these rates.

- Catalysis by HBr produced by the reaction. (The autocatalytic effect of HCl formed as one of the reaction products was observed experimentally for anisole chlorination^[2] and studied theoretically for benzene chlorination:^[11] However, the presence of formed HBr does not influence the benzene bromination rate during the whole time course of the reaction [see e.g., Supporting Information, pp. S6–S7]).
- 2. Catalysis by light.
- **3.** Catalysis by triplet oxygen.

Further attributes of this reaction include:

- 1. The kinetic isotope effect $k_{\rm H}/k_{\rm D}$ measured for a mixture of C₆H₆ and C₆D₆ by ¹H and ²H NMR spectra was found to be 0.97 ± 0.03 (1 σ , Supporting Information, pp. S10–S12).
- **2.** The reaction has only a weak dependence on temperature: $k_1^{300}/k_1^{273} = 1.3$ at a concentration of 14.3 M bromine (Supporting Information, pp. S7–S9). A decrease in







Figure 1. Determination of the reaction order in bromine. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

the bromine concentration increases this dependence slightly (Fig. 1, Supporting Information p. S4)

- **3.** Replacing pure benzene with a 1:5 by volume mixture of benzene and CCl₄ at constant amount of bromine does not significantly affect the reaction rate constant. More polar methylene chloride (CD₂Cl₂) or traces of water markedly accelerate the reaction (Supporting Information, p. S4).
- 4. After keeping the reaction mixture for longer times at high bromine concentrations, traces of *p*- and *o*-dibromobenzenes are slowly formed (Supporting Information, pp. S7, S9), the kinetics of such polybromination being beyond the present study.

Computational Modeling

Our start point involved a search of the Cambridge crystallographic database for likely structures involving aggregated anionic bromine clusters, the outcomes in any initial formation of a putative Wheland intermediate (arenium ion). Unlike iodine, which forms linear zig-zag chains, bromine appears to favor bromine-centered dendrimer-like clusters, with two recent crystal structures shown in Figure 2.

Computational Methodology

The potential energy surface (PES) of benzene bromination characterizing the S_EAr and Ad_E mechanisms is potentially complex, even assuming only one bromine molecule is involved in the reaction. As the number of participating bromine molecules increase, the PES becomes more complex. At the initial stage of our calculations therefore, a fast DFT code as implemented in the PRIRODA program^[14] was used as a pathfinder, using a gas-phase model (See zip-archive in Supporting Information).^[15] This led us to conclude that reinvestigation using a solvent model was essential, as many of the identified stationary points so located were found to have



Figure 2. a) Br₉⁻ cluster^[12] b) Br₁₁⁻ cluster^[13] Bond lengths in Å. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

System $\Delta\Delta G_{298}$ @0.041 M ^[a] $\Delta\Delta G_{298}$ @14.3 M k^{H}/k^{D} , 298 K Data D Separated Benzene + 1 Br ₂ 0.0 0.0 189806.1	OI ^[b] 89804
Separated Benzene + 1 Br ₂ 0.0 0.0 189806. 1	89804
Benzene + 1Br ₂ 1.8 (3.2) -1.7 189804, 1	89806
S _E Ar reaction, Cs symmetry, 2 negative force constants 46.0 (50.9) 42.5 189612, 1	89704
S _E Ar reaction, C1 symmetry, 1 negative force constants 44.3 (47.3) ^e 40.8 0.75 189495, 1	89638
S _E Ar reaction, Cs symmetry, 2 negative force constants, biradical 39.7 36.2 1	89621
S _F Ar reaction, C1 symmetry, 1 negative force constants, biradical 38.6 35.1 0.84 1	89517
Ad _F , <i>cis</i> -1,2-addition 42.9 (47.5) 39.4 189500, 1	89555
Ad _E , <i>cis</i> -1,2-addition, biradical 37.9 34.4 0.83 1	91199
<i>ci</i> -1,2-dibromocyclohexadiene 19.3 15.8 1	91202
<i>trans</i> -di-axial-1,2-dibromocyclohexadiene 14.0 (12.4) 10.5 189526, 1	89706
trans-di-equatorial-1,2-dibromocyclohexadiene 22.0 18.5 1	89529
Bromobenzene + HBr – 9.9 (–11.9) – 13.3 189535, 1	89711
Separated Bromobenzene + HBr -12.7 (-15.0) -12.7 189535, 1	89711
Benzene + 2Br ₂ 4.6 (5.0) -2.3 189501, 1	89612
Benzene + Br ₄ 27.4 (30.2) 20.5 189554, 1	89703
S _E Ar reaction, C. symmetry, 2 negative force constants 33.8 (37.1) 26.9 189498, 1	89598
Ad _e , <i>trans</i> -1,2-addition 31.8 24.9 1	89496
Ad _e , <i>cis</i> -1,4-addition 31.4 24.5 1	89497
Ade. trans-1.4-addition, first C—Br 29.3 22.4 1	89516
Ad-, trans-1.4-addition, Wheland intermediate 23.7 16.8 1	89524
Ade. trans-1.4-addition, second C—Br 30.5 23.6 1	89515
trans-1.4-dibrobromocyclohexadiene + Br ₂ 17.2 10.3 1	89537
$c_{1}-14$ -dibrobromocyclobexadiene + Br ₂ 19.4 12.5 1	89544
trans-1.2-dibrobromocyclohexadiene + Br. 16.3 9.4 1	89538
Bromobenzene + HBr + HBr ₂ $-5.5(-7.6)$ -12.4 189539.1	90787
Separated Bromobenzene + HBr + 1Br ₂ $-12.7(-15.0)$ -12.7 189535.1	89711
Benzene + 3Br., 7.8 – 2.6 1	89505
S-Ar concerted substitution. C., 2 negative FC 30.1 19.7 1	91206
S-Ar concerted substitution (1 1 negative EC 266 162 094 1	91257
Ad- trans-12-addition 262 158 1	91204
SAr stepwise substitution. C—Br bond formation 28.7 18.3 0.91 1	91224
SAr stepwise substitution. Wheland intermediate 17.6 7.2 1	91230
SAr stepwise substitution, proton removal 219 115 1	89581
trans 12-dipropromocyclobexadiene + $2B_{12}$ 20.3 6.8 1	89528
Bromohenzene + HBr + 2Br ₂ -12 -116 1	89599
Separated bromobenzene + HBr + 2Br ₂ $-12.7(-15.0)$ $-12.7(-15.0)$	
Benzene + 4Br., 12.2 - 1.7 1	89750
S-Ar concerted substitution. C., 1 negative EC 36.5 22.6 0.93 1	89722
S-Ar concerted substitution. C., 1 negative FC 26.5 12.6 0.95 1	91241
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	89771
Separated bromobenzene + HBr + $3Br_2$ -127 (-15.0) -127 (-15.0)	0,7,7,1
Benzene + 5Br. 157 -17 1	89768
SAr concerted substitution C. 2 negative EC 356 182 1	89705
SAr stepsize substitution, C-Br formation 32.0 14.6 0.95 1	91237
TS-Ar stepwise substitution. Wheland intermediate 213 39 1	91238
TS-Ar service substitution proton removal 222 4.8 1	91236
Bromohenzene + HBr + 4Br, $70 - 104$ 1	89767
Separated bromobenzene + HBr + $3Br_2$ -12.7 (-15.0) -12.7 (-15.0)	

[a] B3LYP+D3/6-311++G(2d,2p)/SCRF = benzene (B2PLYPD3/6-311++G(2d,2p)/SCRF=benzene). Relative free energies in kcal/mol, for a standard state of 0.041M. [b] A digital repository identifier (DOI), resolved as e.g. http://doi.org/10.14469/ch/189499.



Figure 3. IRC computed for the synchronous asymmetric S_EAr reaction between benzene and $1Br_2$ on a closed-shell pathway, showing a) the energy profile and b) the energy gradient norm. The red arrow indicates the region of a hidden intermediate approximately corresponding to an arenium cation. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

calculated dipole moments >10D. Accordingly, these were then reinvestigated at a higher level with inclusion of a solvation correction as described below. Transition state models based on n = 1-5 Br₂ units were constructed in this manner, informed by the observed reaction order in bromine of ${\sim}5$ at high concentrations and the structural motifs shown in Figure 2. Our chosen computational model used the B3LYP density functional as implemented in the Gaussian program,^[16] which is a thoroughly explored method for a wide variety of reactions, and combined with the 6-311++G(2d,2p) basis set used in the earlier study of this system. $\ensuremath{^{[9]}}$ We have also added Grimme's D3 dispersion correction^[17] together with the Karplus and York smoothed-cavity self-consistent reaction field (SCRF) continuum solvation model with benzene specified as the solvent.^[18] We retained the benzene continuum solvation model for higher mole fractions of Br₂ noting that the dielectric constants of liquid bromine (\sim 3) and benzene (2.3) are similar and that mixed-solvent models are not readily supported. Selected models for n = 1 and 2 Br₂ units were then checked by reoptimization at the B2PLYP+D3 double-hybrid method^[19] using the same basis set and solvation model (such a calculation is too expensive for larger clusters, and especially so for characterization using an intrinsic reaction coordinate [IRC]) The B2PLYP+D3 barriers obtained were only \sim 3 kcal/mol higher than the B3LYP method. IRCs leading from the transition states at the B3LYP-level established the nonstochastic trajectories, leading to reactant and product for all transition states. The relative total energies along the reaction paths are presented in Table 2 for standard states of 1 atm (0.041 M) and 350 atm (14.3 M).

We next discuss individually the results obtained for each of the five models of $(Br_2)_n$. Full interactive 3D models of all the stationary points, along with animations of the IRCs are available in the interactive version of Table 2.^[20]





Figure 4. IRC computed for the synchronous asymmetric S_EAr reaction between benzene and $1Br_2$ on an open-shell pathway, showing a) the energy profile with the computed structure (lengths, in Å) shown as an inset, b) the energy gradient norm. The red arrow indicates the region of a hidden intermediate approximately corresponding to a biradical comprising a bromine atom and bromocyclohexadienyl radical. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Benzene + $1Br_2$

The stationary point for the S_EAr mechanism located when a plane of symmetry is imposed shows as a second-order saddle point. If an IRC is computed based on the most negative force constant, an entirely concerted single-stage profile emerges rather than the classical two stage one involving the Wheland

intermediate, although there is a clear sign of the arenium cation participating as a so-called hidden intermediate^[21] (Fig. 3b). Another characteristic is the relatively flat potential in the region of the transition state with v_1 having the relatively low value of $64i \text{ cm}^{-[1]}$. The second negative force constant ($8i \text{ cm}^{-1}$) corresponds to deviation from C_s symmetry, and the reason for this emerges most clearly with the product, a hydrogen-bonded



Figure 5. IRC computed for the synchronous asymmetric Ad_E reaction between benzene and $1Br_2$ on an open shell biradical pathway, showing a) the energy profile with the computed structures (lengths, in Å) shown as insets, b) the energy gradient norm. The red arrows indicate the region of hidden intermediates. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

complex between bromobenzene and HBr. The proton of the latter is directed away from the plane of symmetry toward the *ortho*-position of the bromobenzene, induced by the *o/p*-directing nature of the bromine substituent. (The positioning of hydrogen bonds to the aryl ring as determined from crystal structures can also be used to demonstrate the directing influence of electron donating and withdrawing groups; H. S. Rzepa, J. Chem. Ed., submitted. See also http://www.ch.imperial.ac.uk/ rzepa/blog/?p =13962. Accessed 5th May, 2015). A true transition state with just one imaginary transition mode reveals a fully concerted, albeit asynchronous reaction with an arenium cation making an appearance only as a hidden intermediate^[21] (Fig. 3). The very high barrier to reaction with 1-2Br₂ has already been remarked upon.^[2,9]

Such high barriers tend also to be associated with multireference character for the wavefunction.^[22] Indeed, a brokensymmetry unrestricted calculation reveals biradical character for the central region close to the transition state, but closed shell behavior closer to reactant or product. Although the barrier decreases by about 4.6 kcal/mol compared with a spin-restricted closed shell calculation, the essential features remain very similar. These are of an asynchronous S_EAr substitution reaction, with the transition state being defined by largely completed C—Br bond formation and C—H bond cleavage occurring only well after the transition state. Both are on the same concerted reaction path with again evidence of a hidden rather than an explicit intermediate, now with biradical rather than ion-pair character (Fig. 4). The overall energetics corresponds to an exo-energic reaction of -12 to -15 kcal/mol.

 Ad_E cis-addition across a double bond was found to correspond to a separate reaction profile. As with the S_EAr route, the wavefunction manifests biradical character close the transition state (Fig. 5) and v₁ has the rather higher value of 230*i* cm⁻¹. The product is *cis*-1,2-dibromobenzene in which one bromine is

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Figure 6. IRC computed for the synchronous asymmetric S_EAr reaction between benzene and $2Br_2$ on the closed-shell pathway forming bromobenzene + HBr + Br₂, showing a) the energy profile with the computed transition state structure (lengths, in Å) shown as an inset, b) the energy gradient norm and starting from a geometry with C_s symmetry and two negative force constants. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

axial and the other is equatorial. Remarkably, the axial C—Br bond is significantly lengthened (2.06 Å) compared with the equatorial one (1.98 Å), because of hyperconjugation of the axial C—Br bond with the diene leads to partial rearomatization of the ring. The free energy barrier for this alternative addition route is only 3 kcal/mol lower than the substitution mechanism; the height of the barriers means that neither is a feasible thermal reaction.

Benzene + 2Br₂

The significant difference for this potential is that the transition state regions now have closed shell character only. The stationary point located when a plane of symmetry is imposed is again a second-order saddle point (v_1 42 and 17*i* cm⁻¹). The IRC following the more negative force constant vectors (of A' symmetry) corresponds to a concerted but asynchronous S_EAr mode, in which C—Br bond formation is largely completed prior to any



Figure 7. IRC computed for the synchronous asymmetric Ad_E reaction between benzene and $2Br_2$ on closed-shell pathway forming *trans*-1, 2-dibromocyclohexadiene showing a) the energy profile with the computed-transition state structure (lengths, in Å) shown as an inset, b) the energy gradient norm. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

C—H bond removal, but with no evidence of hidden (ionic) intermediates (Fig. 6). The free energy barrier (Table 2) is notably reduced compared with the 1Br₂ reaction, but is still too large to be a facile thermal reaction at around room temperatures.

If the symmetry restriction is removed by optimization following the second negative root vectors of A" symmetry, no S_EAr path was located. Instead, only the Ad_E path was identified but with the subtle difference that the product corresponds to *trans* rather than *cis*-1,2-addition (Fig. 7), in which the formation of one C—Br bond is again largely complete and the second is still very incomplete. The transition state free energy is lowered by ~2 kcal/mol compared with the S_EAr second-order stationary point, with a value that is starting to correspond to a slow thermal reaction at reflux temperatures (for benzene). Compared with the formation of bromobenzene and HBr, which is an exo-energic thermodynamic sink, the products of this path are endo-energic by ~13 kcal/ mol, with the implication that the reverse free energy barrier (~15 kcal/mol) corresponds to a rapid thermal reaction at ambient temperatures.

The addition of a second active Br_2 to the system also significantly increases the complexity of the potential surface. Thus, two further alternative Ad_E paths can also be located corresponding to 1,4 addition. The first follows a concerted route (v_1 64 cm^{-1}) but requires an unusual high-energy allotrope of bromine, Br_4 (Fig. 8a) and the product is the *cis*-1,4-adduct (Fig. 8c). The second stepwise alternative mechanism (v_1 48 cm⁻¹) features the first appearance of an intermediate arenium cation (Wheland intermediate) on the path to forming the *trans*-1,4adduct and overall is the lowest energy route (Table 2).



Figure 8. Geometries of key stationary points for Ad_E paths for benzene + $2Br_2$, showing a-c), a concerted addition to form cis-1,4-dibromocyclohexadiene starting from the high energy allotrope Br_4 a). A stepwise route d-h) starting from the low energy form $2Br_2$ d) to trans-1,4-dibromocyclohexadiene involves a Wheland intermediate ion-pair f) and involving two transition states e) and g) either side of f). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]



Figure 9. IRC computed for the asynchronous asymmetric S_EAr reaction between benzene and $3Br_2$ on the closed-shell pathway forming bromobenzene + HBr + 2Br₂, showing a) the energy profile with the computed geometries (lengths, in Å) shown as insets, b) the energy gradient norm, with the red arrow, indicating the position of a hidden Wheland intermediate. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]



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Figure 10. IRC computed for the asynchronous symmetric S_EAr reaction between benzene and $3Br_2$ on the closed-shell pathway forming bromobenzene + HBr + $2Br_2$, showing a) the energy profile computed for the gas phase, b) computed with a continuum solvent model for benzene, c) the dipole moment computed for the gas phase, and d) computed with a continuum solvent model. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

$Benzene + 3Br_2$

As with 2Br₂, the C_s symmetric for S_EAr transition state has two negative computed force constants (v_1 58, 8 cm⁻¹) the vectors again having, respectively, A' and antisymmetric A'' symmetry. A true asymmetric transition stationary point 3.5 kcal/mol lower in energy can be located which reveals a concerted asynchronous nature for the path (Fig. 9a).

The S_EAr route is adjacent to an Ad_E reaction path for *trans*-1,2-addition (v_1 52 cm⁻¹) which is 0.4 kcal/mol lower in free energy (Table 2).

As noted previously, the previous reaction paths are all computed with inclusion of a continuum solvation model. It is instructive at this stage to illustrate the effect solvation has on the reaction. This is illustrated by comparing the energies of the reaction paths with and without inclusion of solvation for the symmetric S_EAr mechanism (Fig. 10). The solvent-stabilization for reactant and product is modest (~3–5 kcal/mol), but substantial (~11 kcal/mol) in the region of the transition state. The dipole moments increase dramatically in the

region of the transition state. When the solvent model is applied, the dipole moment increases by \sim 4D, and the large value persists for longer along the reaction path.

An equally interesting solvent response can be seen in the computed C—H and C—Br bond lengths participating in the transition state (Fig. 11). The more dramatic difference is induced for the former bond, with its removal being significantly postponed until well after the transition state is passed when solvation is included. The response on the C—Br bond is much smaller.

The increasing complexity of the potential surface is further illustrated by the location of an isomeric S_EAr reaction pathway, which is stepwise in nature involving a true rather than a hidden Wheland intermediate (Fig. 12). The rate determining step of this alternative mode is 2.1 kcal/mol above the concerted S_EAr alternative and corresponds to C—Br bond forming (v_1 30 cm⁻¹).

Benzene + $4Br_2$

Whereas all the previous stationary points located for S_EAr mechanisms with an imposed plane of symmetry had an antisymmetric imaginary vibration that forces an out of plane distortion, the incorporation of four Br_2 molecules now reveals (Table 2) a symmetric-concerted pathway for substitution (v_1 25*i* cm⁻¹),



Figure 11. IRC computed for the asynchronous symmetric S_EAr reaction between benzene and $3Br_2$ on the closed-shell pathway forming bromobenzene + HBr + $2Br_2$, showing a) the C—H bond length computed for the gas phase, b) computed with a continuum solvent model for benzene, c) the C—Br bond length computed for the gas phase, and d) computed with a continuum solvent model. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]





Figure 12. IRC computed for the reaction between benzene and $3Br_2$ on the closed-shell pathway forming an arenium cation (Wheland) intermediate showing a) the energy profile with the computed geometries (lengths, in A) shown as insets, b) the energy gradient norm. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

which then follows a valley ridge down from the transition state to a desymmetrization point where the forming HBr bifurcates to one of the two *ortho*-positions in the product bromobenzene to establish a hydrogen bond. More importantly, a secondconcerted transition state can be located which is lower in free energy than the first by 10 kcal/mol (Table 2) and which reveals a new asymmetrical structural motif (Fig. 13). The key feature is the incorporation of a Br_7^- like cluster with a central Br atom from which radiate three dendritic bromine arms. One serves to deliver a Br^+ electrophile to the benzene, the second serves later on the pathway after the transition state as a base to remove the proton from the ring and the final arm anchors the bromine cluster to the benzene via weak noncovalent interactions (NCI)^[23] (Fig. 13b). The structure of the key Br_7^- unit is similar to the crystallographic structure for a Br_9^- system (Fig. 2a). An IRC for this lower energy transition state is shown in Figure 14, along with various computed properties along the path. As with the smaller bromine clusters, the concerted transition state involves almost complete C—Br bond formation and almost no C—H cleavage. After the transition state is passed, a hidden Wheland intermediate precedes the proton removal. The dipole moment reaches its maximum value of almost 16D at the transition state, but this ionic character lasts until the proton is fully transferred.

Benzene + $5Br_2$

As with $3Br_2$, the C_s symmetric geometry for S_EAr substitution again has two computed negative force constants (v_1 45*i*, 12*i* cm⁻¹) but a lower energy asymmetric true transition state can also be



Figure 13. Geometry of the lower energy transition state for the S_EAr path for benzene + $4Br_2$, for concerted reaction to form bromobenzene + HBr + 3Br2 showing a) key lengths, in Å and b) the NCI analysis (color code; blue = strongly stabilizing, green = weakly stabilizing, yellow, red = destabilizing).



Figure 14. Computed properties along the S_EAr_{IRC} path for benzene + $4Br_2$, for concerted reaction to form bromobenzene + $HBr + 3Br_2$ showing a) the relative total energy, b) the gradient norm, with the feature indicated by the arrow corresponding to a hidden Wheland intermediate, c) the dipole moment, d) the forming C—Br length, and e) the cleaving C—H length. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]



Figure 15. Geometry of the lower energy transition state for the S_EAr path for concerted reaction to form bromobenzene + HBr + 4Br2 showing a) key lengths, in Å and b) the NCI analysis (color code; blue = strongly stabilizing, green = weakly stabilizing, yellow, red = destabilizing).

located involving a four-armed Br_9^- cluster (Fig. 15, cf. the crystal structure shown in Fig. 2a). The geometry is very similar to the $4Br_2$ transition state, but the additional fourth bromine chain radiating from the central atom now plays no active role and the gradual decrease in activation barriers from $1Br_2$ to $4Br_2$ is now reversed (Table 2) because of the effects of the entropic organization required.

An IRC reveals the system to be again finely balanced between an asynchronous process in which C—Br bond formation and C—H cleavage are on a concerted path and a stepwise process involving a discrete Wheland/arenium cation intermediate. While the latter can be located as a species with only real vibrational modes (Table 2), it sits in such a shallow energy minimum that the computed IRC path appears to treat it merely as a hidden intermediate (Fig. 16). It has become apparent that with such shallow potentials, a variety of trajectories of similar energy are probable. It is not currently feasible to compute the quantum molecular dynamics trajectory distribution for such systems, but would clearly be desirable when this does become possible.

Energies and Kinetic Isotope Effects

The standard free energy of activation, involving thermal corrections derived from classical vibrational partition functions, has a standard state of 1 atm (0.041 M at 298 K). The procedures for other standard states are explained here^[24] and involve a correction to 14.3 M (350 atm) by subtracting 3.467 kcal/mol from the bimolecular free energies and appropriate multiples of these values for higher order complexes or transition states.

The first two aspects to note are that the models constructed with 1-2 Br₂ units have free energy barriers at 0.041 M that are too large to explain a reaction occurring at ambient temperatures, and that slightly lower free energy pathways corresponding instead to *cis*-1,2 addition (1Br₂) or *trans*-1,2 and 1,4 addition (2-3 Br₂) also exist. The addition products, however, are endo-energic by ~15 kcal/mol, implying the reverse barriers would be easily accessible at these temperatures and that the substitution product bromobenzene + HBr is the thermodynamic sink for the reaction. With 3Br₂, the barriers are lowered by ~6 kcal/mol, revealing the first signs of thermally accessible reactivity, and again the low-

est energy routes correspond to (reversible) addition. Despite the entropic penalty, $4Br_2$ has the lowest barrier for S_EAr substitution, whereas for $5Br_2$ entropy now starts to impact negatively. For the standard state of 14.3 M, the entropic penalty is lessened. For our $4Br_2$ model, we estimate the overall free energy barrier as 12.6 kcal/mol (relative to separated reactants, Table 2), +1.7 (correction relative to the resting state of the reactants) together with an estimated correction of ~+3 kcal/ mol derived from the probably more accurate B2PLYP+D3 barriers for the smaller clusters, giving a final value of ~17.3 kcal/ mol.

As the energetics reveal the viability of reversible addition reactions, we next review what is known about such pathways. The ability of bromine to react with polybenzenoid hydrocarbons forming addition products was known^[25] but for benzene itself this reaction has not hitherto been reported (As far as we know, addition of bromine to benzene in darkness is unknown. α Hexabromocyclohexane is formed with light).^[26] However, we have found that even for benzene, addition products are formed provided that the bromine concentration is high enough (>5 M). The detected addition products include three stereoisomers of 3,4,5,6-tetrabromocyclohexene as well as α - and β -hexabromocyclohexanes, their total amount being about 0.5-2% of the quantity of the reacted benzene (see Supporting Information, pp. S7-S10). The structures of the addition products were determined by 2D NMR (Scheme 2; Supporting Information, pp. S13–S21).

We tried to detect intermediate dibromocyclohexadienes but none were ever observed. The 1,4-addition product, 3,6dibromocyclohexa-1,4-diene was noted^[27] as a product of the reaction of cyclohexa-1,4-diene with N-bromosuccinimide (Scheme 3). However, in our hands, the reaction with Nbromosuccinimide does not yield cyclohexadienes and results instead in formation of a mixture of products containing tribromocyclohexene isomers. Their structures have again been determined by 2D NMR (Supporting Information, pp. 523–526). We believe that dibromocyclohexadienes are kinetically unstable intermediates that can either add a second molecule of bromine, eliminate HBr or reverse back to Br₂ immediately after formation.

We infer that a key intermediate of the addition reaction of bromine to benzene should be 1,2-*trans*-dibromocyclohexadiene according to the following considerations:



Figure 16. The S_EAr path for benzene + $5Br_2$, for concerted S_EAr addition to form bromobenzene + HBr + 4Br2, showing a) the energy profile with the computed stationary point structures structure (lengths, in A) shown as an inset, b) the energy gradient norm with arrow indicating a Wheland-like hidden intermediate preceding the proton removal. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

- Among all possible products of the first stage of addition (1,2-*cis*, 1,2-*trans*, 1,4-*syn*, 1,4-*anti*-dibromocyclohexadienes) 1,2-*trans* is predicted to be the most stable (Table 2 and Fig. 17^[19]).
- **2.** Only three tetrabromocyclohexene isomers are observed experimentally (gray-outlined structures on Fig. 17). Assuming that they all have to be formed by 1,2 and 1,4

additions from a single intermediate, such an intermediate can be only the 1,2-*trans*-dibromocyclohexadiene.

3. It is reported^[29] that for the 1,3-cyclohexadiene system, the 1,2-*trans* (major), and 1,4-*syn* (minor) Br₂ addition pathways are realized. These data are in a good accordance with our supposition: the expected intermediate 1,2-*trans*-dibromocyclohexadiene gives the major products RSRS



Scheme 2.

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and RSSR by 1,2-*trans* addition, and the minor product RRRS by 1,4-*syn* addition (solid paths on Fig. 17, see Supporting Information, p. S15 for kinetic data).

Kinetic Isotope Effects

For an S_EAr reaction in which the rate-limiting step is formation of the carbon-electrophile bond, the change in hybridization at the carbon center from sp² to sp^[3] would induce an inverse isotope effect, whereas if the rate-limiting step is C-H cleavage than a large primary effect would be expected.^[30,31] As these provide a good indication of the nature of the rate-limiting transition state,^[32] we have computed ${}^{1}\text{H}/{}^{2}\text{H}$ kinetic isotope effects for selected transition states using C₆D₆ for comparison with our measured value of 0.97 \pm 0.03. For the $S_{E}Ar$ reaction involving 1Br₂ at 298 K, inverse values of 0.75 and 0.84 for the closed shell and biradical procedures, respectively, were obtained and 0.83 for the biradical Ad_F addition. The latter in particular is typical of addition to an sp² center.^[33] We have already established, however, that the 1Br₂ reaction is not a good model on the basis of the activation barrier alone and the predicted isotope effect confirms this. For the (closed shell) concerted S_EAr reaction involving $3Br_2$ at 298 K, ${}^{1}H/{}^{2}H = 0.94$, whereas a value of 1 H/ 2 H = 0.91 is obtained for the related stepwise route leading to a Wheland intermediate (Table 2). This difference between the fully concerted and the stepwise pathways is probably too small to confidently distinguish between the two alternatives.



Figure 17. Addition reaction paths of bromine with dibromocyclohexadienes. The geometries have been optimized using the riMP2/L1^[28] method without any corrections, the total energy of noninteracting C_6H_6 and $2Br_2$ is assigned to zero. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

The bromine isotope effect for the concerted substitution is $^{79}\text{Br}/^{81}\text{Br} = 1.0053$, which suggests that the product bromobenzene should have a slightly higher ratio of $^{79}\text{Br}/^{81}\text{Br}$ than the natural abundance. Again, this may be too small an effect to be measured. The Ad_E alternative for *trans*-1,2-addition gave the larger inverse value of $^{1}\text{H}/^{2}\text{H} = 0.86$. The calculated isotope effects for the larger 4Br_2 and 5Br_2 models converge to a value of 0.95, which is in good agreement with measurement.

Conclusions

Computational exploration of the reaction between bromine and benzene shows a highly complex energy surface emerging leading to a variety of addition products in addition to the standard substitution products as the reaction sink. As the number of bromine atoms participating in the transition state increases, thermally accessible reaction pathways emerge, especially at higher concentrations such as 14.3 M. The structure of the transition states resembles the crystal structures of the Br9 and Br₁₁ anions, which are unique to bromine as a halogen. These dendritic-like clusters facilitate the bromination of benzene by delivering in a single unit both the electrophile and base needed for substitution, as well as anchoring the unit to the benzene via CH···Br interactions. Both experiment and computation are consistent in revealing an associated high order in bromine concentration, an unusual and possibly unique feature of this mechanism. Pathways for both 1,2- and 1,4-addition emerge as competitive with substitution energies, but as the endo-energic products of these pathways have very low reverse barriers, they only represent kinetically accessible routes and not the thermodynamically stable outcomes. The textbook dogma that under mild conditions (ambient temperatures, no catalyst) bromine and benzene do not react is, therefore, shown to be true only for dilute solutions of bromine. The partial loss of aromaticity required of a Wheland-like species on the S_FA reaction pathway is more than offset by the energy gains, resulting from formation of these bromine anion clusters.

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Keywords: bromination · benzene · polybromide anions

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Additional Supporting Information may be found in the online version of this article.

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