Halogenation of Cubane under Phase-Transfer Conditions: Single and Double C−H-Bond Substitution with Conservation of the Cage Structure

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Abstract: The first highly selective C−H chlorination, bromination, and iodination of cubane (**1**) utilizing polyhalomethanes as halogen sources under phase-transfer (PT) conditions is described. Isomeric dihalocubanes with all possible combinations of chlorine, bromine, and iodine in *ortho*, *meta*, and *para* positions were also prepared by this method; *m*-dihalo products form preferentially. Ab initio and density functional theory (DFT) computations were used to rationalize the pronounced differences in the reactions of **1** with halogen ($Hal^\bullet$) vs carbon-centered trihalomethyl ($Hal_3C^\bullet$) radicals (Hal = Cl, Br). For Hal_3C radicals the C−H abstraction pathway is less unfavorable ($\Delta G^\ddagger_{298} = 21.6$ kcal/mol for $Cl_3C^\bullet$ and 19.4 kcal/mol for $Br_3C^\bullet$ at B3LYP/6-311+G**//B3LYP/6-31G**) than the fragmentation of the cubane skeleton via S_H2-attack on one of the carbon atoms of **1** ($\Delta G^\ddagger_{298} = 33.8$ and 35.1 kcal/mol, respectively). In stark contrast, the reaction of **1** with halogen atoms preferentially follows the fragmentation pathway ($\Delta G^\ddagger_{298} = 2.1$ and 7.5 kcal/mol) and C−H abstraction is more unfavorable ($\Delta G^\ddagger_{298} = 4.6$ and 12.0 kcal/mol). Our computational results nicely agree with the behavior of **1** under PT halogenation conditions (where $Hal_3C^\bullet$ is involved in the activation step) and under free-radical photohalogenation with Hal_2 (Della, E. W., et al. *J. Am. Chem. Soc.* **1992**, *114*, 10730). The incorporation of a second halogen atom preferentially in the *meta* position of halocubanes demonstrates the control of the regioselectivity by molecular orbital symmetry.

Introduction

Haloalkanes, some of the most important starting materials in preparative chemistry, are produced industrially via the free-radical halogenations of alkanes;[1−3] the higher homologues generally react with low selectivities. Only some moderately strained hydrocarbons can be halogenated selectively under free-radical conditions because of strain relief which singles out certain bonds or molecular moieties. Typical examples are hydrocarbons with relatively reactive C−C bonds, such as small-ring propellanes,[4,5] bicyclobutanes,[6] and bicyclohexanes.[7] Highly strained hydrocarbons generally do not undergo C−H bond substitution with halogen atoms because C−C bond breaking and fragmentation reactions are typically more favorable. For instance, highly symmetrical cubane (**1**),[8,9] one of the most strained[10] hydrocarbons ever prepared, does not react selectively with halogen radicals.[11] Bromination with elementary bromine under photoinitiation[12] induces homolytic cleavage of two C−C bonds and gives 30% of tetrabromide **2** (Scheme 1). The free radical chlorination of **1** is even less selective, forming complex mixtures of oligochlorocubanes and tetrachloride **3** in 3% yield.[12] The only example for a direct radical C−H substitution of the cubane skeleton with halogen radicals was reported for the oxidation of **1** with *tert*-butyl hypoiodite: Irradiation in Freon-113 gave a mixture of polyiodinated cubanes as well as some iodocubane.[13]

Recently, we demonstrated that a wide range of alkanes, from linear or branched to polycyclic, can be halogenated selectively and conveniently in high yields under phase-transfer (PT) conditions. Bromination[14] and even iodination[15] of secondary and tertiary C−H bonds occurs readily utilizing polyhalomethanes under phase-transfer conditions. The initiation step involves the reduction of the tetrahalomethane with the OH^- anion (Scheme 2) via single electron transfer (SET); further

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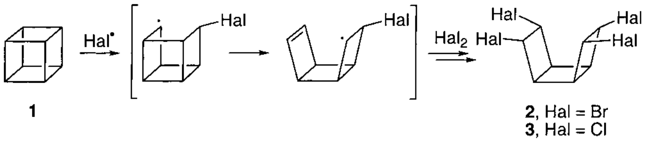
Scheme 1. Photoinitiated Free Radical Halogenation of Cubane with Br_2 and Cl_2



Scheme 2. Halogenation of Alkanes (R−H) with Tetrahalomethanes under Phase-Transfer Conditions

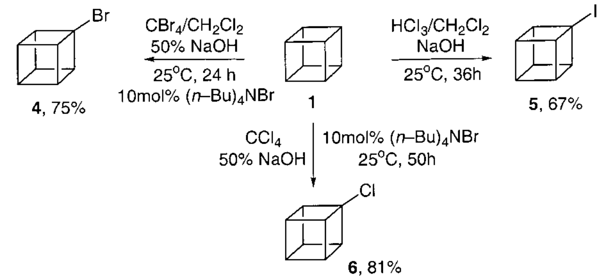
Initiation $\quad CHal_4 + OH^- \rightleftharpoons CHal_4^{\bullet -} + HO^\bullet \quad (1)$

$$CHal_4^{\bullet -} \downarrow Hal_3C^\bullet + Hal^-$$

Activation $\quad R\text{–}H + Hal_3C^\bullet \longrightarrow R^\bullet + HCHal_3 \quad (2)$

Halogenation/Propagation $\quad R^\bullet + CHal_4 \longrightarrow R\text{–}Hal + Hal_3C^\bullet \quad (3)$

Scheme 3. Monohalogenation of Cubane under Phase-Transfer Conditions



decomposition of the tetrahalomethane radical anion leads to the trihalomethyl radical (eq 1) which is involved in C−H activation and propagation steps (eqs 2 and 3).[16]

Since PT halogenations do not involve halogen radicals, we hoped that our method would allow clean and efficient C−H halogenations of cubane *without* loss of the cubane structure. Here we present combined experimental and computational data that **1** and its monohalo derivatives can be halogenated in high yields under PT conditions. These protocols are also useful for the preparation of polysubstituted cubane derivatives,[17] which are very high-energy materials or can be used *en route* to multiply substituted cubanes.

Results and Discussion

Halogenation of Cubane under PT Conditions. Utilizing the tetrabromoethane/50% aqueous sodium hydroxide/CH_2Cl_2 PT system with 10 mol % (relative to hydrocarbon) of $Bu_4N^+Br^-$ (Scheme 3),[14] **1** selectively gives bromocubane (**4**) in 75% yield; no detectable side reactions occur (GC/MS). It is reasonable to suggest that this reaction also involves the cubane radical in accord with Scheme 2 (R = cubyl and Hal = Br). This radical was previously generated[18] in solution through thermolysis of *tert*-butyl cubanepercarboxylate,[19] the Hunsdiecker reaction,[20] or hydrogen abstraction from cubane with *tert*-butoxy radicals.[13] Although the cubyl radical[21] is relatively unstable compared to other tertiary cage radicals, apparently it can be effectively trapped in solution with halomethanes[19] (in our case with CBr_4) without skeletal rearrangements. Iodination takes place in a similar manner: CI_4 is generated in situ through a base-catalyzed exchange reaction ($2HCI_3 \rightarrow CI_4 + CH_2I_2$).[15] Hence, PT iodination of cubane in the presence of HCI_3 affords iodocubane **5** in 67% preparative yield (Scheme 3).

Herein we also report a new method for *chlorination* under PT conditions. Chlorocubane **6** was prepared from **1** in 81% preparative yield in the CCl_4/50% aqueous NaOH PT system. Since CCl_4 can be removed easily, this method is convenient for the selective chorination of hydrocarbons;[22] it is highly probable that the initiation step for the chlorination (Scheme 2, Hal = Cl) also involves SET from the OH^- anion to CCl_4. This peculiar reduction (eq 1), first suggested by Sawyer and Roberts,[23] is −30.3 kcal/mol exothermic at B3LYP, in reasonable agreement with the experimental value (−24.6 ± 7.9 kcal/mol) calculated from the heats of formation.[24,25]

In marked contrast to free-radical halogenations with Hal_2, which cause fragmentation of the cubane skeleton, PT halogenations do give the desired halocubanes *without* rearrangement. This must be due to the differences in the nature of the abstracting radicals (abstraction is rate determining,[16] i.e., $Hal^\bullet$ vs. $Hal_3C^\bullet$), as also found for the reactions of other strained alkanes such as cyclopropane with halogen and carbon-centered radicals.[26−30] To rationalize these findings, we studied these reactions computationally (Scheme 4, see Computational Methods below).[31] Labels ***A1*** and ***A2*** refer to the hydrogen abstraction reaction with the halogen and trihalomethyl radicals, respectively; direct attack of these radicals at the carbon atom of cubane is presented by fragmentation pathways ***B1*** and ***B2***.

Cubane exergonically forms initial η^1-complexes with the halogen radicals (**MIN1**); these complexes are considered as the ground states for the H-abstraction reactions with $Hal^\bullet$ (for optimized geometries see Figures 4 and 5 in the Supporting Information). Although enthalpically favored, carbon-centered ($Hal_3C^\bullet$) radicals do not form initial complexes when thermal and entropic effects are included.

C−H bond activation proceeds through **TS1** and **TS2** (pathways ***A1*** and ***A2***) and is mildly endergonic due to the relative instability of the resulting cubane radical $\mathbf{1}^\bullet$. In contrast, the ring-opening pathways ***B1*** and ***B2*** are highly exergonic due to strain relief in the fragmentation products **MIN2** and **MIN3**. This double fragmentation of the cubane cage proceeds as a stepwise process via **TS3-TS6** and intermediates **MIN4** and **MIN5**.

The H-abstraction (***A1***) and carbon-bond-breaking (***B1***) pathways have relatively low barriers in the case of $Hal^\bullet$; the fragmentation pathway ***B1*** via **MIN4** is favored for the Br

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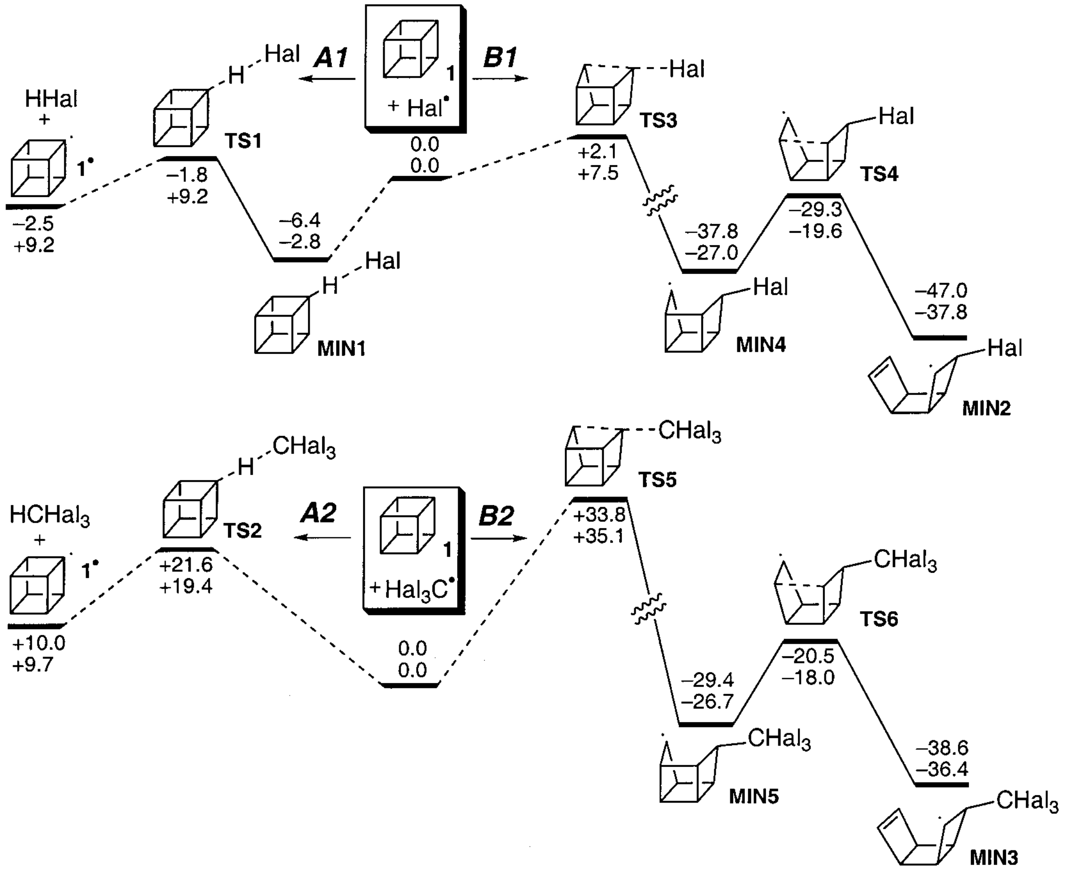
(31) The transformations shown in Scheme 4 were computed also at the MP2/6-31G**. The geometries (see Supporting Information) are very similar (±0.02 Å) to those obtained at DFT. As some structures (e.g., TS3-TS6) show substantial spin contamination at MP2 ($\langle S^2 \rangle = 0.8−1.0$), the projected energies were used in energetic evaluations; the PMP2 ΔE values are very similar to those obtained at DFT.

Scheme 4. Computed H-Abstraction (***A1*** and ***A2***) and Bond Fragmentation (***B1*** and ***B2***) Pathways for the Reaction of Cubane with Halogen and Trihalomethyl Radicals (Hal = Cl, first line, and Hal = Br, second line, ΔG_{298} values in kcal/mol at B3LYP/6-311+G**//B3LYP/6-31G**)



radical both kinetically and thermodynamically. H-abstraction has a much lower barrier for chlorine than for bromine radicals (4.6 vs 12.0 kcal/mol, respectively). This is consistent with the free-radical chlorination of cubane, where chlorocubanes as well as open-cage products form (vide supra), while free-radical bromination exclusively leads to ring-opened fragmentation products.[12]

The hydrogen abstraction pathway ***A2*** with the Hal$_3$C$^\bullet$ radicals (via **TS2**) has substantially lower barriers (21.6 kcal/mol for Cl$_3$C$^\bullet$ and 19.4 kcal/mol for Br$_3$C$^\bullet$) than the direct attack on carbon through **TS5** (***B2***, the barriers are 33.8 and 35.1 kcal/mol, respectively). Hence, the computations demonstrate that although cage fragmentation with the Hal$_3$C$^\bullet$ radicals is favored thermodynamically, the cubane radical $\mathbf{1}^\bullet$ may form under kinetic control.

The Halogenation of Halocubanes. The effects of halogen substitution on the reactivity of cubane C−H bonds are expected to be high due to its unique shape and structural rigidity.[32,33] A peculiarity are cross-cage[34] *para* (or through bond) interactions,[35−37] where the SOMO is collinear to the C−Hal fragment (in the cubyl radical the nonbonding 1,4-distance is 2.64 Å at B3LYP/6-31G**). A halogen substituent destabilizes the radical in the *para* position (Figure 1) by about 1 kcal/mol, due to antibonding MO interactions of the collinear bonds. This finding is in agreement with the interpretation that a cross-diagonal 1,4-bond through the cubane cage cannot be realized.[35−37] However, as we have noted for the C−H substitution reactions of adamantane (the secondary radical is 2.5 kcal/mol more stable, but tertiary products predominate) under identical conditions, the radical stabilities do *not* necessarily reflect the product distributions.[14−16,38] Furthermore, there is very little orbital interaction between the radical site and the halogen bonds or orbitals in the singly occupied orbitals (SOMOs). Although the relative energies of the radical intermediates agree nicely with our product distributions (Figure 1), is clear that this cannot be the only factor. Orbital symmetries and polar effects must be considered.[39]

When considering orbital interactions we first have to decide whether the CHal$_3$ radicals are electrophilic or nucleophilic, i.e., if they interact more with the HOMO or the LUMO of the hydrocarbon. Matching the orbital energies does not help much in this respect as the interactions with filled shells may be attractive or repulsive, depending on the overall energy change. The reactivity toward the positively charged hydrogens of cubane (natural bond orbital (NBO) charge on H: +0.20 e, Figure 2) indicates that the trihalomethyl radicals are probably

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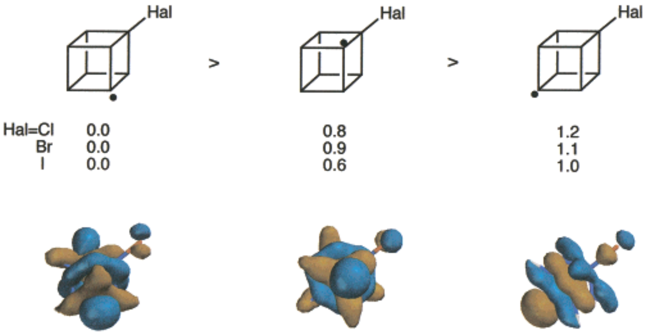

Figure 1. The relative stabilities (kcal/mol) of isomeric halocubyl radicals from B3LYP/6-31G** data. SOMOs of the radicals for Hal = Cl.

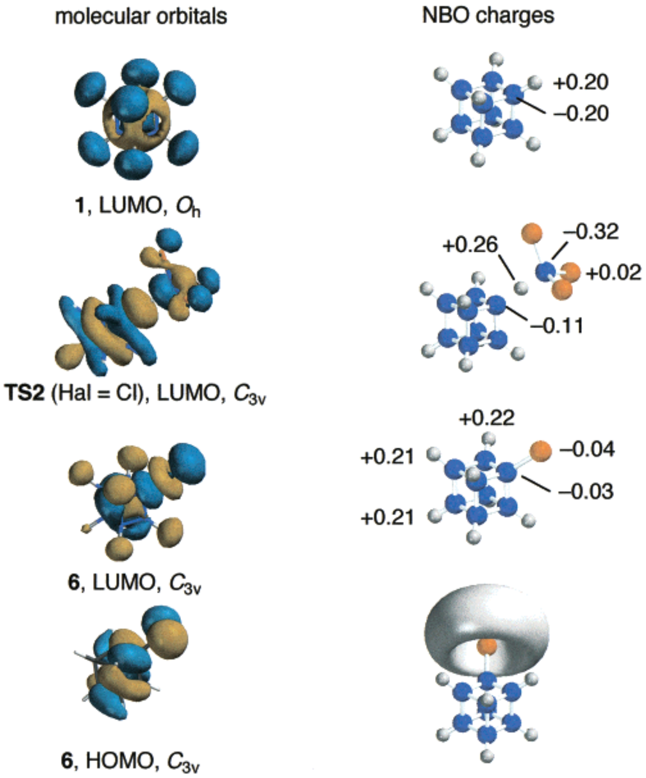

Figure 2. Selected molecular orbitals of cubane (**1**), chlorocubane (**6**), and the transition structure for H-abstraction (**TS2**); natural bond orbital (NBO) charges (right); constant electrostatic potential around the chlorine substituent in **6** (gray, bottom right).

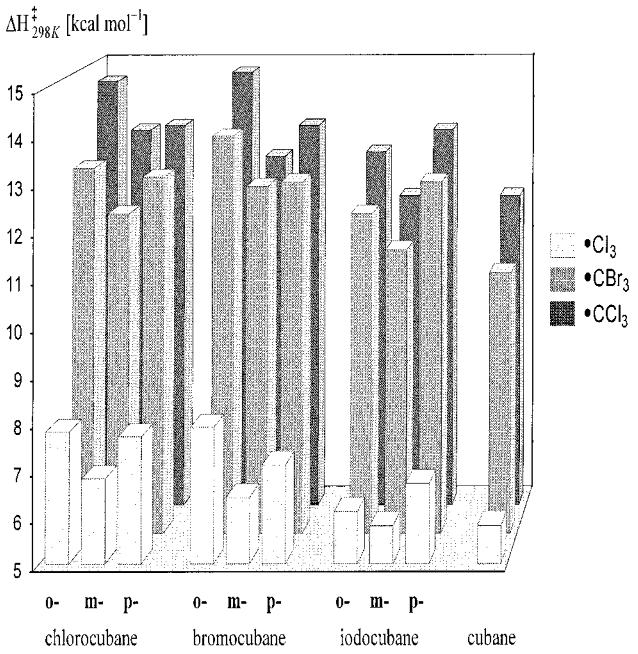

Figure 3. The activation enthalpies ($\Delta H^{\ddagger}_{298\ \mathrm{K}}$, kcal/mol) for hydrogen abstraction from cubane and halocubanes with trihalomethyl radicals at B3LYP/6-311+G** (H, C, Cl, Br), 3-21G* (I)//B3LYP/6-31G** (H, C, Cl, Br), and 3-21G* (I).

very slightly nucleophilic in this reaction.[40] This also agrees with the experimental findings that electrophilic halogen radicals ($\mathrm{Cl}^{\bullet}$ and $\mathrm{Br}^{\bullet}$) attack the slightly negatively charged (−0.20 e) carbons of **1**, leading to cage opening (vide supra); note that the HOMO coefficients on the carbon−carbon bonds in **6** are large but negligible on the hydrogens. Hence, the interaction of $^{\bullet}\mathrm{CHal}_3$ with the LUMO of **6** should be important (Figure 2) for determining the selectivity of the second hydrogen abstraction. Due to the inherent C_{3v} symmetry of monohalogenated cubanes, there is a negligible LUMO coefficient on the hydrogen in the *para* position and products derived from this mode of attack should be a minor component (irrespective of statistical factors). The *ortho* and *meta* coefficients are of similar magnitude.

Polarization also is important in the transition states for hydrogen abstraction.[41−44] This is evident from the NBO charges in **TS2** (Hal = Cl, Figure 2), where the chlorine atoms of the trichloromethyl moiety are essentially neutral due to π-back-bonding to help bind the migrating positively polarized hydrogen atom. The polarization in the product chlorocubane is, apart from the almost neutral C−Cl bond, almost unchanged relative to **1**.

The reaction enthalpies for hydrogen abstraction from **1** and halocubanes **4**−**6** were computed at the B3LYP level (Figure 3). The computed activation energies are very similar for $\mathrm{Cl_3C}^{\bullet}$ and $\mathrm{Br_3C}^{\bullet}$ ($\Delta H^{\ddagger}_{298}$, 11−15 kcal/mol) but are much lower for $\mathrm{I_3C}^{\bullet}$ ($\Delta G^{\ddagger} = 6$−8 kcal/mol), also due to substantial polarization of the TSs for H-abstraction.[39] The developing negative charge on the trihalomethyl carbon atom in the course of H-abstraction is much higher for Hal = I ($\delta = -0.37$, due to its high polarizability) than for the other halogens (Hal = Br, $\delta = -0.19$; Hal = Cl, $\delta = +0.07$). This is in line with the increase of the relative stabilities of the trihalomethyl anions ($\mathrm{Cl_3C^-} < \mathrm{Br_3C^-} < \mathrm{I_3C^-}$): The isodesmic equation $\mathrm{Br_3CH} + \mathrm{Cl_3C^-} \rightarrow \mathrm{Br_3C^-} + \mathrm{Cl_3CH}$ is only slightly exothermic ($\Delta E = -6.3$ kcal/mol at B3LYP, −14 ± 9 experimental, based on the heats of formation[24,45,46]); $\mathrm{I_3CH} + \mathrm{Cl_3C^-} \rightarrow \mathrm{I_3C^-} + \mathrm{Cl_3CH}$ gives $\Delta E = -8.3$ kcal/mol. As a consequence, the hydrogen abstraction barriers are the lowest for $^{\bullet}\mathrm{CI_3}$ and the highest for $^{\bullet}\mathrm{CCl_3}$ (Figure 3).

All halocubanes react more slowly under PT conditions relative to **1**; iodocubane **5** is the most reactive among the three halocubanes studied. As demonstrated in Figure 3, the hydrogen abstraction from the *m*-C−H positions of halocubanes is associated with the lowest barriers for *all* $\mathrm{Hal_3C}$ radicals and the regioselectivity is *meta* > *ortho* > *para*. This parallels the

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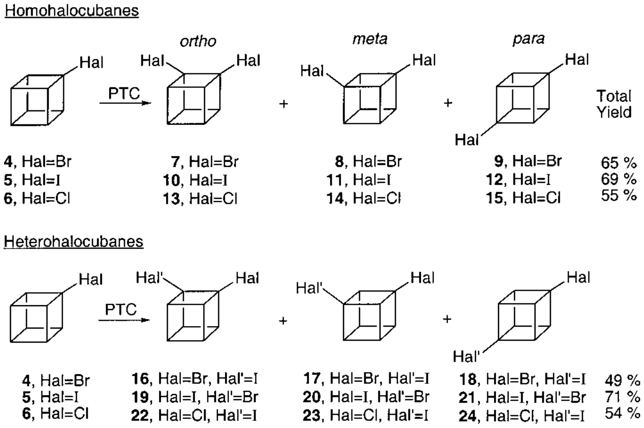
Scheme 5. Halogenation of Halocubanes under PT Conditions



above-mentioned relative stabilities of the halocubyl radicals (*m*-halocubyl$^\bullet$ > *o*-halocubyl$^\bullet$ > *p*-halocubyl$^\bullet$).

These computational predictions were verified with the preparation of dihalocubanes from monohalocubanes (Scheme 5). The second halogenation requires much longer reaction times due to the deactivation of the halocubanes (cf. Figure 3); all possible isomeric dihalocubanes (**7**−**15**) were found in variable proportions (Scheme 5). The *ortho*:*meta*:*para* ratios determined from GC/MS and NMR data are 0.63−0.70:1.00:0.09−0.10.[47] The preference for *meta* substitution agrees nicely with our computational assessment (Figure 3).

It seemed feasible to extend our PT approach to the first preparation of *mixed* halocubanes (heterohalocubanes, Scheme 5) because halogen exchange does not occur under these conditions. The dihalocubanes (**16**−**24**) containing *all* possible combinations of chlorine, bromine, and iodine in the *ortho*, *meta*, and *para* positions of cubane were prepared and characterized spectroscopically. The regioselectivities for the halogenations follow the above pattern, i.e., *meta* substitution prevails, while the *para* isomers form in less than 7% yield on average.

Conclusions

Cubane could be selectively halogenated under PT conditions involving Hal_3C radicals in the C−H activation step; cubane radical intermediates are trapped effectively by halomethanes. These results are distinctly different from the reactions of cubane with elementary halogens under photoinitiation, where products form from cage-opening. The introduction of a second halogen atom under PT conditions is also preparatively useful, leading to homo or hetero dihalocubanes *without* halogen exchange reactions. Introducing a second halogen atom into cubane shows pronounced *meta* selectivity due to molecular orbital symmetry control and polarization in the transition structures.

Computations also reveal substantial differences in the interactions of cubane with halogen (Hal$^\bullet$) and carbon-centered ($Hal_3C^\bullet$) radicals. For the Hal_3C radicals the C−H abstraction pathway is much more favorable than the fragmentation of the cubane skeleton via S_R2-attack on a carbon atom. In contrast, the reaction of **1** with Hal$^\bullet$ preferentially leads to ring-opening and fragmentation.

In summary, we demonstrate that our newly developed phase-transfer protocol for the activation of secondary and tertiary aliphatic C−H bonds is a mild and hence selective method applicable also to highly strained alkanes such as cubane. The original protocol for bromination and iodination can also be adopted for aliphatic chlorination reactions which can be conducted with unparalleled selectivities.

Computational Methods

All computations were performed with the Gaussian98 program.[48] Geometries were fully optimized at the density functional three-parameter hybrid B3LYP functional[49,50] and at the Møller−Plesset[51,52] (MP2, not reported here, included in the Supporting Information) levels of theory; we used the 3-21G(d) basis set for iodine and 6-31G(d,p) for all other atoms. The $\Delta H^{\ddagger}_{298}$ values computed at our level of theory for the H-abstractions with $Cl_3C^\bullet$ from cyclohexane (14.8 kcal/mol) and $(CH_3)_3CH$ (9.9 kcal/mol) are in good agreement with experimental values (13.2 and 10.2 kcal/mol, respectively[53,54]). Thus, DFT appears suitable for such types of reactions.[16,55] As MP2 sometimes suffers from spin contamination (we found $\langle S^2 \rangle$ values of 0.75−0.99 for doublets), we used spin-projected PMP2 energies. Harmonic vibrational frequencies were computed at the B3LYP level to ascertain the nature of all stationary points (NIMAG = 0 for minima and 1 for transition structures). Zero-point vibrational energies (ZPVE, unscaled), thermal corrections to enthalpies, and free energies were used to improve our energy evaluations. MP2 vibrational frequencies were not computed due to the large size of the molecules. Unless noted otherwise, the energies discussed in this paper refer to B3LYP/6-311+G** (C, H, Cl, Br); 3-21G* (I)//B3LYP/6-31G** (C, H, Cl, Br); and 3-21G* (I). Absolute DFT and MP2 energies (not discussed) as well as *xyz*-coordinates for optimized species are collected in the Supporting Information.

Experimental Section

NMR spectra were recorded on a Varian VXR-300 spectrometer at 300 (^{1}H NMR) and 75 MHz (^{13}C NMR) in $CDCl_3$. The chemical shifts are given on the δ scale in ppm; the internal standard was HMDS. The GC/MS analyses were performed on an HP5890 with an H5971A detector (HP GC-MS capillary column 50 m−0.2 mm, Ultra1, Silicone, 80−250 °C). The compounds gave satisfactory elemental analysis and showed adequate IR and DEPT ^{13}C NMR spectra. The yields for the dihalocubanes were determined as follows: *o*-Dihalocubanes could be separated preparatively (column chromatography, see text) from *m*- and *p*-dihalocubanes which could be identified unambiguously by their ^{1}H and ^{13}C NMR spectra. Their relative proportions were determined by GC/MS.

A. Bromination of Cubane (1). A mixture of 208 mg (2 mmol) of **1**, 1.28 g (4 mmol) of CBr_4, 5 mL of CH_2Cl_2, 3 mL of 50% aqueous NaOH, and 25 mg of tetrabutylammonium bromide was stirred at room temperature for 24 h,[56] then diluted with 10 mL of water and extracted with CH_2Cl_2 (3 × 5 mL). The extracts were washed with water and

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(47) These values were not corrected by calibration of the relative abundances of the components. The signals of ortho and para isomers are not fully separated in the GC; the ratio of these isomers was obtained from the integration of NMR spectra of the mixture of ortho and para isomers, obtained by preparative LC. Reddy, D.; Sivakumar, S. G. P.; Eaton, P. E. *J. Org. Chem.* **1989**, *54*, 722−723.

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dried over Na_2SO_4; excess CH_2Cl_2 was removed at atmospheric pressure. Column chromatography (silica/pentane) gave 20 mg of **1** and 274 mg (75%) of bromocubane (**4**) identical to the material described earlier by NMR[57,58] and MS[59] data.

B. Iodination of Cubane (1). A mixture of 208 mg (2 mmol) of **1**, 1.6 g (4 mmol) of HCI_3, 5 mL of CH_2Cl_2, and 3 g of solid NaOH was stirred at room temperature for 36 h, then diluted with 10 mL of CH_2Cl_2 and filtered; the solid was washed with CH_2Cl_2 and the solvent removed at atmospheric pressure. The residue was separated by column chromatography (silica/pentane): 25 mg of cubane **1** were recovered; 308 mg (67%) of iodocubane **5** were isolated. The material was identical to that described earlier by NMR[60] data. MS *m/z* (%) 230 (1), 204 (4), 127 (22), 103 (40), 77 (100), 51 (33).

C. Chlorination of Cubane (1). A mixture of 208 mg (2 mmol) of **1**, 15 mL of CCl_4, 5 mL of 50% aqueous NaOH, and 25 mg of tetrabutylammonium bromide was stirred under reflux for 5 days, diluted with 10 mL of water, and extracted with CCl_4 (3×5 mL). The extracts were washed with water and dried over Na_2SO_4, and excess CCl_4 was removed at atmospheric pressure with use of a Vigreux column. Separating by column chromatography (silica/pentane) gave 10 mg of **1** and 227 mg (81%) of chlorocubane **6**, which was identical to the material described earlier by MS[12] data. ^1H NMR: 4.18 (m, 3H), 4.03 (m, 4H). ^{13}C NMR: 72.76, 56.69, 48.22, 43.87. Mp = 28−29 °C.

D. Bromination of Bromocubane (4). A mixture of 183 mg (1 mmol) of **4**, 640 mg (2 mmol) of CBr_4, 3 mL of CH_2Cl_2, 1.5 mL of 50% aqueous NaOH, and 10 mg of tetrabutylammonium bromide was allowed to react following procedure ***A*** (5 days); after column chromatography, 25 mg of **4** was recovered and 183 mg (65%) of a mixture of 1,2- (**7**), 1,3- (**8**), and 1,4- (**9**) dibromocubanes was obtained in a ratio of **7**:**8**:**9** = 0.63:1.00:0.09 according to GC/MS and NMR data. 1,2-Dibromocubane (**7**): ^1H NMR δ 4.34 (m, 4H), 4.19 (m, 2H); ^{13}C NMR δ 67.9, 55.11, 46.19; MS *m/z* (%) 262 (0.5%), 236 (1%), 182 (2%), 156 (5%), 102 (100%), 76 (10%), 50 (8%). 1,3-Dibromocubane (**8**): ^1H NMR δ 4.47 (m, 2H), 4.11 (m, 2H), 4.18 (m, 2H); ^{13}C NMR δ 65.25, 58.27, 57.41, 43.18; MS *m/z* (%) 262 (0.4%), 236 (2%), 182 (2%), 156 (5%), 102 (100%), 76 (8%), 50 (6%). 1,4-Dibromocubane was identical to the material described earlier by NMR data.[32,58]

E. Iodination of Iodocubane (5). A mixture of 115 mg (0.5 mmol) of iodocubane **5**, 0.79 g (2 mmol) of HCI_3, 5 mL of CH_2Cl_2, and 1.5 g of solid NaOH was stirred at room temperature for 3 days; then the reaction mixture was filtered and an additional amount of 0.79 g (2 mmol) of HCI_3, 3 mL of CH_2Cl_2, and 1.5 g of solid NaOH was added to the reaction mixture. After another 5 days of stirring, the reaction mixture was worked up as in ***B***; 16 mg of **5** were recovered and 123 mg (69%) of a mixture of 1,2- (**10**), 1,3- (**11**), and 1,4- (**12**) diodocubanes was obtained in a ratio of **10**:**11**:**12** = 0.70:1.00:0.08 according to GC/MS and NMR data. 1,2-Diiodocubane (**10**):[61] ^1H NMR δ 4.43 (m); ^{13}C NMR δ 57.45, 48,72, 45.94; MS *m/z* (%) 228 (0.3%), 204 (3%), 127 (2%), 102 (100%), 76 (14%), 50 (9%). 1,3-Diiodocubane (**11**): ^1H NMR δ 4.46 (m, 4H), 4.33 (m, 2H); ^{13}C NMR δ 65.80, 57.69, 48.76, 32.21; MS *m/z* (%) 228 (0.5%), 204 (4%), 127 (6%), 102 (100%), 76 (16%), 50 (12%). 1,4-Diiodocubane (**12**) was identical to the material described earlier by NMR and MS data.[58,62]

F. Chlorination of Chlorocubane (6). From 137 mg (1 mmol) of chlorocubane **6**, following procedure ***C*** (10 days) after column chromatography, was obtained 35 mg of unreacted **6** and 95 mg (55%) of a mixture of 1,2- (**13**), 1,3- (**14**), and 1,4- (**15**) dichlorocubanes in a ratio of **13**:**14**:**15** = 0.70:1.00:0.09 identified according to GC/MS and NMR data. 1,2-Dichlorocubane (**13**): ^1H NMR δ 4.17 (m, 4H), 4.03 (m, 2H); ^{13}C NMR δ 69.94, 53.35, 44.53; MS *m/z* (%) 172 (0.3%, 137 (12%), 112 (19%), 102 (100%), 75 (21%), 50 (14%). 1,3-Dichlorocubane (**14**): ^1H NMR δ 4.32 (m, 2H), 4.17 (m, 2H), 4.03 (m, 2H); ^{13}C NMR δ 67.53, 64.59, 56.93, 39.67; MS *m/z* (%) 172 (0.7%), 146 (18%), 136 (21%), 112 (27%), 102 (100%), 75 (38%), 51 (23%). 1,4-Dichlorocubane (**15**) was identical to NMR and MS literature data.[32]

G. Iodination of Bromocubane (4). From 183 mg (1 mmol) of bromocubane **4**, following procedure ***E*** (4 days), 53 mg of unreacted **4** and 151 mg (49%) of a mixture of 1,2- (**16**), 1,3- (**17**), and 1,4- (**18**) iodobromocubanes was obtained in a ratio of **16**:**17**:**18** = 0.68:1.00:0.09 according to GC/MS and NMR data. 1-Iodo-2-bromocubane (**16**): ^1H NMR δ 4.42 (m, 2H), 4.35 (m, 2H), 4.30 (m, 2H); ^{13}C NMR δ 57.25, 54.94, 53.10, 48.64, 45.99, 45.22; MS *m/z* (%) 310 (0.3%), 282 (1%), 228 (2%), 204 (4%), 156 (5%), 127 (8%), 102 (100%), 76 (10%), 50 (7%). 1-Iodo-3-bromocubane (**17**): ^1H NMR δ 4.48 (m, 2H), 4.27 (m, 2H), 4.22 (m, 2H); ^{13}C NMR δ 65.59, 60.55, 57.72, 57.24, 46.01, 30.09; MS *m/z* (%) 282 (0.8%), 228 (0.5%), 204 (2%), 156 (3%), 127 (6%), 102 (100%), 76 (9%), 50 (4%). 1-Iodo-4-bromocubane (**18**) was described previously:[63] ^{13}C NMR δ 63.37, 57.00, 54.81, 31.12; MS *m/z* (%) 282 (0.8%), 228 (0.5%), 204 (2%), 156 (3%), 127 (6%), 102 (100%), 76 (9%), 50 (4%).

H. Bromination of Chlorocubane (6). From 137 mg (1 mmol) of chlorocubane **6**, following procedure ***D*** (4 days**)**, 17 mg of unreacted **6** and 154 mg (71%) of a mixture of 1,2- (**19**), 1,3- (**20**), and 1,4- (**21**) bromochlorocubanes was obtained. The ratio of **19**:**20**:**21** = 0.67:1.00:0.09 according to GC/MS and NMR data. 1-Bromo-2-chlorocubane (**19**): ^1H NMR δ 4.26 (m, 4H), 4.12 (m, 2H); ^{13}C NMR δ 67.94, 54.99, 53.60, 53.43, 46.47, 44.42; MS *m/z* (%) 216 (0.3%), 192 (3%), 156 (5%), 136 (7%), 112 (9%), 102 (100%), 75 (18%), 51 (11%). 1-Bromo-3-chlorocubane (**20**): ^1H NMR δ 4.01 (m, 2H), 4.23 (m, 2H), 4.10 (m. 2H); ^{13}C NMR δ 68.77, 64.99, 57.56, 57.48, 56.74, 41.49; MS *m/z* (%) 216 (0.2%), 192 (4%), 156 (6%), 136 (5%), 112 (8%), 102 (100%), 75 (15%), 51 (10%). 1-Bromo-4-chlorocubane (**21**) was identical to NMR and MS spectra described previously.[12]

M. Iodination of Chlorocubane (6). From 137 mg (1 mmol) of chlorocubane **6**, following procedure ***E***, 50 mg of unreacted **6** and 143 mg (54%) of a mixture of 1,2- (**22**), 1,3- (**23**), and 1,4- (**24**) iodochlorocubanes was obtained in a ratio of **22**:**23**:**24** = 0.65:1.00:0.09 according to GC/MS and NMR data. 1-Iodo-2-clorocubane (**22**): ^1H NMR δ 4.33 (2H), 4.23 (m, 2H), 4.18 (m, 2H); ^{13}C NMR δ 74.82, 57.12, 53.23, 48.85, 45.04, 44.87; MS *m/z* (%) 264 (0.3%), 228 (0.7%), 204 (2%), 127 (7%), 102 (100%), 75 (21%), 51 (12%). 1-Iodo-3-chlorocubane (**23**): ^1H NMR δ 4.41 (m, 2H), 4.29 (m, 2H), 4.14 (m, 2H); ^{13}C NMR δ 70.68, 65.27, 57.96, 56.72, 44.25, 29.07; MS *m/z* (%) 238 (1%), 204 (3%), 127 (5%), 112 (6%), 102 (100%), 75 (21%), 51 (12%). 1-Iodo-4-chlorocubane (**24**) was prepared previously:[18] ^{13}C NMR δ 70.62, 56.58, 53.15, 29.18; MS *m/z* (%) 238 (1%), 204 (3%), 127 (5%), 112 (6%), 102 (100%), 75 (21%), 51 (12%).

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Supporting Information Available: Tables with absolute energies, including ZPVEs, as well as thermal corrections to enthalpies and *xyz*-coordinate energies of all computed species and Figures 4S and 5S depicting ground and transition structures for different halogenation reactions described in the present work (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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