system can gain maximal benefit from resonance stabilization. In the deprotonated species, the system relaxes into a geometry which is twisted in this region, albeit slightly.[9] In rhodopsin, the chromophore is certainly not deprotonated. However, according to two photon spectroscopic measurements the binding site of rhodopsin is neutral;[15] that is the charge balanced by a negatively charged counter ion, most probably the carboxylate group of glu 113, which interacts with the chromophore in the C12–C13 region[16] and may cause not only partial fixation of the double bond but also additional steric distortion.

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Selective C–H Activation of Aliphatic Hydrocarbons under Phase-Transfer Conditions**

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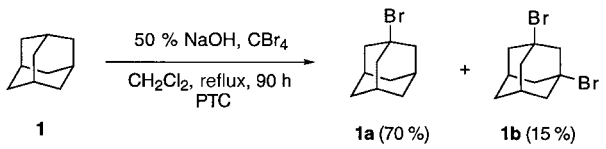
Dedicated to Professor Paul von Ragué Schleyer

The selective activation of aliphatic hydrocarbons,[1] is mostly achieved with electronically unsaturated transition metal complexes,[2–6] superacids,[32] or enzymatic processes.[7, 8] In this paper we present a highly unusual C–H activation of aliphatic hydrocarbons by phase-transfer catalysis (PTC) in mixed aqueous/organic solvents.

When treated with tetrabromomethane and sodium hydroxide under standard PTC conditions (catalyst: triethylbenzylammonium chloride), adamantane **1**[9] gives 1-bromo- (**1a**) and 1,3-dibromoadamantane (**1b**) in 85 % conversion and 70 % yield [Eq. (1); Table 1]. The dibromide **1b** can also



(1)

be obtained from **1a** under the same conditions but with longer reaction times, which indicates a stepwise incorporation of bromine into the adamantane core. Although the synthesis of polybromoadamantanes[10] is straightforward,[11–15] we have chosen **1** as a model for studying tertiary C–H bond activations.[1]

We arrived at these reaction conditions in the course of derivatizing adamantane **1** to its bridgehead substituted analogues[9, 10] by dibromocarbene (from $HCBr_3$/50 % $NaOH/CH_2Cl_2$/PTC, 16 h, reflux) insertion into the bridgehead C–H bond. Apart from the desired dibromomethyladamantane (**1c,** 33 %),[16] we also found **1a** (41 %), **1b** (16 %), and traces of 2-bromoadamantane (**1d**) (2 %). Since isolated **1c** does not form **1a** or **1b** under the same reaction conditions, we surmized that it is not the reaction of $:CBr_2$ with **1** that yields the bromoadamantanes. Rather, we reasoned that the halogen may be transferred from CBr_4. This compound is known to equilibrate with $HCBr_3$ under the reaction conditions used.[17, 18]

The transformation is highly regiospecific for the bridgehead position of **1** (the methyl groups of methyladamantanes

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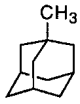
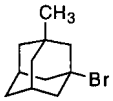
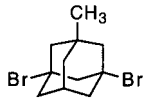
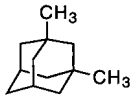
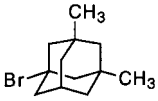
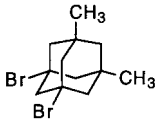
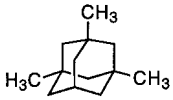
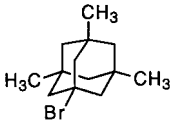
Table 1. Bromination of some aliphatic hydrocarbons with 50% NaOH/CBr_4 in CH_2Cl_2 under phase-transfer conditions ($T = 40\,^{\circ}C$, unless indicated; catalyst: triethylbenzylammonium chloride). Product yields [%] (preparative yield in parentheses) according to GC/MS and NMR analysis.

Entry	Substrate		t [h]	Product 1		Yield [%]	Product 2		Yield [%]
1		**1**	4		**1a**	31 (26)		**1b**	traces
2		**1**	16		**1a**	46 (40)		**1b**	5
3		**1**	90		**1a**	70 (61)		**1b**	15 (11)
4		**1**[a]	16		**1a**	71 (61)		**1b**	11 (8)
5		**1a**[a]	90		**1b**	40 (35)		–	
6		**3**	16		**3a**	35 (29)		**3b**	3
7		**3**	40		**3a**	38 (30)		**3b**	4
8		**3**	64		**3a**	38 (31)		**3b**	5
9		**4**	16		**4a**	24		**4b**	traces
10		**4**	40		**4a**	38 (31)		**4b**	3
11		**4**	64		**4a**	44 (35)		**4b**	5
12		**5**	40		**5a**	43 (34)		–	
13		**5**	64		**5a**	46 (37)		–	
14		**6**[b–d]	16		**6a**	37		–	
15		**7**[b,c]	16		**7a**	44		–	
16		**7**[b,c]	90		**7a**	70		–	
17		**8**	90		**8a**	45 (41)		–	

[a] Subsequent addition of two equivalents of CBr_4. [b] Substrate + 5 mL CH_2Cl_2 used as solvent. [c] Yield determined relative to amount of CBr_4 used. [d] At 25 °C.

3–**5** remain intact, Table 1, entries 6–13) but it is not limited to the functionalization of adamantanes. Even acyclic hydrocarbons like **6** can be converted into the corresponding bromides selectively; only the tertiary C–H bond is activated. In the absence of tertiary C–H bonds, secondary C–H bonds can also be functionalized: cyclohexane (**7**) gives cyclohexyl bromide (**7a**) in 70% yield (90 h, Table 1, entry 16)!

Although this paper presents a new synthetic method, we wish to communicate some preliminary findings concerning the reaction mechanism, which is complicated because of the two-phase system.[18] Electrophilic catalysis by traces of impurities, as suggested for classical bromination reactions, is rather unlikely under these reaction conditions.[12] For instance, electrophilic activation (with Br_2/Al_2Br_6) of 2-oxaadamantane (**8**) only gives 4-bromo-2-oxaadamantane in low yields.[19] Here, however, we exclusively find 5-bromo-2-oxaadamantane (**8a**) in moderate yields (45%, Table 1, entry 17).

A plausible mechanism is the formation of carbanions through deprotonation with "highly activated" OH^-.[20, 21] While the hydroxide ion is able to deprotonate even allyl benzene ($pK_a = 34$)[22, 23] and other weak C–H acids[24, 25] under similar phase-transfer conditions, we did not find H/D exchange[24] in **1** in NaOD/D_2O under otherwise identical reaction conditions. No alkyl bromides were detected in the reaction with HOBr (from NaOH + Br_2), which should also transfer a bromonium ion onto an intermediate carbanion. While it is common that the phase-transfer agent is used up in carbanion reactions, we were able to recover most of the catalyst unchanged.[18, 24, 25] Hence, though it cannot yet be entirely excluded, the formation of carbanions is rather unlikely.

Although the rate of the reaction is only very slightly reduced in the dark under N_2 atmosphere, a radical[26] or single-electron transfer (SET) process[17, 27–30] is indicated. This is supported by the fact that no alkyl bromides were detected in the presence of TEMPO (tetramethylpiperidyl *N*-oxide), an efficient radical trapping agent. The reaction mixtures turn dark after a short while due to polymer formation;[17] CBr_4 is used up, and the transformation comes to a standstill after long reaction times. Addition of a second equivalent of CBr_4 restarts the conversion and increases the yields significantly (Table 1, entry 4). While lower NaOH concentrations decrease the yields considerably, the absence of the phase-transfer catalyst can in part be compensated by thorough mixing (high stirring speeds). The latter finding and the

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observation that the reaction practically stops when not stirred hints at an interphasic PTC rather than an extraction mechanism.[18]

Hence, we propose that the reaction is initiated by single-electron oxidation of OH^- by CBr_4 [Eq. (2)]. This is likely to be a thermodynamically inefficient process in solution where the equilibrium lies to the far left. Similar equilibria were postulated for the reactions of carbanions with CBr_4.[30] This mechanistic picture is supported by the findings that the reaction is rather slow and that no conversion occurs at much lower NaOH concentrations. The $^{\bullet}CBr_3$ radical, possibly formed from $CBr_4^{\bullet-}$ [Eq. (3)], can then start the chain reaction [Eqs. (4) and (5)]. This mechanism may, at least in part, also

$$CBr_4 + OH^- \rightleftharpoons CBr_4^{\bullet-} + HO^{\bullet} \quad (2)$$

$$CBr_4^{\bullet-} \rightarrow {}^{\bullet}CBr_3 + Br^- \quad (3)$$

$$RH + {}^{\bullet}CBr_3 \rightarrow R^{\bullet} + HCBr_3 \quad (4)$$

$$R^{\bullet} + CBr_4 \rightarrow RBr + Br_3C^{\bullet} \quad (5)$$

explain the observed selectivities for **1**. Although the 1- and 2-adamantyl radicals have similar thermodynamic stabilities ($\Delta H_f^{\circ} = 14.8$ and 12.3 kcal mol^{-1}, respectively),[33] 2-adamantyl products only form in trace amounts.[31] This last observation is likely to be due to the larger steric demands of the 2-adamantyl radical in both the hydrogen abstraction [Eq. (4)] and the radical substitution step [Eq. (5)]. It is important to emphasize the unusually high selectivity of tertiary over secondary C–H bonds and the monobromination in **6**–**8**. In stark contrast, free radical bromination of **1** with CBr_4/AIBN in CH_2Cl_2 under reflux afforded a mixture of **1a** and **1d** (2:1) in only 5% yield after 30 h.

In conclusion, we have found a new, highly selective method for the direct bromination of aliphatic hydrocarbons under phase-transfer conditions. The reaction is likely to proceed by single-electron-transfer initiation followed by a radical substitution with unusually high selectivity. A detailed elucidation of the reaction mechanism and the extension of this synthetic approach are well underway in our laboratories.

Experimental Section

General procedure: To a stirred solution of tetrabromomethane (1.33 g, 4.0 mmol), CH_2Cl_2 (15 mL), triethylbenzylammonium chloride (60 mg, 0.26 mmol), and substrate (4.0 mmol) was added 50% aqueous NaOH (10 mL). The solution was heated to 40 °C (25 °C for **6**) and stirred for various lengths of time (t[h]; (see Table 1). The organic phase was separated off and the aqueous phase extracted with CH_2Cl_2 (4×10 mL). Excess reagents and solvents were removed by vacuum distillation. The residues were separated by column chromatography (silica gel, petroleum ether). All products were analyzed and identified by GC, MS, and NMR analysis. Preparative yields (Table 1, in parentheses) were determined for the reactions of **1**–**5** (entries 1–13) and **8** (entry 17).

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