

Bromide and Iodide-cucurbit[6]uril Complexes: Preparation and Applications in Synthetic Organic Chemistry

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1. Experimental Procedures

1.1. Cucurbit[6]uril and Its Halogen Inclusion Complexes

Cucurbit[6]uril was prepared and purified according to the procedure described by Day and his group.¹ I₂-CB[6] and Br₂-CB[6] were prepared by diffusing the halogens vapor through solid CB[6] in a closed flask. 0.5046 grams ($5.066 \cdot 10^{-4}$ mol) of CB[6] were placed in a 50 mL beaker. The later was placed in a closed flask containing solid iodine 1000 times excess at room temperature. The same was done using 0.5104 grams ($5.124 \cdot 10^{-4}$ mol) of CB[6] and liquid bromine. The solids were exposed to the halogen vapors for a week, and they were revolved daily, in order to guarantee homogeneous gas contact. After this period a coffee-brown solid (I₂-CB[6], 0.6776 grams) and a light-orange solid (Br₂-CB[6], 1.0484 grams) were collected (Figure SI1). The inclusion compounds were left at open air for 96 hours to remove any excess of halogen that could be weakly bonded or trapped in the solids. The solids were weighted 4 times during this period (see fig. SI2).

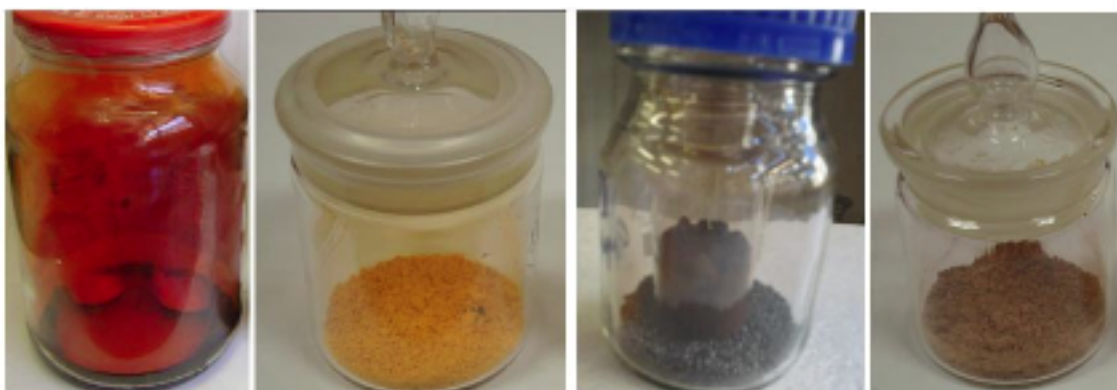


Figure SI1. From left to right, pictures of: Bromine inclusion, Br₂-CB[6], iodine inclusion, and I₂-CB[6].

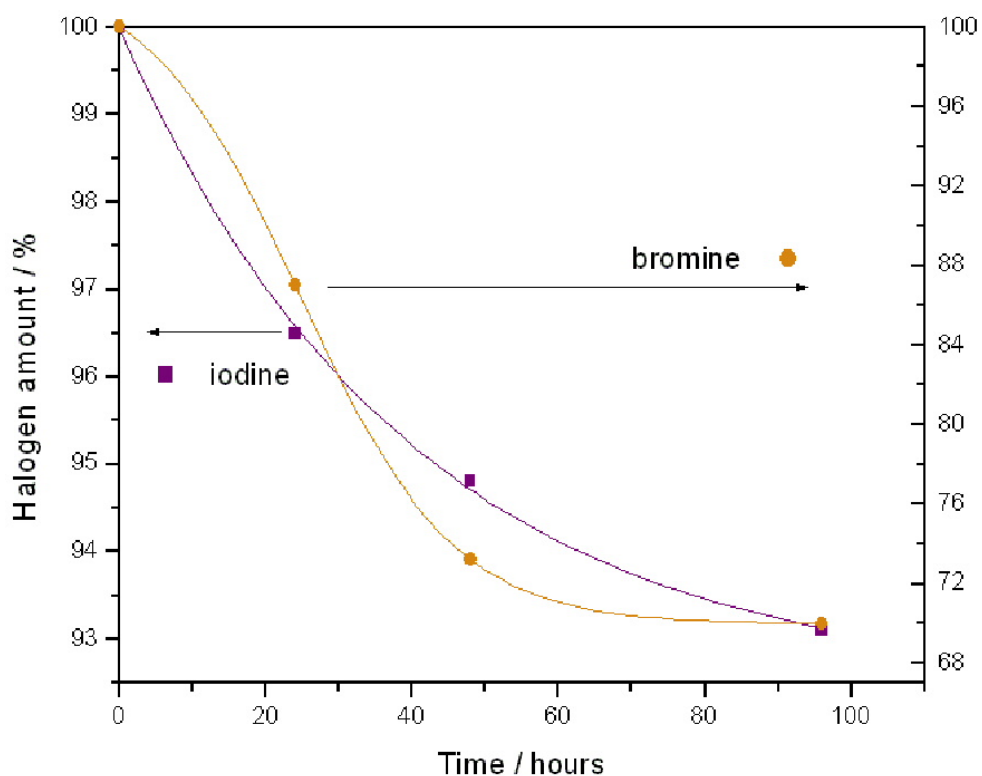


Figure SI2: Desorption isotherms for Iodine and Bromine inclusion compounds, fitted using sigmoidal decay functions.

The solids were weighted again, this time I_2 -CB[6], 0.6656 grams and Br_2 -CB[6], 0.8854 grams. These values corresponds to $(I_2)_{1.25}$ -CB[6] and $(Br_2)_{4.25}$ -CB[6]. Thermogravimetry was carried out on a SDT 2960 simultaneous DTA–TGA equipment in O_2 atmosphere to confirm these compositions (1 °C/min until 200 °C and 5 °C /min until 700 °C). Pure CB[6] presents 4 decomposition steps, one between 25 and 100 °C, assigned to water loss and 3 others, above 200 °C assigned to the macrocycle decomposition itself (Figure SI2). I_2 inclusion compound presents an additional weight loss between 100 and 191 °C, which

corresponds to halogen loss (Figure SI3). For bromine it is the same except for the fact that an additional bromine loss is verified at the very beginning of the experiment ($\text{temp} < 75$ °C). It is the adsorbed bromine leaving the sample (Figure SI3).

Data corresponds to $\text{CB}[6] \cdot 5 \text{H}_2\text{O}$, $(\text{Br}_2)_{4,2}\text{-CB}[6] \cdot 10\text{H}_2\text{O}$; probably 2.5 Br_2 adsorbed in external halogen bonds and 1.5 included, and $(\text{I}_2)\text{-CB}[6] \cdot 4\text{H}_2\text{O}$. Apparently no adsorbed iodine is present.

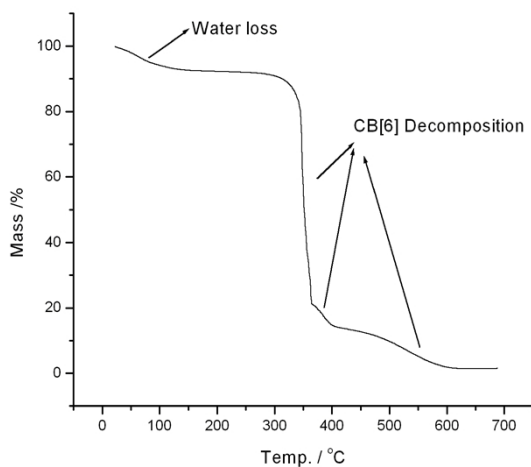


Figure SI3. Thermal decomposition of CB[6].

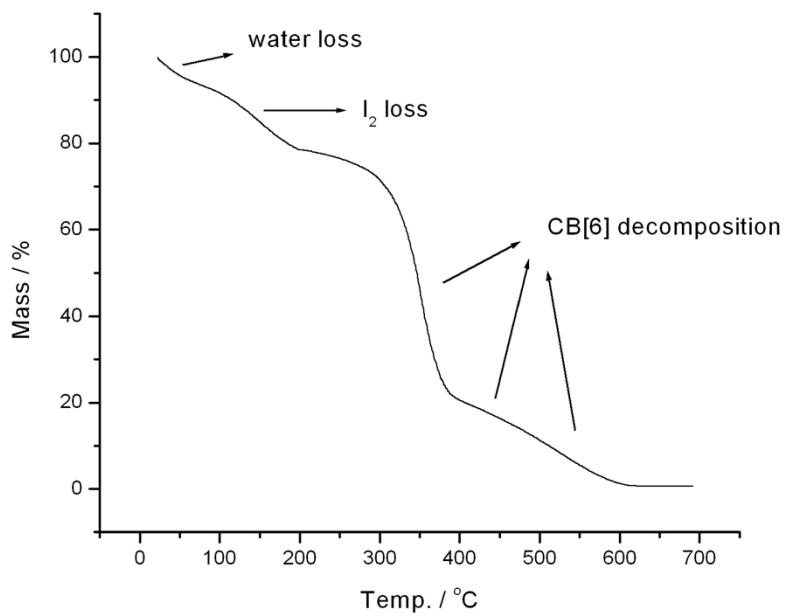
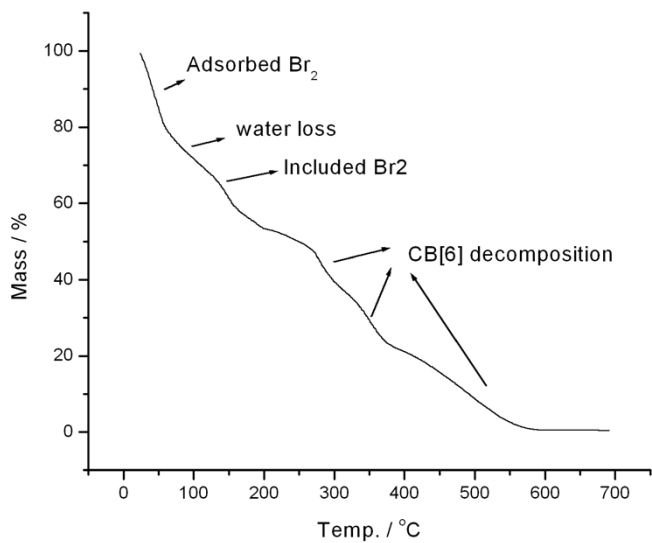


Figure SI4. Thermal decomposition of Br₂-CB[6] and I₂-CB[6].

1.2. Applications of Bromide and Iodide-cucurbit[6]uril Complexes in Synthetic Organic Chemistry

1.2.1. General information

All commercially available reagents were used without further purification unless otherwise noted. CH₂Cl₂ was freshly distilled over CaH₂. MeOH was dried by refluxing with magnesium turnings. TLC analyses were performed in silica gel plates, using UV and/or *p*-anisaldehyde solution for visualization. Flash column chromatography was performed using silica gel 200-400 Mesh. Melting points are uncorrected. All NMR analyses were recorded using CDCl₃ as solvent and TMS internal pattern.

1.2.2. Iodine Catalyzed Prins Cyclization²

To a stirred solution of alkenol **1** (0.113 g, 0.600 mmol) and diethyl ketone **2** (0.06 mL, 0.6 mmol) in CH₂Cl₂ (5 mL), was added I₂ (0.030, 0.076 mmol). The mixture was refluxed for 3 h. Na₂SO₃ (0.0104 g, 0.076 mmol) and H₂O (10 mL) were added. The aqueous phase was extracted with AcOEt (3x5 mL). The combined organic phase was washed with brine (5 mL) and dried over anhydrous MgSO₄. The solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (5% AcOEt in hexanes), affording the product **3**² (0.115 g, 0.450 mmol, 75%) as solid (mp: 58-60 °C).

1.2.3. I₂-CB[6] Catalyzed Prins Cyclization

As in 1.2.2, but using alkenol **1** (0.113 g, 0.600 mmol), diethyl ketone **2** (0.059 mL, 0.60 mmol), and I₂-CB[6].4H₂O (0.016 g, 0.012 mmol). The product **3**² (0.126 g, 0.492 mmol, 82%) was obtained as a colorless solid (mp: 58-60 °C).

1.2.4. Iodine-Catalyzed *N*-Boc Protection of Benzyl Amine³

To a stirred mixture of benzyl amine **4** (0.11 mL, 1.0 mmol) and of (Boc)₂O (0.23 mL, 1.0 mmol) was added a catalytic amount of I₂ (0.025 g, 0.10 mmol) under solvent-free conditions at rt. After 15 min, Et₂O (10 mL) was added to the reaction mixture. The reaction mixture was washed with aqueous Na₂S₂O₃ (5%, 5 mL) and with saturated NaHCO₃ (5 mL). The organic layer was dried over anhydrous MgSO₄, filtered and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography (gradient elution, 5-15% AcOEt in hexane) to afford the product **5** as a colorless solid (0.195 g, 0.943 mmol, 94%). mp: 58-60 °C (Lit.⁴ 57 °C).

1.2.5. I₂-CB[6]-Catalyzed *N*-Boc Protection of Benzyl Amine

As in 1.2.4, but using benzyl amine **4** (0.11 mL, 1.0 mmol), (Boc)₂O (0.23 mL, 1.0 mmol) and I₂-CB[6].4H₂O (0.053 g, 0.040 mmol). *N*-boc benzyl amine **5** was obtained as a colorless solid, mp: 57-58 °C (Lit.⁴ 57 °C) (0.194 g, 0.935 mmol, 93%).

1.2.6. β -Keto enol Etherification of Dimedone with Iodine⁵

To a stirred solution of dimedone **6** (0.140 g, 1.00 mmol) in MeOH (10 mL) was added I₂ (0.0076 g, 0.030 mmol). The reaction was monitored by TLC. After the reaction was complete, the solvent was removed under reduced pressure. The residue was extracted with AcOEt (2x5 mL) and washed with aqueous Na₂S₂O₃ (5 mL), with H₂O (5 mL), and with brine (5 mL). The organic layer was dried over anhydrous MgSO₄, filtered and the solvent was removed under reduced pressure. The product was purified by flash column chromatography (10% AcOEt in hexane) affording the enol ether **7⁶** as a colorless oil (0.136 g, 0.881 mmol, 88%).

1.2.7. β -Keto enol Etherification of Dimedone with I₂-CB[6]

As in 1.2.6, but using dimedone **6** (0.140 g, 1.00 mmol), MeOH (10 mL) and I₂-CB[6].4H₂O (0.016 g, 0.012 mmol) as a catalyst instead of I₂. Enol ether **7⁶** was obtained as a colorless oil (0.141 g, 0.916 mmol, 92%).

1.2.8. Iodine-Catalyzed Cross-Aldol condensation of cyclohexanone and *p*-tolylaldehyde⁷

To a stirred solution of *p*-tolylaldehyde **9** (0.129 mL, 1.10 mmol) and cyclohexanone **8** (0.052 mL, 0.50 mmol) in CH₂Cl₂ (5 mL) was added I₂ (0.038 g, 0.30 mmol). The mixture was stirred at rt. The reaction was monitored by TLC. After completion of the reaction, the mixture was treated with aqueous Na₂S₂O₃ (5 mL) solution.

The aqueous phase was extracted with EtOAc (3x5 mL). The organic layer was dried over anhydrous MgSO₄, filtered and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography (gradient elution, 5-15% AcOEt in hexane) to afford the product **10** as a yellow solid (0.143 g, 0.947 mmol, 95%). mp 172-173 °C (Lit.⁷ 172-173 °C).

1.2.9. I₂-CB[6]-Catalyzed Cross-Aldol Condensation of Cyclohexanone and *p*-Tolylaldehyde

As in 1.2.8, but using *p*-tolylaldehyde **9** (0.129 mL, 1.10 mmol), cyclohexanone **8** (0.052 mL, 0.50 mmol) and I₂-CB[6].4H₂O (0.053 g, 0.040 mmol). The product **10** was obtained as a yellow solid, mp 170-173 °C (Lit.⁷ 172-173 °C) (0.112 g, 0.372 mmol, 74%).

1.2.10. Iodine-catalyzed Synthesis of 14-(4-Methylphenyl)-14*H*-dibenzo[*a,j*]xanthene⁸

p-Tolylaldehyde **9** (0.059 mL, 0.50 mmol), β-naphthol **11** (0.168 g, 1.00 mmol) and I₂ (0.0032 g, 0.013 mmol) were ground well and transferred to a 50 mL flat-bottomed flask and heated on a hot plate at 90–95 °C for 50 min. After complete conversion (monitored on TLC), the system was cooled to rt. The mixture was washed with Na₂S₂O₃ (10%, 5 mL) solution and the separated precipitate was purified by recrystallization from aqueous ethanol to afford xanthene **12** as a colorless solid (0.172 g, 0.462 mmol, 92%). mp. 227-229 °C (lit.⁸ 228 °C).

1.2.11. I₂-CB[6]-catalyzed Synthesis of 14-(4-Methylphenyl)-14H-dibenzo[*a,j*]xanthene.

As for 1.2.10, but using *p*-tolylaldehyde **9** (0.059 mL, 0.50 mmol), β-naphthol **11** (0.168 g, 1.00 mmol) and I₂-CB[6].4H₂O (0.0067 g, 0.0051 mmol). Xanthene **12** was obtained as a colorless solid, mp: 229-230 °C (Lit.⁸ 228 °C) (0.136 g, 0.365 mmol, 73%).

1.2.12. Bromination of Benzene with Br₂⁹

To a stirred solution of anhydrous benzene **13** (0.067 g, 0.85 mmol) and anhydrous pyridine (0.0068 ml, 0.085 mmol) was added carefully Br₂ (0.0600 mL, 1.16 mmol) at 0 °C. The temperature of the water bath was slowly raised to 65-70 °C. After 15 min, NaOH (10%, 5 mL) was added to the reaction mixture. The aqueous phase was extracted with hexane (2x5 mL) and with water (10 mL). The organic layer was dried over anhydrous MgSO₄, filtered and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography (hexane) to afford bromobenzene **14** as a pale yellow oil (0.072 g, 0.459 mmol, 54%).

1.2.13. Bromination of Benzene with Br₂-CB[6]

As in 1.2.12, but using benzene **13** (0.0645 g, 0.820 mmol), anhydrous pyridine (0.0065 ml, 0.082 mmol), CH₂Cl₂ (5 mL), and (Br₂)₄-CB[6].10H₂O (0.391 g, 0.215 mmol). Bromobenzene **14** was obtained as a pale yellow oil (0.0716 g, 0.459 mmol, 56%).

1.2.14. Formation of *trans*-2-Bromo-cyclohexanol from Cyclohexene with NBS¹⁰

To a suspension of cyclohexene **15** (0.082 g, 1.0 mmol) and NH₄OAc (0.0077 g, 0.10 mmol) in acetone (4 mL), were added NBS (0.20 g, 1.1 mmol) and H₂O (1 mL). The mixture was stirred at rt. After completion of the reaction, the mixture was concentrated in vacuum and extracted with EtOAc-H₂O (1:1) (3x5 mL). The organic layer was dried over anhydrous MgSO₄, filtered and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography (2% AcOEt in Hexane) to obtain pure *trans*-2-bromo-cyclohexanol (**16**)¹⁰ (0.15 g, 0.85 mmol, 85%).

1.2.15. Formation of *trans*-2-Bromo-cyclohexanol from Cyclohexene with Br₂-CB[6]

As in 1.2.14, but using cyclohexene **15** (0.082 g, 1.0 mmol), NH₄OAc (0.0077 g, 0.10 mmol), (Br₂)₄-CB[6].10H₂O (0.45 g, 0.25 mmol) in H₂O (5 mL). The product **16**¹⁰ (0.12 g, 0.70 mmol, 70%) was obtained as a pale yellow oil.

1.2.16. Preparation of *trans*-2-Bromo-cyclopentanol from Cyclopentene with Br₂-CB[6]

As in 1.2.15, but using cyclopentene **18** (0.068 g, 1.0 mmol), NH₄OAc (0.0077 g, 0.10 mmol), (Br₂)₄-CB[6].10H₂O (0.45 g, 0.25 mmol) in H₂O (5 mL). *trans*-Bromocyclopentanol **19**¹⁰ (0.12 g, 0.74 mmol, 74%) was obtained as a pale yellow oil.

1.2.17. Allylic Bromination of Cyclohexene with NBS⁹

Cyclohexene **15** (0.51 mL, 5.0 mmol) was added to a suspension of (PhCO₂)₂ (0.012 g, 0.050 mmol) and NBS (0.18 g, 1.0 mmol) in anhydrous CCl₄. The mixture was refluxed for 15 h, filtered, and concentrated on vacuum. The crude product was purified by flash column chromatography (5% AcOEt in hexane) to obtain 3-bromo-cyclohexene (**20**) (0.089 g, 0.056 mmol, 56%) as a colorless liquid.

1.2.18. Formation of *trans*-1,2-Dibromocyclohexane from Cyclohexene with Br₂-CB[6]

As in 1.2.17, but using cyclohexene **15** (0.51 g, 5.0 mmol), (PhCO₂)₂ (0.012 g, 0.050 mmol), and (Br₂)₄-CB[6].10H₂O (2.27 g, 1.25 mmol) in anhydrous CCl₄. *trans*-1,2-Dibromocyclohexane (**17**) (0.16 g, 0.65 mmol, 65%) was obtained as a pale yellow oil.

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