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Kinetic Isotope Effects for the C–H Activation Step in Phase-Transfer Halogenations of Alkanes

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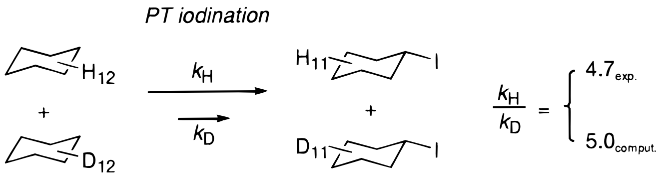
ABSTRACT



Within the scope of phase-transfer halogenations (Br and I) of alkanes, significant H/D kinetic isotope effects (KIE = 4–5) indicate that hydrogen abstraction is rate limiting. The excellent agreement of computed and experimentally determined H/D KIE as well as trapping experiments support the involvement of trihalomethyl radicals in the activation step.

H/D kinetic isotope effects (KIEs), predicted as early as the 1930s,[1,2] have developed into one of the most important tools for elucidating reaction mechanisms.[3−5] The main advantage is that absolute rate constants need not be determined which is particularly useful for mechanistic studies of phase-transfer (PT) reactions[6−8] where absolute rate data can only be obtained in the best of circumstances.[9]

Very recently, we reported novel PT-catalytic processes for the bromination[10] and iodination[11] of aliphatic hydrocarbons utilizing polyhalomethanes (Scheme 1). In a combined experimental−computational study, this Letter reveals key mechanistic data for these and related transformations, where H atom transfer is rate-determining. Our mechanistic proposal suggests hydrogen abstraction from the alkane by ${}^{\bullet}CX_3$ (eq 3) formed via reduction of CX_4 by HO^- (eq 1, $\Delta_r H^0 = -4.1$ kcal mol^{-1})[12,13] and fragmentation of the resulting radical

Scheme 1

$$CX_4 + HO^- \rightleftharpoons CX_4^{-\bullet} + HO^\bullet \qquad (1)$$

$$CX_4^{-\bullet} \longrightarrow {}^\bullet CX_3 + X^- \qquad (2)$$

$$^\bullet CX_3 + R\text{-}H \longrightarrow HCX_3 + R^\bullet \qquad (3)$$

$$R^\bullet + CX_4 \longrightarrow R\text{-}X + {}^\bullet CX_3 \qquad (4)$$

X = Br, I

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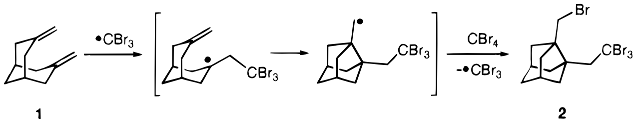
anion (eq 2). The hydrocarbon radical abstracts a halogen atom from the polyhalomethane, thereby regenerating the radical chain carrier $^{\bullet}CX_3$ (eq 4).[14,15]

The haloforms may also be used as halogen sources because they disproportionate in the presence of base into tetrahalomethane and dihalomethane ($2\ HCX_3 \rightarrow CX_4 + H_2CX_2$).[11,16,17] Considering the high stability and availability of HCI_3 over CI_4, the former is the best choice for iodinations[11] while brominations are better performed with tetrabromomethane;[10] dihalocarbene insertion reactions are negligible in both cases.

In contrast to the observed low regioselectivities for the free radical bromination of adamantane[18,19] ($Br_2/h\nu$, 1-AdBr/2-AdBr = 0.96),[19] the bromination under PT conditions with CBr_4 is much more selective (1-AdBr/2-AdBr = 8.3); the product ratio for the iodination with HCI_3 is even higher (1-AdI/2-AdI = 40.0). Taking into account that radical iodinations are generally not feasible and bearing in mind the high regioselectivities of the halogenations under PT conditions, the involvement of halogen radicals is unlikely (vide infra). As the differences in the heats of formation ($\Delta_f H°$) of the tertiary and the secondary adamantyl radicals is only 2.5 kcal mol^{-1} in favor of the latter,[20,21] the high selectivities must be due to the steric demand of a larger abstracting species such as a trihalomethyl radical. The formation of $^{\bullet}CBr_3$ is strongly supported by successful trapping with **1** under our typical PT conditions (Scheme 2).[22]

Scheme 2



Further evidence for the involvement of $^{\bullet}CBr_3$ in the hydrogen abstraction is provided by comparison of computed[23] and the experimentally[28] determined KIEs (Table 1). The theoretical KIEs were computed for the abstraction of hydrogen by $^{\bullet}CBr_3$ as well as $^{\bullet}CI_3$ from adamantane and cyclohexane, which are suitable model compounds, utilizing the differences of the thermally corrected enthalpies ($\Delta H_0 - \Delta H_{298}$) of the nondeuterated and the deuterated transition states (TSs, Figure 1) relative to their corresponding ground states.[3] The experimental KIEs were determined by measur-

Table 1. Computed[23] (UB3LYP/6-31G(d,p) (C,H,Br), 3-21G(d) (I)),[24−27] and Experimentally[28,29] Determined KIEs

TS		KIE (comput.)	KIE (exp.)
$Br_3C\cdots H\cdots$Ad-1-yl	(**TS1**)	4.9	4.9 ± 0.3
$Br_3C\cdots H\cdots$Ad-2-yl[a]	(**TS2**)	1.0	1.1 ± 0.1
$I_3C\cdots H\cdots$Ad-1-yl	(**TS5**)	5.3	5.1 ± 0.7
$I_3C\cdots H\cdots$Ad-2-yl[a]	(**TS6**)	1.0	1.0 ± 0.1
$Br_3C\cdots H\cdots$*eq*-*c*-C_6H_{11}[b]	(**TS3**)	4.7	4.0 ± 0.5
$I_3C\cdots H\cdots$*eq*-*c*-C_6H_{11}[b]	(**TS7**)	5.0	4.7 ± 0.4
$Br\cdots H\cdots$*eq*-*c*-C_6H_{11}[b]	(**TS4**)	2.3[c]	2.4[d]

[a] Secondary KIE: 1,3,5,7-tetradeuterioadamantane was used.[28] [b] The equatorial TSs are energetically lower than the axial TSs. [c] Cyclohexane forms an initial complex with $^{\bullet}Br$ exothermically (−3.4 kcal mol^{-1}); this complex was used as the reference ground state. [d] From ref 5.

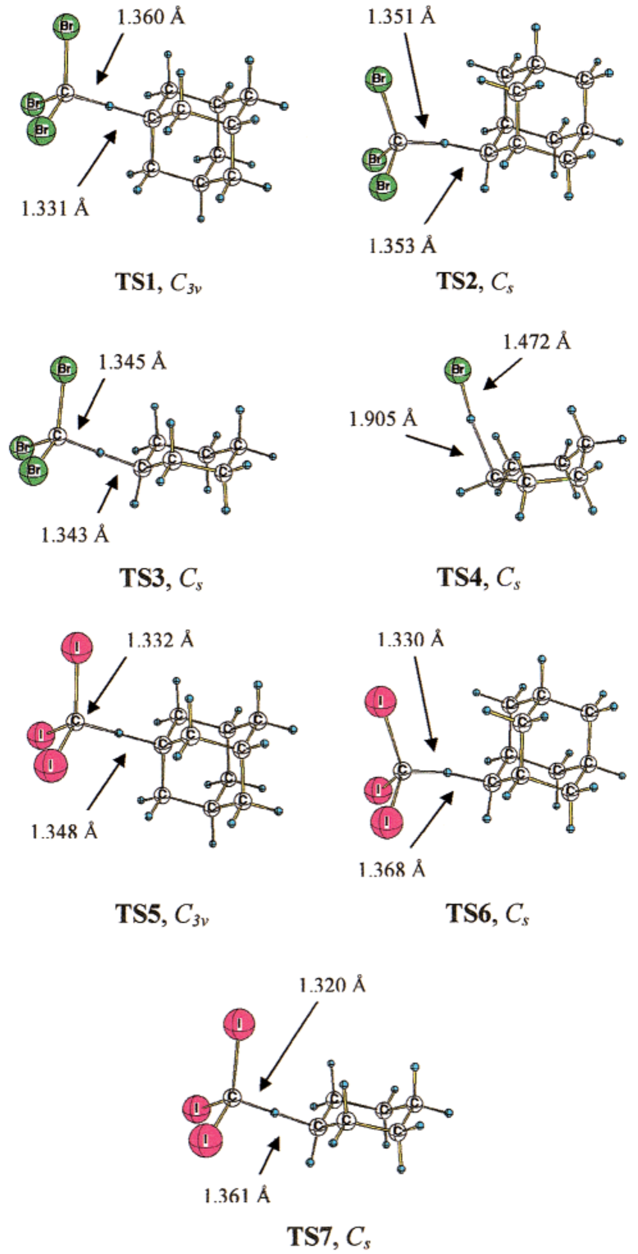


Figure 1. Computed[23] TSs for hydrogen abstraction from the tertiary (**TS1**, **TS5**) and secondary (**TS2**, **TS6**) positions of adamantane and from cyclohexane (**TS3, TS7**) by $^{\bullet}CBr_3$ and $^{\bullet}CI_3$ as well as for cyclohexane by $^{\bullet}Br$ (**TS4**) at UB3LYP/6-31G(d,p) (H,C,Br), 3-21G(d) (I).[24−27]

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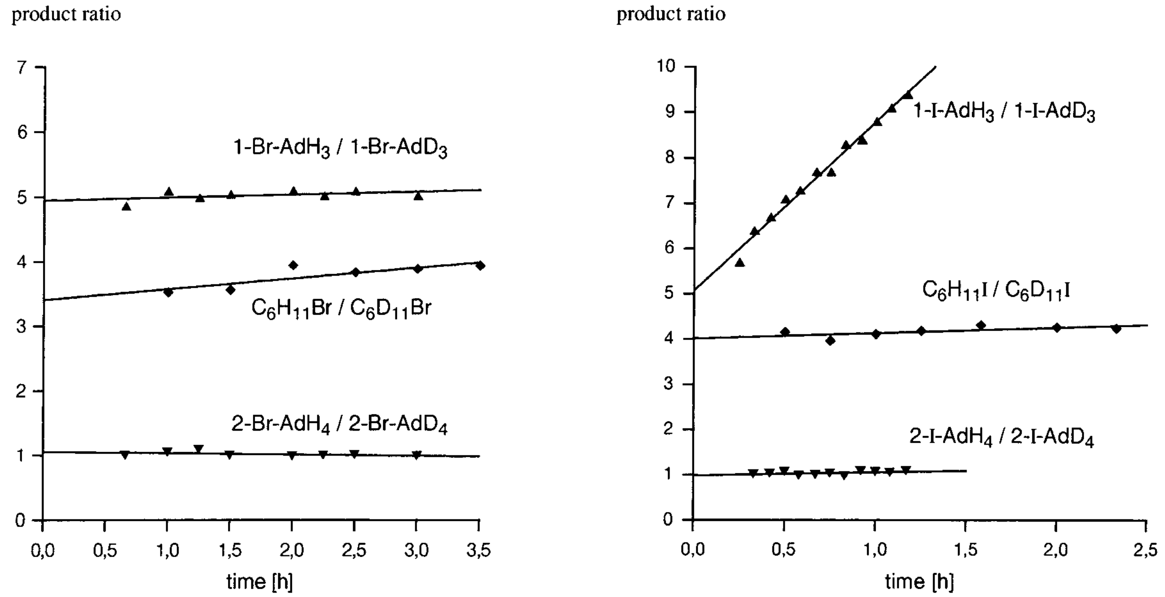

Figure 2. The ratio of deuterated and nondeuterated products for bromination (left) and iodination (right) of cyclohexane as well as of the tertiary and secondary positions of adamantane under PTC conditions.[28]

ing[28] the ratio of the deuterated and nondeuterated products at early stages of the reaction (conversion $<$ 7%).[3,30−32] The KIEs were extrapolated from plots of the product ratios (H/D) vs time (Figure 2).

As both bromination and iodination under PT conditions are accompanied by a considerable primary H/D KIE, hydrogen abstraction must be rate-determining. As found in earlier studies using the B3LYP method[24−26] for hydrogen abstraction reactions,[33−35] the computed[23] KIEs for the adamantane reactions are in good to excellent agreement with experiment (Table 1). Therefore, the computed TSs are likely to be good representations of the key bond breaking/forming processes. In view of this, the experimental KIEs for the cyclohexane reactions may be slightly underestimated, possibly due to inevitable side reaction such as elimination. As the KIEs are around 5 (the theoretical maximum is about 7),[3] the TSs are roughly located halfway along the reaction path. This is confirmed by the computed geometries (Figure 1) which indicate rather similar bond lengths between the hydrogen and the respective carbon atom.

These findings are clearly different from other radical halogenation processes such as Gif-type reactions (KIE $=$ 2.1−2.4 for cyclohexane (**3**) vs d_{12}-cyclohexane (**4**)),[36] Fenton-type reactions (KIE $=$ 1.5 for **3** vs **4**),[36] or free radical bromination (KIE $=$ 2.4 for **3** vs $C_6H_{11}D$).[5] The computed H/D KIE for the hydrogen abstraction from cyclohexane is 2.3 which is also in excellent agreement with experiment.[5] This is another indication that bromine radicals cannot be responsible for the hydrogen abstraction. Note that bromine radicals also show a much lower selectivity for the two different positions in adamantane.[19]

The observed high tertiary over secondary selectivities in the adamantane halogenations may be explained by minor but decisive differences in the hydrocarbon C−H bond

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(22) Trapping experiment: 200 mg (1.35 mmol) of 3,7-dimethylenobicyclo-[3.3.1]nonane (**1**) and 1.20 g of CBr_4 (3.6 mmol) were dissolved in 10 mL of CH_2Cl_2, and 4 g of NaOH (solid) was added. This mixture was stirred in a closed 25 mL vial for 30 h at room temperature. After removing solvents under reduced pressure, 0.7 g of crude products were obtained. Column chromatography (silica gel Merck 60, *n*-hexane, $R_f = 0.30$) and recrystallization from *n*-hexane gave 400 mg (60%) of 3-(1′-bromomethyl)-7-(2″,2″,2″-tribromoethyl)tricyclo[3.3.1.0^{3,7}]nonane (**2**). ^{1}H NMR (δ ppm, $CDCl_3$) is identical to that described the literature.[37] ^{13}C NMR (δ ppm, $CDCl_3$): 33.46 (C9); 35.57 (C1, C5); 36.72 (C2"); 41.58 (C1"); 48.22 (C6, C8); 49.52 (C2, C4); 53.61 (C7); 54.13 (C3); 64.83 (C1′). Anal. (C, H). Calcd: 30.20, 3.41. Found: 30.03, 3.36. MS (70 eV): *m/z* (%) = 403, 321, 265, 214, 133, 105, 91, 41. IR (KBr): 2910, 2849, 1454, 1244, 1071, 899, 785, 736, 664, 635, 581 cm^{-1}.

(23) All computations were performed with the GAUSSIAN98 program suite (Gaussian98, Rev. A.7: Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Gill, P. M. W.; B. G. Johnson; Robb, M. A.; Cheeseman, J. R.; Keith, T.; Petersson, G. A.; Montgomery, J. A.; Raghavachari, K.; Al-Laham, M. A.; Zakrzewski, V. G.; Ortiz, J. V.; Foresman, J. B.; Cioslowski, J.; Stefanov, B. B.; Nanayakkara, A.; Challacombe, M.; Peng, C. Y.; Ayala, P. Y.; Chen, W.; Wong, M. W.; Andres, J. L.; Replogle, E. S.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Binkley, J. S.; Defrees, D. J.; Baker, J.; Stewart, J. P.; Head-Gordon, M.; Gonzalez, C.; Pople, J. A. Gaussian, Inc.: Pittsburgh, PA, 1995) utilizing analytical first and second energy derivatives, employing the three-parameter hybrid functional (B3LYP).[24,25] We used 6-31G(d,p) basis sets for hydrogen and carbon and a 3-21G(d) basis set for iodine.[26,27] Vibrational frequencies and zero-point vibrational energies (ZPVE) were not scaled; tunneling effects were not considered. All computed structures are available from the authors upon request.

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distances of the breaking bonds in the TSs (1.331 Å in **TS1** vs 1.353 Å in **TS2**). While the absolute barriers for C−H abstraction are not likely to be very reliable, the *relative* differences for **TS1** vs **TS2** and **TS5** vs **TS6** are 2.6 kcal mol^{-1} and 2.9 kcal mol^{-1}, respectively, in favor of tertiary C−H bond activation; this also reflects the higher selectivity for the iodination.

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(28) Kinetic isotope effect measurements: All kinetic experiments were performed competitively for adamantane (**5**) vs 1,3,5,7-tetradeuterioadamantane (**6**) and cyclohexane (**3**) vs *d*$_{12}$-cyclohexane (**4**) by stirring the reaction mixture in closed 25 mL vials at 23 °C using the following conditions. Bromination of cyclohexanes: 7 mL of a solution of $[\mathbf{3}]_0 = [\mathbf{4}]_0 = 0.143$ mol L^{-1}, $[CBr_4]_0 = 0.429$ mol L^{-1}, TBAB (tetrabutylammonium bromide) (10 mol %) in CH_2Cl_2 and 3 mL of NaOH (aq. 50%). Iodination of cyclohexanes: 20 mL of a solution of $[\mathbf{3}]_0 = [\mathbf{4}]_0 = 0.050$ mol L^{-1}, $[HCI_3]_0 = 0.190$ mol L^{-1}, TBAB (10 mol %) in CH_2Cl_2 and 3 mL of NaOH (aq. 50%). Bromination of adamantanes: 7 mL of a solution of $[\mathbf{5}]_0 = [\mathbf{6}]_0 = 0.071$ mol L^{-1}, $[CBr_4]_0 = 0.429$ mol L^{-1}, TBAB (10 mol %) in CH_2Cl_2 and 3 mL of NaOH (aq. 50%). Iodination of adamantanes: 20 mL of a solution of $[\mathbf{5}]_0 = [\mathbf{6}]_0 = 0.025$ mol L^{-1}, $[HCI_3]_0 = 0.190$ mol L^{-1}, TBAB (10 mol %) in CH_2Cl_2 and 3 mL of NaOH (aq. 50%). In the case of bromination, the results were confirmed by experiments in separate vials. Determination of the relative concentrations of deuterated and nondeuterated products were carried out by GC/MS analysis (HP5890 Series II GC, column HP Ultra1 (50 m × 0.2 mm × 0.33 mm film: cross-linked methyl silicone with HP5971A mass selective detector) by mass selective integration.

(29) Calibration of the relative abundance of deuterated and nondeuterated products led to scaling factors of 1.15 and 1.18 for bromination and iodination of **3** vs **4**, respectively; the scaling factors for the adamantane reactions were 1.0.

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