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Selective methylation of phloroglucinol in the presence of a glycoluril clip

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ABSTRACT

Methylation of phloroglucinol was performed using dimethyl sulfate as the methylating agent in the presence and absence of a glycoluril clip. The results showed that the yield of the di-methylated product decreased significantly in the presence of a glycoluril clip (host), due to the formation of a host–guest complex between the clip and phloroglucinol. Also, the reaction was conducted with different quantities (mol %) of the host.

Reaction control through complexation of a substrate by a supramolecular host is a relatively new concept. Complexation influences the chemical reactivity, including chemo-, regio-, and stereoselectivity of the complexed substrate.[1] Several host systems have been introduced and developed for enhancing the reactivity and/or selectivity in various chemical transformations in supramolecular systems. For example, molecular clips derived from propanediurea promoted regioselectivity in the SO_2Cl_2-mediated electrophilic aromatic chlorination of *o*-cresol.[2] Breslow and Campbell reported the selective aromatic substitution of anisole bound in the cavity of cyclodextrin.[3] The host cyclodextrin has also been used for increasing positional selectivity in the bromination of acetanilide with pyridinium dichlorobromate, so that only the *para*-isomer was produced in the presence of α-cyclodextrin.[4] Oxidation of benzene to phenol using N_2O as the oxidant in the presence of a zeolite host has been reported with selectivity close to 100%.[5] Calix[*n*]arenes, which possess cavities of various sizes, have been utilized to increase the selectivity in organic reactions. For example, Ramamurthy et al. investigated the selectivity in the photochemistry of benzoin alkyl ethers using calix[6]arene and calix[8]arene systems as supramolecular hosts.[6]

A series of host molecules derived from the concave molecule, glycoluril, have been developed by Nolte's group.[7,8] These hosts possess a well-defined and rigid U-shaped cavity, which is formed by the glycoluril framework and two aromatic side walls. With their preorganized cleft, they are good hosts for a 1,3-dihydroxybenzene guest molecule in a chloroform solution through hydrogen bond, π–π stacking interactions, and a so-called 'cavity effect'.[9–11] For example, a value of $K_a = 200\ M^{-1}$ has been reported for the complex of a glycoluril host with resorcinol in $CDCl_3$.[10]

The binding properties of the glycoluril hosts encouraged us to investigate their possible roles in the selectivity of reactions with a guest, for example, resorcinols. Phloroglucinol (**1**) was a good substrate for this study; this compound has the resorcinol skeleton and therefore, behaves as a good guest toward glycoluril hosts. Glycoluril **2**, which is readily prepared in two steps from benzil,[12]

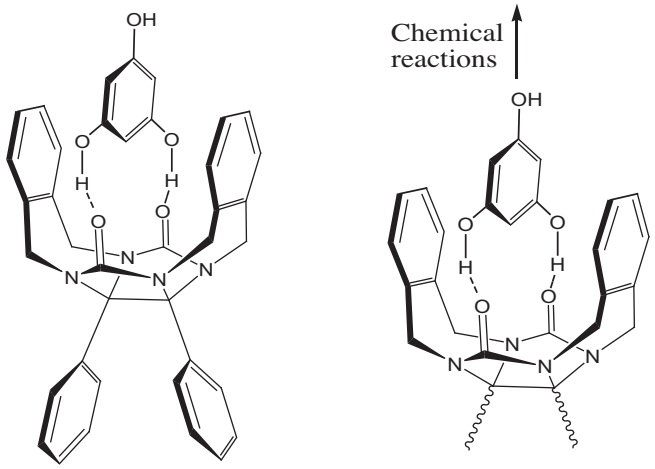

Figure 1. Schematic presentation of the formed complex between the guest phloroglucinol (**1**) and the glycoluril host **2** (dashed lines indicate hydrogen bonds).

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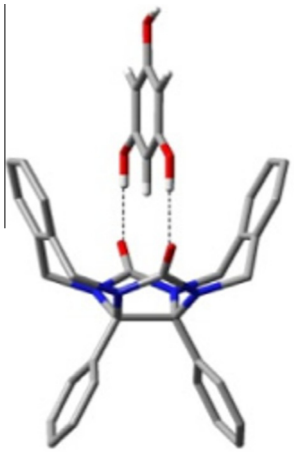

Figure 2. Computer-optimized complex of guest **1** and host **2** (hydrogen atoms in the host have been omitted for clarity, dashed lines indicate hydrogen bonds).

Table 1
Calculated interaction energy between host **2** and guest **1**, and the distances between atoms in the formed complex at the B3LYP/6-311G level

Host	Interaction energy[a] (kJ/mol)	Distances[b] (Å)	
2	−87.69196923	1.84023	1.84770

[a] The interaction energy was calculated by subtracting the energies of the host and guest from the minimum complex energy.
[b] Distances (lengths) of the two formed hydrogen bonds between the host and guest molecules (see Fig. 2).

was selected as the host for this work. First, we assumed that due to the formation of a host–guest complex between host **2** and guest **1**, the guest molecule entered into the cavity of the host and two of its hydroxyl groups were engaged in hydrogen bonding with the carbonyl groups of the host (Fig. 1). Accordingly, the third hydroxyl group of the guest remains free (compared to the other hydroxyl groups), and it can be manipulated selectively.

The formation of a host–guest complex between host **2** and guest **1** was also examined computationally. As shown in Figure 2, guest **1** in the optimized structure of the host–guest complex is bound into the cavity of the host, and only one of its hydroxyl groups is free. Moreover, the calculations gave a value of −87.69196923 kJ/mol for the interaction energy of the computer-optimized complex shown in Figure 2 (Table 1).

To demonstrate this experimentally, two methylation reactions were run under commonly-used O-methylation reaction conditions as follows: reaction of guest **1** with dimethyl sulfate in the presence of sodium carbonate in acetonitrile at 35 °C for 72 h (reaction 1),[13] and reaction of guest **1** with dimethyl sulfate in the presence of sodium carbonate and host **2** in acetonitrile–dichloromethane (reaction 2).[14] The two reaction mixtures were analyzed by TLC and for reaction 1 (control reaction) three spots including the unreacted guest **1**, the mono-methylated product **3** (5-methoxyresorcinol), and di-methylated product **4** (3,5-dimethoxyphenol) were observed on the TLC plate. In contrast, the

Table 2
Isolated yields of the products of reactions 1 and 2

Reaction	Isolated yield (%)		**3**:**4** Ratio	Selectivity[a] (%)
	Compound 3	Compound 4		
1	36	16	2.1:1	69
2	41	5	8.4:1	89

[a] Selectivity is defined as mono-methylated product/(mono-methylated product + dimethylated product) × 100.

Table 3
Effect of the host/guest molar ratio on the isolated yields and selectivity

Host/guest molar ratio	Isolated yield (%)		**3**:**4** Ratio	Selectivity[a] (%)
	Compound 3	Compound 4		
1:1	41	5	8.4:1	89
0.75:1	39	11	3.7:1	79
0.5:1	38	12	3.2:1	76
0.25:1	37	12	3.0:1	75

[a] Selectivity is defined as mono-methylated product/(mono-methylated product + dimethylated product) × 100.

TLC of reaction 2 showed spots belonging to unreacted guest **1**, 5-methoxyresorcinol (**3**) [and 3,5-dimethoxyphenol (**4**)], and host **2** (Scheme 1). Moreover, no *tri*-methylated product was observed under either reaction conditions. The products of the reactions were purified by column chromatography, and their isolated yields obtained (Table 2).

In the next step, the effect of the host/guest molar ratio on the selectivity of reaction 2 was investigated. Thus, reaction 2 was run in various host/guest molar ratios of less than 1:1 and the results showed a decrease in the selectivity due to fewer host–guest interactions (Table 3).

To find other features of our reaction, we examined the recycling and reusability of the host **2**. Therefore, once reaction 2 was completed, the mixture was worked-up in such a manner that it yielded the purified host **2** with nearly complete recovery.[15]

In conclusion, we have shown that host **2** promotes the selectivity of phloroglucinol O-methylation through the formation of a host–guest complex. The mono- and di-methylated derivatives were obtained as the major and minor products respectively. Moreover, the host was readily recycled and reused.

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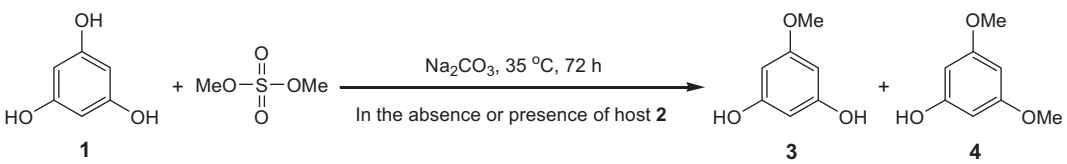

Scheme 1. Methylation of guest **1** in the absence or presence of host **2**.

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12. Step 1, *Synthesis of 3a,6a-diphenylglycoluril*. This compound was synthesized according to a literature procedure.[16] Step 2, *Synthesis of host* **2**. This compound was prepared using a procedure described previously,[17] with slight modification as follows: 3a,6a-diphenylglycoluril (1.65 g, 5.6 mmol) and freshly ground KOH (3.14 g, 56.0 mmol) in DMSO (40 mL) were heated at 120 °C with vigorous stirring for 20 min. 1,2-Bis(bromomethyl)benzene (3.17 g, 12.0 mmol) was added in one portion and stirring was continued at this temperature for 2 h. On cooling, the mixture was added to H_2O (400 mL) and stirred for 30 min. The resulting precipitate was collected by filtration, washed with H_2O (3 × 100 mL) and Et_2O (3 × 50 mL), and then dried under vacuum to yield 1.71 g (61%) of host **2**.
13. A mixture of phloroglucinol (0.32 g, 2.5 mmol) and Na_2CO_3 (1.98 g) in MeCN (30 mL) was stirred at rt for 45 min. Then, Me_2SO_4 (0.12 mL, 2.8 mmol) was added and the mixture was heated at 35 °C for 72 h. The mixture was filtered and the brown mother liquor was evaporated to dryness in vacuo. The residue (0.42 g) was purified by column chromatography (silica; CH_2Cl_2/MeOH, 30:1 v/v) to yield **3** (114 mg, 36%) and **4** (52 mg, 16%).
14. A mixture of phloroglucinol (0.32 g, 2.5 mmol) and Na_2CO_3 (1.98 g) in MeCN (30 mL) was added to a solution of host **2** (1.25 g, 2.5 mmol) in CH_2Cl_2 (20 mL), and the resulting mixture was stirred at rt for 45 min. Then, Me_2SO_4 (0.12 mL, 2.8 mmol) was added and the mixture was heated at 35 °C for 72 h. The mixture was filtered and the brown mother liquor was evaporated to dryness in vacuo. The residue (0.45 g) was purified by column chromatography (silica; CH_2Cl_2/MeOH, 30:1 v/v) to yield **3** (132 mg, 41%) and **4** (16 mg, 5%).
15. After completion of reaction 2, the mixture was filtered, and the mother liquor was evaporated to dryness. The resulting brown residue was heated in refluxing MeOH (40 mL) for 20 min. Then, the mixture was filtered and the precipitate was washed with boiling H_2O (40 mL). The precipitate was dissolved in CH_2Cl_2, filtered, and the solution was finally concentrated to yield the purified host **2** with nearly 100% recovery. The recovered host **2** was recycled, and reused without difficulty.
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