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Superelectrophilic bromination of deactivated aromatic rings with tribromoisocyanuric acid—an experimental and DFT study

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ABSTRACT

The reaction of deactivated arenes with tribromoisocyanuric acid (TBCA) in 98% H_2SO_4 produced bromoarenes in good yields. The acidity of the medium controls the strength of the brominating agent and the amount of polybrominated products. DFT calculations at B3LYP/6-311++G** level showed that the protonated TBCA (a superelectrophilic species) can easily transfer Br^+ to deactivated arenes, in order to decrease internal charge–charge repulsion.

Bromoarenes are very useful intermediates in organic synthesis, since they can be efficiently converted into a series of other functionality by well known methodologies such as halogen–metal exchange,[1] palladium-catalyzed Heck and related couplings,[2] and radical nucleophilic substitution.[3] There are many known methods for the bromination of aromatic rings, especially electron-rich systems.[4] However, severe experimental conditions are required for the halogenation of deactivated arenes.

N-Halo compounds are reported to react with activated arenes to produce efficiently haloarenes.[5] The halogenation of deactivated aromatic rings with *N*-halo compounds promoted by strong acids has also been reported.[6] During the past decade, Olah and Klumpp have carried out extensive experimental as well as theoretical studies on superelectrophilic activation of electrophiles by protosolvation with superacidic systems, allowing electrophilic reactions to take place with weakly nucleophilic substrates.[7]

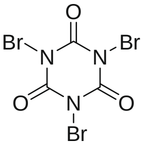

Figure 1. Tribromoisocyanuric acid (TBCA).

The tribromoisocyanuric acid (TBCA, Fig. 1) is an efficient source of electrophilic bromine (Br^+) that has been used for the brominating 1,3-dicarbonyl compounds[8] and activated aromatic rings,[9] dibromination[10] and cobromination[11] of alkenes, and also in diverse oxidation reactions.[12] TBCA is a stable solid that can be easily synthesized from isocyanuric acid and NaBr in the presence of oxone®.[10] It has the advantage of high atom economy in comparison to similar systems such as *N*-bromosuccinimide (NBS) and 3,3-dibromo-5,5-dimetilidantoin (DBH). Furthermore, in the reactions involving TBCA, isocyanuric acid left at the end of the reaction as a by-product can be recovered by filtration and reused to produce more TBCA.[11]

Continuing our interest in electrophilic halogenation using trihaloisocyanuric acids,[13] in the present work, we show our results on the reaction of deactivated aromatic rings with TBCA under strong acidic conditions (98% H_2SO_4).

The results of the bromination of some deactivated arenes with 0.34 mol equiv of TBCA in 98% H_2SO_4 at room temperature are shown in Table 1.[14] Nitrobenzene does not react with TBCA at ordinary conditions. On the other hand, it can easily be brominated if the reaction is performed in 98% H_2SO_4 to produce mainly *m*-bromonitrobenzene along with dibrominated products in small quantities. Bromination of *m*-dinitrobenzene occurs nicely even at room temperature in 98% H_2SO_4 affording the monobrominated product in 79% yield. On the other hand, the reaction with 1,3,5-trinitrobenzene does not occur, meaning that the electrophilic species is still lacking reactivity to brominate such highly deactivated system.

The above results show that acid catalysis plays an important role in the reaction of TBCA with deactivated arenes. TBCA can be O-protonated with strong Brønsted acids to form a superelectrophilic

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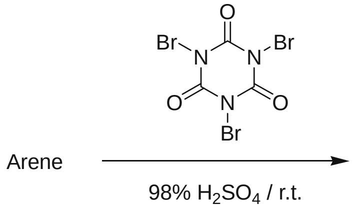
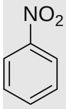
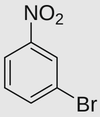
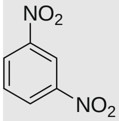
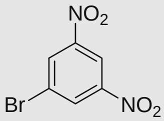
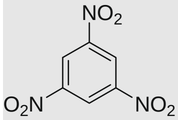
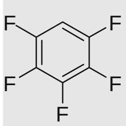
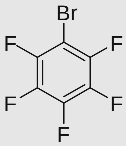
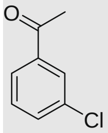
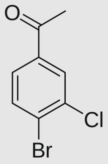
Table 1

Bromination of deactivated arenes with TBCA in 98% H_2SO_4



Arene	Product	T (h)	Yield[a] (%)
		4	69[b]
		4	79
	–	4	–
		1	52
		0.3	75

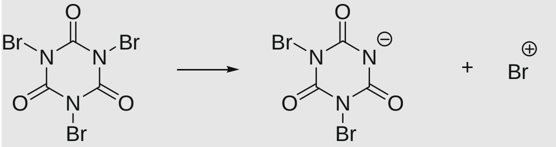
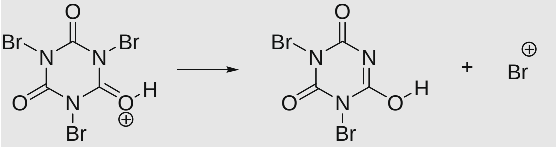
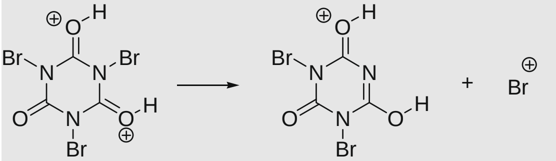
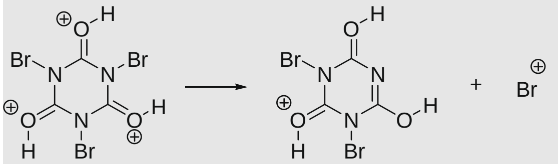
[a] Yield of pure product based on arene.

[b] Formed along with minor amount of dibromonitrobenzenes (<10%, by HRGC).

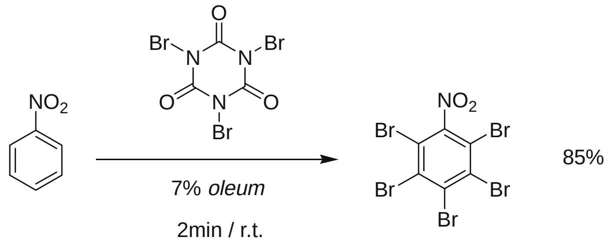
trication at the limit (Scheme 1) or a protosolvated analog, which can act as an efficient bromenium-transfer agent. This highly reactive species is able to attack even relatively unreactive arene nucleophiles. The driving force for the Br^+ release from protonated TBCA is believed to be due to the decrease in internal charge–charge repulsion.

Table 2

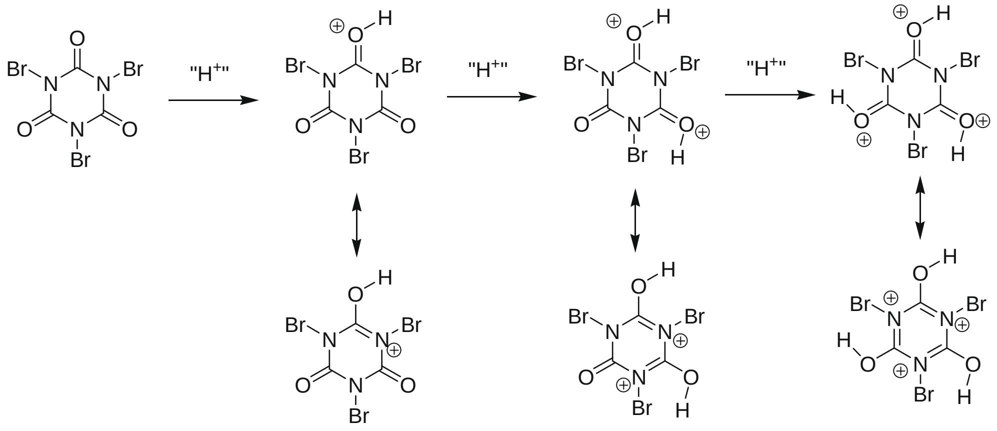
Enthalpy difference (298 K, 1 atm) for bromenium release from TBCA and its protonated species

Reaction	ΔH^{298} [a] (kcal/mol)
	269.5
	154.0
	41.3
	−33.9

[a] Performed at the B3LYP/6-311++G**//B3LYP/6-31++G** level, taking into account zero-point energy and thermal expansion correction.



Scheme 2.



Scheme 1.

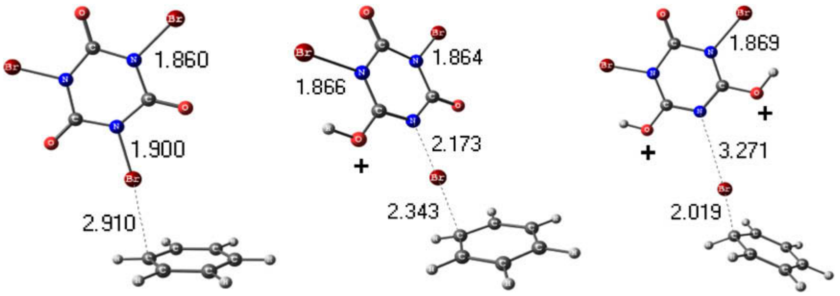


Figure 2. DFT calculations of transfer of Br^+ from TBCA and protonated species to benzene. All structures correspond to minima on the respective potential energy surface.

In order to verify such hypothesis, we investigated the reaction by DFT (density functional theory, see Supplementary data for computational details) calculations on TBCA and its protonated species that could estimate their ability to release Br^+, and hence would be correlated with its reactivity as an electrophile. DFT calculations at B3LYP/6-311++G**//B3LYP/6-31++G** level showed that the enthalpy change for the release of Br^+ from polyprotonated species of TBCA becomes more exothermic with the increase in protonation degree leading to a more reactive intermediate (Table 2). This can be attributed to the relief of the coulombic (charge–charge) repulsion within the polyprotonated TBCA upon Br^+ transfer to the substrate. As expected, N–Br bond length increases from TBCA (1.860 Å) to the triprotonated species (1.898 Å) as a reflection of the coulombic repulsion (Fig. S1 in Supplementary data).

Hence, the highly protonated TBCA-species works as a very powerful electrophile, whose reactivity can be regulated by the acid strength of the medium. As an example, nitrobenzene reacted with excess TBCA in 7% *oleum* to produce pentabromonitrobenzene in only 2 min at room temperature (Scheme 2).[15] Unfortunately, once more, 1,3,5-trinitrobenzene also did not react under these conditions.

The transfer of Br^+ from TBCA to the benzene ring using DFT calculations (B3LYP/6-31++G** level) is not possible (Fig. 2). It was also observed that increasing the protonation degree of TBCA led to the increase in the N–Br bond length whilst Br–C (from benzene) decreases significantly. In other words, based on coulombic repulsion, Br^+ transferring to benzene is much more effective in protonated species. However, transfer of Br^+ from the triprotonated species is strongly repelled by the intermediate (coulombic explosion) suggesting that this species is not formed.

The CPMAS ^{13}C NMR spectrum of TBCA in solid-phase (Fig. S2 in Supplementary data) shows a signal in δ 151.79 ppm, while the ^{13}C NMR of TBCA in 98% H_2SO_4 (Fig. S3 in Supplementary data) displays two signals (δ 147.13 and 146.18 ppm) referring to two different carbonyl groups—see Supplementary material. Comparing these chemical shifts with the calculated ones at GIAO/B3LYP/6-311++G**//B3LYP/6-31++G** level (Fig. S4 in Supplementary data) for the polyprotonated species of TBCA, it is possible to note that they probably refer to the monoprotonated species. Thus, probably there is a higher concentration of monoprotonated species in this media. However, the de facto reacting species could either be any of the polyprotonated species, with the species with higher protonation degree having a stronger electrophilic character.

In conclusion, we have shown that the activation, due to highly acidic medium, can be used to promote reaction of TBCA with deactivated arenes affording brominated products in good to excellent yields. DFT calculations at B3LYP/6-31++G** level suggest that the diprotonated form of TBCA would be responsible for the high reactivity of TBCA in strong acid medium. The driving force for this reaction with deactivated aromatics is due to relief of the intramolecular charge–charge repulsion in TBCA.

Acknowledgment

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Supplementary data

Optimized geometries for TBCA and its protonated species; CPMAS ^{13}C NMR spectrum of TBCA; ^{13}C NMR spectrum of TBCA in 98% H_2SO_4; ^{13}C NMR chemical shifts calculated for TBCA and its protonated species and computational details are available. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.02.010.

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14. *Typical procedure: 1-Bromo-3,5-dinitrobenzene.* To a well stirred solution of *m*-dinitrobenzene (2 mmol) in 98% sulfuric acid (4 mL) was added TBCA (0.74 mmol). The reaction was monitored by HRGC and after 4 h the reaction medium was poured onto crushed ice (100 g), carefully neutralized with 5% NaOH followed by addition of 10% Na_2SO_3 solution (20 mL). The aqueous solution was extracted with CH_2Cl_2 and the combined organic layer was dried (anhydrous Na_2SO_4). After evaporation of the solvent on a rotatory evaporator, the product was collected and recrystallized from hexane (79%, mp 74–76 °C, lit. 77 °C[16]). δ_H 8.70 (s, 2H), 8.98 (s, 1H) ppm. δ_C 117.9, 123.8, 132.0, 148.8. IR (KBr) ν 3095, 2873, 1808, 1614, 1594, 1346, 1307, 1160, 1072, 1000, 914, 894, 836, 725, 636, 514, 487 cm^{-1}. MS (70 eV) *m/z* 246 (M^+), 248 (M^++2), 200, 202, 170, 172, 153, 155, 75 (100%), 63.

15. *Pentabromonitrobenzene.* To a well stirred solution of TBCA (1.67 mmol) in 7% w/w SO_3 fuming sulfuric acid was carefully added nitrobenzene (1 mmol). The reaction medium displayed a reddish color that disappeared within 2 minutes, forming a white suspension. The work-up was similar to that described above. After evaporation of the solvent on a rotatory evaporator, the product was collected and recrystallized from hexane (85%, mp 226–228 °C, lit. 230 °C[17]). δ_C 116.4, 129.9, 131.8, 156.4 ppm. IR (KBr) v 1548, 1502, 1363, 1321, 1305, 1222, 1168, 1066, 894, 761, 598 cm^{-1}.
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