JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

Communication

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Cavity-Directed Chromism of Phthalein Dyes

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Supporting Information

ABSTRACT: Phthalein dyes in the quinone dianion form (pseudo-D_3, colored) are transformed into the lactone dianion form (pseudo-T_d, colorless) through encapsulation in a T_d-symmetric host even under basic conditions (pH ~10). The compatibility in size and symmetry between the lactone and the cavity is essential to the transformation. Upon addition of a guest that strongly binds to the cavity, the encapsulated phenolphthalein is expelled, the color of the basic solution is regained, and the host–guest complexation is thus visualized.

Phthalein dyes are widely used pH indicators that exist as colored quinone dianions (open form, **o**) at high pH (typically, pH 8–12) but as colorless lactones (closed form, **c**) at low pH (typically, pH < 8).[1] When the quinone dianion is lactonized, the sp^2 hybridized central carbon is converted to an sp^3 carbon, resulting in a distinct change in the molecular shape from pseudo-D_3 to pseudo-T_d. Although the pH-dependent chromism of the dyes has been thoroughly documented, scant attention has been paid to their pH-dependent shape conversion. It is anticipated that, if the molecules are placed in a confined cavity, the spatial constraint will work in favor of one of the two forms, pushing the equilibrium toward it.[2] As a result, the structural conversion will not be pH-dependent, but instead restricted by the cavity. Accordingly, the encapsulation of phthalein dyes in a cavity was examined with self-assembled coordination cage **1** (Figure 1a).[3] We found that the rigid and T_d-shaped cavity of **1** allowed the phthalein dyes to exist only in the lactone form even in a basic solution, and this provides a unique example of the cavity-directed chromism of organic dyes (Figure 1b).

First, the binding ability of cage **1** for phenolphthalein (**2**) was examined. In an aqueous solution of cage **1a**, colorless powder **2c** (lactone form, 2 equiv) was suspended at 80 °C for 2 h. After removal of excess **2c** by filtration, ^{1}H NMR spectroscopy revealed the formation of inclusion complex **1a**·**2c** in 77% yield (Figure 2a). An upfield shift of the guest signals was observed. The apparent symmetry of inclusion complex **1a**·**2c** observed in the NMR spectrum remained T_d, which indicates the rapid tumbling motion of **2c** in the cavity. Inclusion of more bulky tetrabromophenolphthalein **3c** was also examined. Under the same conditions, inclusion complex **1a**·**3c** was formed in 80% yield (Figure 2b). In this case, the symmetry of cage **1a** dropped from T_d to C_s (24 signals for the pyridyl protons),[3b] which suggests restricted guest motion in the cavity.

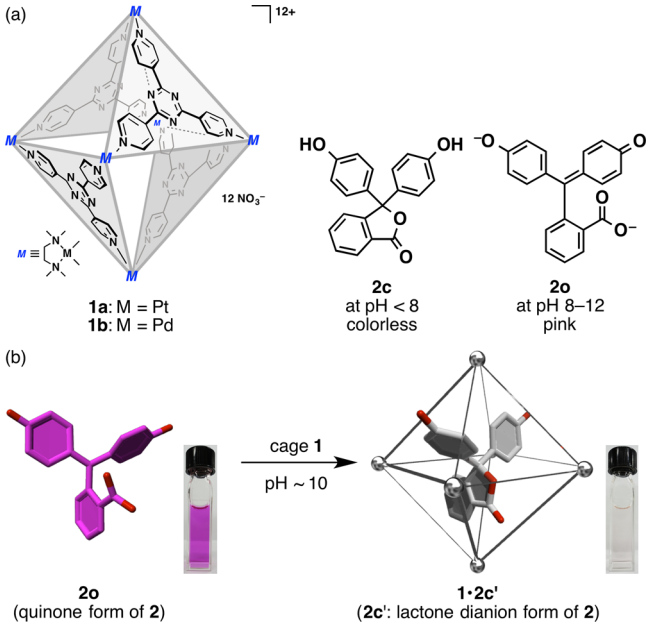

Figure 1. (a) Chemical structures of cage **1** and phenolphthalein (**2c**, lactone form; **2o**, quinone form). (b) Cartoon representation of the cavity-directed chromism of phenolphthalein.

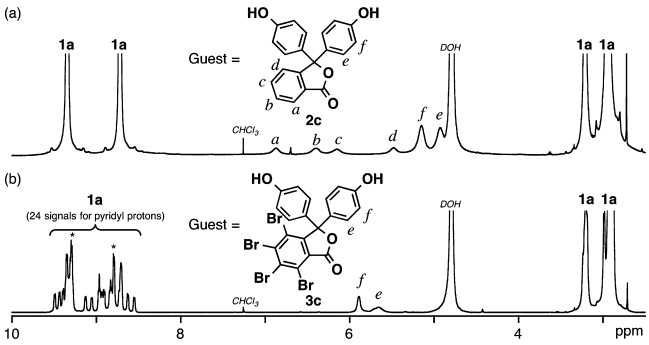

Figure 2. ^{1}H NMR spectra (500 MHz, 300 K, D_2O) of (a) **1a**·**2c** and (b) **1a**·**3c** (asterisk (*) labels denote signals of free cage **1a**).

Received: April 8, 2015
Published: May 27, 2015

DOI: 10.1021/jacs.5b03618
J. Am. Chem. Soc. 2015, 137, 7043–7046

The structure of the inclusion complex with phenolphthalein **2c** was revealed by X-ray crystallography, and **2c** was encapsulated in the expected lactone form (Figure 3). The

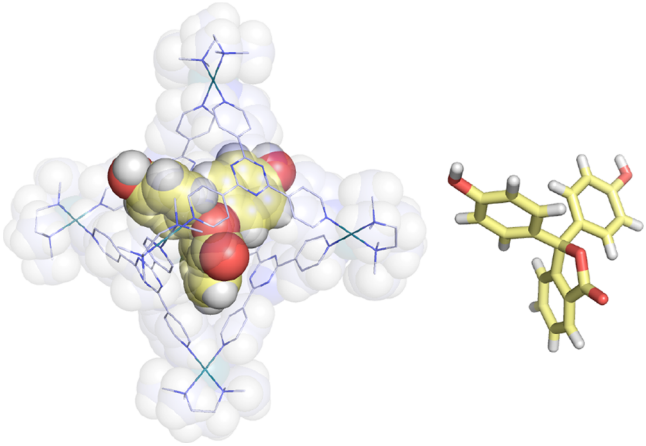

Figure 3. (Left) X-ray single crystal structure of **1b**·**2c**. Nitrate anions and solvent molecules have been omitted for clarity. Only the guest molecule in the cavity is represented. (Right) Guest **2c** as a stick model.

single crystal X-ray diffraction study of the inclusion complex was carried out using cage **1b**, a Pd(II) analogue of cage **1a**.[3c] In the crystal structure, one guest molecule is located at the center of the cavity and one phenol ring shows $\pi-\pi$ stacking with the triazine core of a panel ligand.[4] The two phenol portions point to the portals of the cage, and the phthalic moiety is sandwiched between two panel ligands.

Having confirmed that the cavity of cage **1** fits the lactone form of phenolphthalein (**2c**), we next investigated the behavior of the phthalein dyes on addition of the cage under basic conditions (Figure 4). Phthalein dye **2** was dissolved in an aqueous carbonate buffer (pH = 10.0, [**2**] = 40 μM) and a carbonate buffer solution of cage **1a** (pH = 10.0, [**1a**] = 1.6 mM) was added dropwise. UV/vis spectra were recorded after each addition (0.053 equiv to **2**) of the solution of cage **1a** (Figure 4a). Upon addition of **1a**, the absorption maximum at 552 nm, diagnostic of quinone dianion form **2o**, significantly decreased. After addition of 2.0 equiv of cage **1a**, the pink color of the initial solution completely disappeared. This color change of the phthalein dyes is effected only by the cage cavity: addition of (tmeda)Pt(ONO_2)$_2$ (tmeda = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine) or the panel ligand of cage **1** did not result in any color change. Curve fitting[5] revealed the association constant K_a to be 1.0×10^6 M^{-1}. The highly effective decoloration is probably caused by the recognition of the whole molecule of the phthalein dye by cage **1a**. The same titration experiment was carried out with phthalein dye **3**. Because of the closer packing in the cage (Figure 2b), **3** showed a stronger affinity to **1a** and the pink color disappeared more quickly ($K_a > 10^7$ M^{-1}).

To confirm that phenolphthalein was indeed in lactone form **2c** in cage **1a**, NMR studies were carried out (Figures 5 and S14). For a mixture of cage **1a** and **2** (5:3) (deuterated carbonate buffer, pD = 10.0), a significant upfield shift of the signals of **2** was observed (Figure S14). The ^{13}C NMR spectrum of the solution revealed that phthalein dye **2** adopted the lactone dianion form **2c**′ in the cavity even under basic conditions (Figure 5). The central carbon (C-1) of lactone

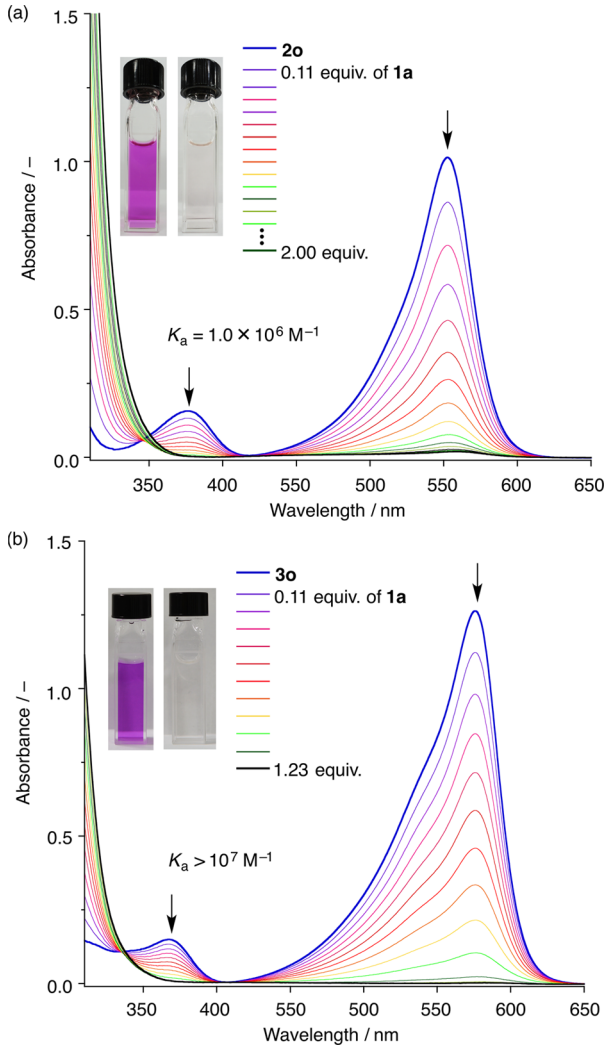

Figure 4. UV/vis spectra of (a) **2** and (b) **3** in carbonate buffer (pH = 10.0, [**2**] = 40 μM, [**3**] = 20 μM) after addition of increasing amounts of cage **1a**. Photographs before (left) and after (right) addition of **1a** (2.00 equiv for **2** and 1.23 equiv for **3**) are shown in the insets.

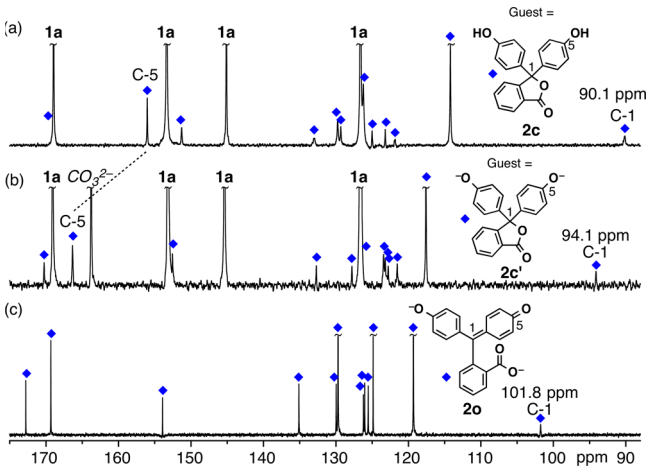

Figure 5. ^{13}C NMR spectra (300 K) of (a) **1a**·**2c** under neutral conditions (in D_2O, 125 MHz), (b) **1a**·**2c**′ in carbonate buffer (in D_2O, pD = 10.0, 150 MHz), and (c) **2** with 2 equiv sodium hydroxide (in 1:1 D_2O/DMSO-d_6, [**2**] = 20 mM, 125 MHz).

DOI: 10.1021/jacs.5b03618
J. Am. Chem. Soc. 2015, 137, 7043−7046

form **2c** is known to appear at 92.5 ppm (in DMSO-d_6)[1b] and C-1 of quinone form **2o** appeared at 101.8 ppm (in 1:1 D_2O/DMSO-d_6, Figure 5c). The central carbon of phenolphthalein in **1a**·**2c** under neutral conditions appeared at 90.1 ppm (Figure 5a). In carbonate buffer, the corresponding signal was observed at 94.1 ppm, suggesting the lactone form. Moreover, the signal of the carbon adjacent to the oxygen atom of the phenol ring (C-5) exhibited a significant downfield shift, which indicates deprotonation of the phenol.[1b,6] In the case of **3**, C_s symmetry of the inclusion complex was retained even under basic conditions (Figure S19), and its ^{13}C NMR spectrum showed similar behavior to **2** (Figures S5, S20). From these results, it was concluded that dyes **2** and **3** adopt lactone dianion form **2c**′ and **3c**′ in the cavity of cage **1a** under basic conditions. Thus, the quinone dianion forms of the phthalein dyes were converted to the lactone dianion forms by inclusion in T_d-symmetric cage **1a**.

Finally, the cavity-directed chromism of **2** was applied to the visualization of host–guest complexation. Since the **2c**′–**2o** transformation is reversible, colorless **2c**′ turns back to pink **2o** when it is expelled from the cavity upon addition of competitive guest compounds (Figure 6).[2b] Thus, 1-adamantanecarboxylic

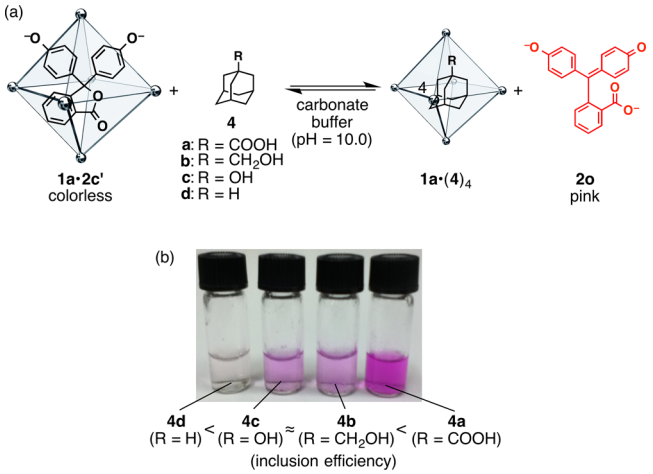

Figure 6. Visualization of guest inclusion into cage **1a** using **1a**·**2c**′.

acid (**4a**, 4.0 equiv to **1**) was added to a carbonate buffer solution of **1a**·**2c**′ (pH = 10.0, [**1a**] = 0.12 mM, [**2c**′] = 60 μM).[7] After the addition, the colorless solution of **1a**·**2c**′ immediately turned pink, suggesting the reversion of **2c**′ to quinone dianion form **2o** following the release of **2c**′ from the cage (Figures 6, S24). Consequently, guest exchange from **2c**′ to **4a** was directly observed by the significant color change. In the same manner, other adamantane derivatives **4b–d** were tested (see the Supporting Information (SI) for details). The solution color (colorless–deep pink) reflects the efficiency of guest exchange; the relative affinity of **4** for cage **1a** was estimated as **4d** (R = H) < **4c** (R = OH) ≈ **4b** (R = CH_2OH) < **4a** (R = COOH) from the intensity of the pink color. In this way, the otherwise visually imperceptible guest inclusion was visualized by using **1a**·**2c**′. Similar visualization of host–guest complexation has been examined with cyclodextrin, although a large excess of host (~100 equiv) was required because of the weak binding of the dyes.[2a–c]

In summary, we achieved the cavity-directed chromism of phthalein dyes. The shape compatibility between the tetrahedral lactone dianion and the T_d-symmetric cavity of a coordination cage resulted in the relative stability of the lactone form, and pushed the equilibrium toward lactonization. Because this process is reversible, the colored form of the phthalein dye recovers when the dye is ejected from the cavity, and this feature allows the visualization of guest encapsulation. More generally, this approach enables control of the properties of a target compound and its responsiveness to external stimuli without any chemical modifications.[8]

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, physical properties, and crystallographic data (CIF). The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b03618.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by Grants-in-Aid for Specially Promoted Research (24000009) and for Young Scientists (A) (25708008). H.T. is grateful for JSPS Research Fellowship for Young Scientists.

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(4) Although NMR studies in solution suggested a 1:1 host–guest complex, a 1:2 complex was observed in the crystalline state. The second guest was located between the two cages. See the SI for details.

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DOI: 10.1021/jacs.5b03618
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DOI: 10.1021/jacs.5b03618
J. Am. Chem. Soc. 2015, 137, 7043−7046