# LETTER



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## Bromine and iodine-cucurbit[6]uril complexes: preparation and applications in synthetic organic chemistry<sup>†</sup>

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lodine and bromine inclusion compounds were easily prepared by gas diffusion of the halogens using finely powdered CB[6]. A brown powder consisting of  $I_2$ -CB[6]·4H<sub>2</sub>O and an orange one of (Br<sub>2</sub>)<sub>4</sub>-CB[6]·10H<sub>2</sub>O were employed in several different reactions.  $I_2$ -CB[6] can be used in catalytic reactions giving yields comparable to those reported in the literature. Br<sub>2</sub>-CB[6] was effectively applied in electrophilic bromination of benzene and formation of bromohydrin. However, the radical substitution at cyclohexene could not be performed. Overall, based on these results, several applications can be envisioned for these complexes.

A variety of outstanding properties are associated with cucurbit[n]urils (CB[n]),<sup>1</sup> which are hollow thoroidal molecules, made up of n (n = 5, 6, 7, 8, 10 or higher) glycoluril units held together by 2n methylene bridges. Their pumpkin shape presents two identical portals (Fig. 1), made of n oxygen atoms each, delimiting a symmetric  $D_{nh}$  hydrophobic cavity (164 Å<sup>3</sup> for CB[6]). The chemical and thermal stabilities of these macrocyclic host molecules, allied to low solubility make them good candidates for heterogeneous agents. Considering our growing interest in the chemistry of cucurbiturils<sup>1b,2</sup> and the broad range of applications of halogens in synthetic organic chemistry,<sup>3</sup> we decided to investigate the preparation and organic synthesis applications of halogen inclusion in CB[6]. Herein, we disclose our first results of this ongoing project.

We easily prepared iodine and bromine inclusion compounds by gas diffusion of the halogens using finely powdered CB[6] (see the ESI† for details). A brown powder consisting of



Fig. 1 Representation of I<sub>2</sub>–CB[6] obtained by molecular mechanics using Ghemical V 2.99.2 engine MM tripos 5.2., further information at http://www.uku.fi/~thassine/ghemical. Carbon in black, nitrogen in blue and iodine in violet.

I<sub>2</sub>-CB[6]·4H<sub>2</sub>O and an orange one of (Br<sub>2</sub>)<sub>4</sub>-CB[6]·10H<sub>2</sub>O were obtained using this method (see the image in the ESI<sup>†</sup>). These complexes are stable in closed flasks, and retain their properties after two years. For simplicity, these compounds will be called I<sub>2</sub>-CB[6] and Br<sub>2</sub>-CB[6]. Gas phase synthesis, however, generates inclusion compounds but also loosely bonded adsorbed molecules, probably attached to the carbonyl groups from the outside. Adsorption seems to be more effective for bromine than iodine, and the converse is verified for inclusion. During the development of our study, Nau and coworkers<sup>4</sup> investigated halogen bonds inside cucurbit[*n*]uril cavities and urea molecules, showing that iodine and bromine inclusion compounds in solution adopt a 1:1 stoichiometry and that water helps in stabilizing the structure.

Our strategy included the selection of known reactions using  $Br_2$  and  $I_2$  and the reactivity was compared with  $Br_2$  and  $I_2$ -CB[6] complexes.  $Br_2$  and  $I_2$ -CB[6] complexes are solids,



Fig. 2 Iodine-catalyzed Prins cyclization.

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which facilitates the manipulation. In the case of  $Br_2$ -CB[6], this is a great advantage when compared to the volatile and liquid  $Br_2$ . For a better comparison, the procedure in the



Fig. 7 Bromination of benzene.

#### Table 1 Formation of bromohydrin from cyclohexene

literature was always reproduced first. Free CB[6] can be easily recovered after the reaction by filtration because it is almost insoluble in most solvents (except water–formic acid mixtures). Once recovered, CB[6] can be recycled and reused. The first reaction was the iodine-catalyzed Prins cyclization developed by our group.<sup>5</sup> The reaction between alcohol **1** and ketone **2** using  $I_2$ –CB[6] gave the expected product **3** in a slightly better yield than that obtained using  $I_2$  (Fig. 2).

Another important reaction performed using a catalytic amount of iodine is the introduction of the Boc protecting group in nitrogen compounds.<sup>6</sup> Treatment of benzyl amine (4) with Boc<sub>2</sub>O in the presence of either the  $I_2$  or the  $I_2$ -CB[6] complex gave the desired product 5 in an excellent yield (Fig. 3).

The preparation of enol ethers can be achieved using iodine in the presence of MeOH.<sup>7</sup> This transformation can be performed using the  $I_2$ -CB[6] complex in a yield similar to that reported in the literature, as exemplified for dimedone (6) (Fig. 4).

Cross-aldol condensation can be catalyzed by iodine. An example is the synthesis of  $\alpha, \alpha$ -bis(substituted-benzylidene) cycloalkanones from aromatic aldehydes and a cycloalkanone.<sup>8</sup> The desired product **10** was obtained in 70% yield employing cyclohexanone (**8**), benzaldehyde **9** and I<sub>2</sub>–CB[6], as catalysts (Fig. 5).

The use of the I<sub>2</sub>–CB[6] complex in a solvent-free reaction was investigated in the preparation of xanthane 12 from the aromatic aldehyde 9 and  $\beta$ -naphthol (11) catalyzed by iodine.<sup>9</sup> Indeed, the complex can also be used in a solvent-free reaction, although the yield was slightly lower (73 *vs.* 92%) (Fig. 6). Although compounds 10 and 12 were obtained in lower yields using I<sub>2</sub>–CB[6] than using I<sub>2</sub>, the yields are still very good.

Reactions using the  $Br_2$ -CB[6] complex were also investigated. It is important to mention that each molecule of the complex provides four  $Br_2$ . This was used to adjust the stoichiometry of the following reactions. The electrophilic bromination of benzene (13) was first explored using the procedure of a classic textbook as the reference.<sup>10</sup> A comparable yield of bromobenzene (14) was obtained using either the  $Br_2$  or the  $Br_2$ -CB[6] complex (Fig. 7).

A typical source of bromine is NBS. A highly used transformation using this reagent is the formation of bromohydrins.<sup>11</sup> Using cyclohexene (**15**) as substrate, the condition described in the literature was easily reproduced (Table 1, entry 1).<sup>11</sup> When NBS was replaced by Br<sub>2</sub>–CB[6] complex, a mixture of the desired product **16** and *trans*-1,2-dibromocyclohexene (**17**) was

	OH ''Br Br Br Br	
Entry	<b>15 16 17</b> Conditions	Product: isolated yield
1 2 3	1 equiv. NBS, NH <sub>4</sub> OAc, H <sub>2</sub> O: acetone $(1:4)$ 0.25 equiv. Br <sub>2</sub> -CB[6], NH <sub>4</sub> OAc, H <sub>2</sub> O: acetone $(1:4)$ 0.25 equiv. Br <sub>2</sub> -CB[6], NH <sub>4</sub> OAc, H <sub>2</sub> O	<b>16</b> : 85% (lit. 91) <b>16</b> : 20%; <b>17</b> : 15% <b>16</b> : 70%



Fig. 8 Formation of bromohydrin from cyclopentene

 Table 2
 Allylic bromination of cyclohexene



obtained in a low yield (entry 2). However, bromohydrin **16** was obtained in 70% yield changing the solvent to only water (entry 3). To confirm the effect of the solvent, the behavior of another substrate was investigated. Indeed, this condition was also successfully applied to convert cyclopentene (**18**) into **19** (Fig. 8).

Another important reaction employing NBS is allylic radical substitution. Using again cyclohexene (**15**) as the substrate, we investigated the possibility of replacing NBS by Br<sub>2</sub>–CB[6] complex to obtain bromocyclohexene **20** (Table 2, entry 1).<sup>10</sup> Nevertheless, only *trans*-1,2-dibromocyclohexene (**17**) was obtained (entry 2). The amount of the radical initiator was increased, but a similar result was obtained (entries 3 and 4). AIBN was tested instead of  $(PhCO_2)_2$ , giving again **17** (entry 5). In summary, only electrophilic addition of bromine to cyclohexene was observed. Probably, the radical initiator reacts with the CB part of the complex and the radical chain does not occur.

### Conclusions

In conclusion, an efficient protocol for the preparation of iodine and bromine inclusion compounds was developed. A brown powder consisting of  $I_2-CB[6]\cdot 4H_2O$  and an orange one of  $(Br_2)_4-CB[6]\cdot 10H_2O$  were employed in several different reactions.  $I_2-CB[6]$  can be used in catalytic reactions giving yields comparable to those reported in the literature.  $Br_2-CB[6]$  was effectively applied in electrophilic bromination of benzene and in the formation of bromohydrin. However, the radical substitution at cyclohexene could not be performed. Overall, based

on these results, we envision that these complexes can be employed as a source of halogens in a variety of reactions.

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