Through-Shell Oxidation and Reduction Reactions of Guests in a Hollow Container Single Molecule[1]

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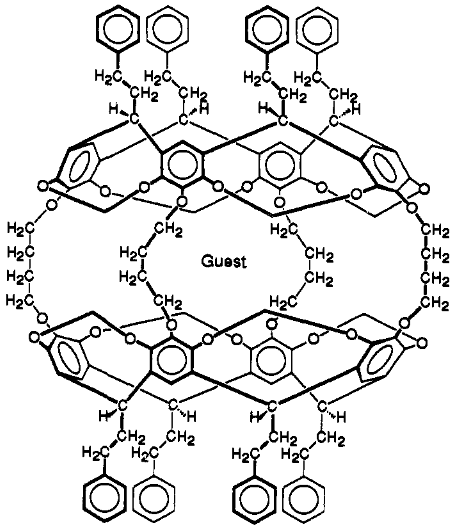
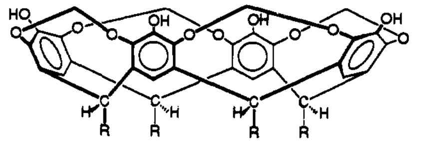
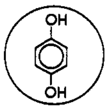
A new family of 30 hemicarceplexes, **1**·guest, has been synthesized by shell closure of **2** with four $TsO(CH_2)_4OTs$ in Cs_2CO_3–$(CH_3)_2NCOCH_3$ at 75 °C to give **1**·$(CH_3)_2NCOCH_3$ (20–30%). This complex dissolved in $(C_6H_5)_2O$ and heated at 195 °C for 5 days gave empty **1**. By heating **1** solutions in neat potential guest [e.g., $O_2NC_6H_5$, 1,4-$(HO)_2C_6H_4$, 1,2-$(HO)_2C_6H_4$, 2-CH_3-1,4-$(HO)_2C_6H_3$, or 4-CH_3-1,2-$(HO)_2C_6H_3$], **1**·guests were formed, the incarcerations being partially driven by mass law. These hemicarceplexes were fully characterized, **1**·$O_2NC_6H_5$ by crystal structure determination.[2]



1·Guest



2, R = $C_6H_5CH_2CH_2$



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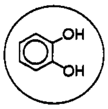

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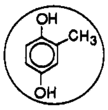

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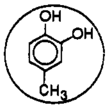

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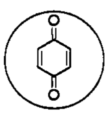

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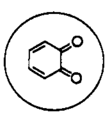

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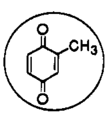

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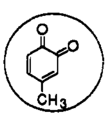

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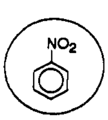

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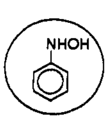

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Essentially quantitative oxidation reactions were carried out on **1**·1,4-$(HO)_2C_6H_4$, **1**·1,2-$(HO)_2C_6H_4$, **1**·2-CH_3-1,4-$(HO)_2C_6H_3$, and **1**·4-CH_3-1,2-$(HO)_2C_6H_3$ to give the corresponding incarcerated quinones, which were fully characterized.[3] These quinones could not be introduced directly into **1** by heating due to extensive decomposition, particularly the *o*-quinones, which are intrinsically unstable. Both $Ce(NH_4)_2(NO_2)_6$–silica gel–CCl_4[4] at 25 °C and $Tl(O_2CCF_3)_3$–CCl_4[5] at reflux (external to the shell of dissolved **1**·guest) served as oxidizing agents. The four incarcerated guests **3–6**[3] and their products **7–10**[3] are formulated, enclosed by a circle to indicate their occupation of the inner phase of the hemicarcerand throughout their reactions. These quinones were stable to chromatography and in solution below 100 °C, and they were storable in the absence of light. The stability of the ordinarily unstable *o*-quinones is noteworthy, and as in the case of incarcerated cyclobutadiene,[6] the shell protects the compounds from undesired reactions.

When the four incarcerated quinones **7–10** were heated at reflux in $(CH_2)_4O$ solutions containing 2 drops of MeOH with SmI_2,[7,8] the corresponding incarcerated hydroquinones **3–6** were produced. When a solution of **7** in $(CH_2)_4O$ was shaken with a 0.23 M aqueous solution of $Na_2S_2O_4$ for 5 min, a mixture of 30% **3** and 70% **7** was obtained (^1H NMR). When heated at reflux in $(CH_2)_4O$ plus 2 drops of MeOH with SmI_2, **1**·$O_2NC_6H_5$[2] reduced to **1**·$HONHC_6H_5$.[3] These reductions also proceeded without generation of side products. The water produced in these reactions apparently escaped the inner phase through the 26-membered-ring portals located in the equatorial–temperate regions of the globe.

These redox reactions and the reduction of $C_6H_5NO_2$ to C_6H_5NHOH were carried out at temperatures much lower than those required to allow a reaction mechanism to apply in which the hemicarceplex dissociates, the liberated guest undergoes reaction, and the product undergoes complexation. The high yields, the instability of free *o*-benzoquinones, and the reduction of $C_6H_5NO_2$ to C_6H_5NHOH rather than $C_6H_5NH_2$ all indicate that these reactions occurred in the inner phase of the hemicarcerand.

These reactions[9] demonstrate that electrons, protons, and H_2O can be transferred into and out of the interior phase of **1**. The interior of **1** is too small to accommodate both reactants at the same time, and therefore reaction mechanisms involving coordination of the guest with the reagent are not a necessary condition for these reactions to occur. The oxidation of the hydroquinones with $Ce(NH_4)_2(NO_2)_6$ adsorbed on silica is particularly noteworthy, since three phases, the inner phase of **1**, the solvent, and the solid phase, are all involved.

The nine reactions reported here coupled with the six thermal and photochemical reactions, one addition–elimination reaction,[6] and one acid–base reaction[10] suggest that the inner phase of hemicarcerands, tailored to the dimensions of potential transition states, is a unique place to carry out highly specific reactions involving ordinarily unstable reactants. The scope of such reactions is being investigated, including reactions in which ordinarily unstable catalysts are incarcerated in small-molecule-permeable hosts.

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(1) We warmly thank the U.S. Public Health Service for supporting Grant GM-12640.

(2) Robbins, T. A.; Knobler, C. B.; Bellew, D. R.; Cram, D. J. *J. Am. Chem. Soc.*, submitted.

(3) Elemental analyses within 0.30% of theory, ^1H NMR spectra as expected, and FABMS *m/e* ($M^+ + 1$) as parent ions.

(4) Fischer, A.; Henderson, G. N. *Synthesis* **1985**, 641–643.

(5) McKillop, A.; Swann, B. P.; Taylor, E. C. *Tetrahedron* **1970**, *26*, 4031–4039.

(6) Cram, D. J.; Tanner, M. E.; Thomas, R. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1024–1027.

(7) Zhang, Y.; Lin, R. *Synth. Commun.* **1987**, 329–332.

(8) Kagan, H. B. *New J. Chem.* **1990**, *14*, 453–460 and earlier papers.

(9) Oxidations and reductions were carried out on a 50–12-mg scale under a blanket of argon in degassed solvents with 5–100 equiv of oxidizing or reducing agent for 30 min to 1 h. In oxidations with the cerium reagent, the reaction mixture was filtered, the solid was washed with CH_2Cl_2, and the combined filtrates were evaporated in vacuo to 5 mL and poured into 40 mL of CH_3OH to precipitate the incarcerated quinone. In oxidations with the thallium reagent, the reaction mixture was cooled, and the product was isolated as before. In the reductions with SmI_2, the reaction mixtures were cooled and shaken with 2 mL of 2 M aqueous HCl in 20 mL of water, and the product was extracted with $CHCl_3$ and isolated as before.

(10) Cram, D. J.; Blanda, M. T.; Paek, K.; Knobler, C. B. *J. Am. Chem. Soc.* **1992**, *114*, 7765–7773.

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