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Chemo-selective oxidation of hydroxybenzyl alcohols with IBX in the presence of hemicucurbit[6]uril†

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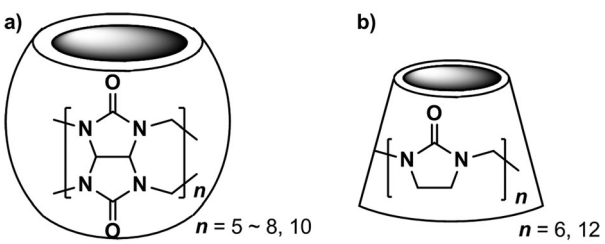
The chemo-selective oxidation of bifunctional substrates *via* a supramolecular strategy has been achieved. IBX (*o*-iodoxybenzoic acid) oxidations of hydroxybenzyl alcohols produce the corresponding aldehyde and *o*-quinones, while the presence of HemiQ[6] can restrain the IBX oxidation of phenolic hydroxyl groups to afford the aldehyde product. The conversion and reaction rate are greatly affected by the structures of substrates, and the stereo effect and electronic effect play very important roles in the selective oxidation system. Various spectroscopies, including ^{1}H NMR (proton nuclear magnetic resonance), IR (infrared), and UV-vis (ultra violet-visible) have been employed to confirm the host–guest interaction of HemiQ[6] with hydroxybenzyl alcohols.

Introduction

The oxidation of hydroxyl groups is a foundation in organic synthesis, which frequently employs chromium- and ruthenium-based reagents, Fremy's salt [$(KSO_3)_2NO$] and TEMPO-mediated oxidants.[1] Organic oxidants of a serial of hypervalent iodine compounds have been developed since the beginning of 1990s due to the interest in their effective oxidizing properties. The Dess–Martin reagent is an important member of the hypervalent oxidants,[2] and *o*-iodoxybenzoic acid (IBX) was found as a precursor, which has received a lot of attention as a result of its ability to oxidate hydroxyl groups in an extraordinarily efficient and selective manner.[3] Actually, IBX had not been considered as a useful reagent in organic synthesis because of its poor solubility in common organic solvents. However, it has been found that IBX can dissolve in DMSO to oxidize alcohols with very satisfying conversions.[4] In the last twenty years, IBX chemistry has experienced significant development in order to prove the oxidation activity of hydroxyl and amino groups.[5] The importance of this reagent lies in the advantage of regio-selective oxidation, for example, the oxidation of phenol with IBX provides *o*-quinone as the only product,[5b,6] but there are two products (*o*- and *p*-quinones) formed with the use of Fremy's salt.[1e] Recently, the IBX oxidation of alcohols in aqueous solution with the supramolecular catalysis of cucurbit[8]uril has been reported by our group.[7]

Cucurbit[*n*, *n* = 5–8, 10]uril (Q[*n*], Scheme 1a) are a family of cage-like macrocyclic compounds, which are made of methylene-bridged glycoluril units with hydrophilic portals and a hydrophobic cavity.[8] Based on the host–guest interactions, the application of cucurbiturils to chemical processes includes stabilization of the chemical structures, stereo-selective control in photochemical dimerizations, and the improvement of reaction activity.[9] The Qs binding of the active group on substrates usually slows the reaction,[10] and the encapsulation of a guest in the cavity of cucurbituril controls the stereostructure of the product and improves the reactivity by changing the orientation of the guest to form a suitable intermediate.[11] Unfortunately, the virtual lack of solubility of cucurbiturils in common organic solvents restricts the further exploration of their applications in organic chemistry. However, the appearance of hemicucurbiturils (HemiQ[*n*, *n* = 6 or 12], Scheme 1b) involving two members, HemiQ[6] and HemiQ[12], provides a new platform for the exploitation of the supramolecular properties of the cucurbituril family.[12] Very recently, HemiQ[6] has been successfully used to catalyze the esterification of acids in a combined solvent of $CHCl_3$ with CH_3OH.[13] Here, the chemo-selective IBX oxidation of



Scheme 1 Structures of (a) cucurbit[*n*]urils and (b) hemicucurbit[*n*]urils.

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hydroxybenzyl alcohols, a serial of substrates with bifunctional groups, in the presence of HemiQ[6] is described.

Results and discussion

For hydroxybenzyl alcohols, there are two kinds of hydroxyl groups on every substrate, both of which can be oxidized by IBX in the absence and presence of different amounts of HemiQ[6] to provide different products, aldehyde and quinones (Scheme 2). The products formed by the IBX oxidation of different hydroxybenzyl alcohols have been collected in Table 1.

Pioneering work found that the IBX oxidation of phenols always produces *o*-quinones,[5b,6] where two *o*-quinones [3-(hydroxymethyl)-*o*-quinone and *o*-benzoquinone] have been found to form from the oxidation of 2-hydroxybenzyl alcohol, with yields of 25.8% and 24.7%, respectively, and the product 2-hydroxybenzaldehyde has also been detected with 30.7% yield. For the purpose of the regio-selective oxidation of a bifunctional substrate *via* a supramolecular strategy, HemiQ[6] has been introduced into this system. The yields of the aldehyde product and quinones decrease with increasing amounts of HemiQ[6], namely, the yields of the quinones decreased by half in the presence of 25 mol% HemiQ[6], and the oxidation of the phenolic hydroxyl group has been resisted completely in the presence of HemiQ[6] to afford 2-hydroxybenzaldehyde as the only product, with a slightly decreasing yield when using a HemiQ[6] : 2-hydroxybenzyl alcohol ratio of 0.5 : 1, and an increase in the amount of IBX to two times that of the substrate improves the yields of quinones, but the yield of the aldehyde remains almost constant (entry 1, Table 1).

For the 3-hydroxybenzyl alcohol substrate, there are two active sites on the benzene ring for the oxidation of the phenolic hydroxyl group, producing 12.6% 3-(hydroxymethyl)-*o*-quinone and 23.4% 4-(hydroxymethyl)-*o*-quinone, which reveals a steric hindrance effect – that the oxidation at the 4-position is easier than at the 3-position, and brings about the double yield of 3-(hydroxymethyl)-*o*-quinone. In the mean time, 39.5% of 3-hydroxybenzaldehyde has been found as the product of the oxidation of benzyl alcohol. With the increasing addition of HemiQ[6], the oxidation of the phenolic hydroxyl group has been cut down and finally resisted with a 0.5 : 1 ratio of HemiQ[6] to the substrate, while the yield of the aldehyde product is increased from 39.5% to 55.3%. Using double the amount of IBX improves the conversion of 3-hydroxybenzyl alcohol to 88.9%; however, further increasing the amount of oxidant does not achieve more aldehyde product, instead the yields of the *o*-quinones are increased (entry 2, Table 1).

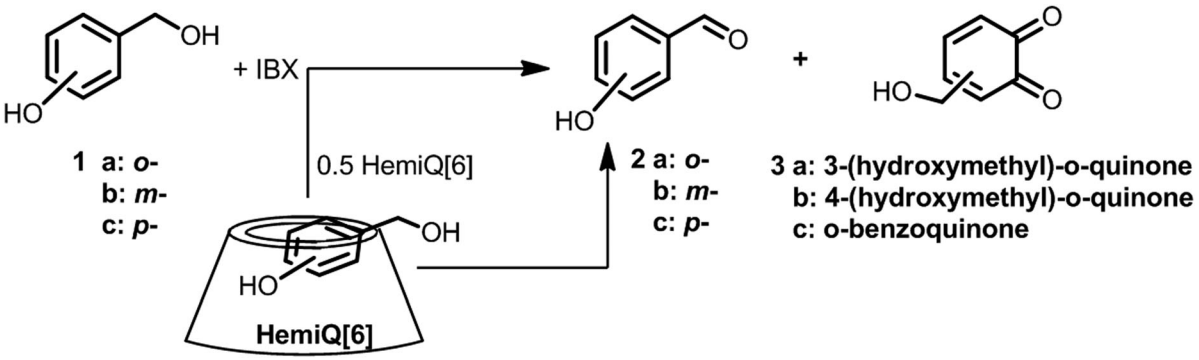
Table 1 Product distribution of the IBX oxidation of hydroxybenzyl alcohols after 1.0 hour, in the presence or absence of HemiQ[6][a]

Entry	Substrate	Amount of HemiQ[6] (mol%)	Ratio of IBX to substrate	Products			
				2	3a	3b	3c
1	**1a**	0	1 : 1	31	26	—	25
		25	1 : 1	29	14	—	13
		50	1 : 1	25	—	—	—
		50	2 : 1	21	19	—	36
2	**1b**	0	1 : 1	40	13	23	—
		25	1 : 1	43	3	10	—
		50	1 : 1	55	—	—	—
		50	2 : 1	52	16	21	—
3	**1c**	0	1 : 1	63	—	14	—
		25	1 : 1	56	—	10	—
		50	1 : 1	51	—	—	—
		50	2 : 1	87	—	13	—

[a] The yield of each product was directly confirmed by ^{1}H NMR spectral data.

The results of the IBX oxidation of 4-hydroxybenzyl alcohol in the absence of HemiQ[6] are simpler than the above cases, and only two products, 4-hydroxybenzaldehyde and 4-(hydroxymethyl)-*o*-quinone, have been obtained with yields of 62.7% and 14.4%, respectively. The presence of HemiQ[6] causes the phenolic hydroxyl groups to become chemically inert, that is, the corresponding quinone has vanished and only 4-hydroxybenzaldehyde has been observed with 50 mol% HemiQ[6], moreover, the yield of the aldehyde product has been improved by 36% in company with 13.1% *o*-quinone by the addition of more than 1 equiv. IBX (entry 3, Table 1), which reveals that the ternary complex of the substrate, IBX and HemiQ[6], and additionally the reaction rate of the IBX oxidation would be slower than the dynamic interaction of 4-hydroxybenzyl alcohol with HemiQ[6].

The IBX oxidation of 2-hydroxybenzyl alcohol was carried out with 50 mol% HemiQ[6], and the ^{1}H NMR spectra traces suggest that only the corresponding aldehyde product has been formed (Fig. 1a). Comparing this result with that of the reaction without the protection, the oxidation conversion of



Scheme 2 IBX oxidation of hydroxybenzyl alcohols in the absence and presence of HemiQ[6].

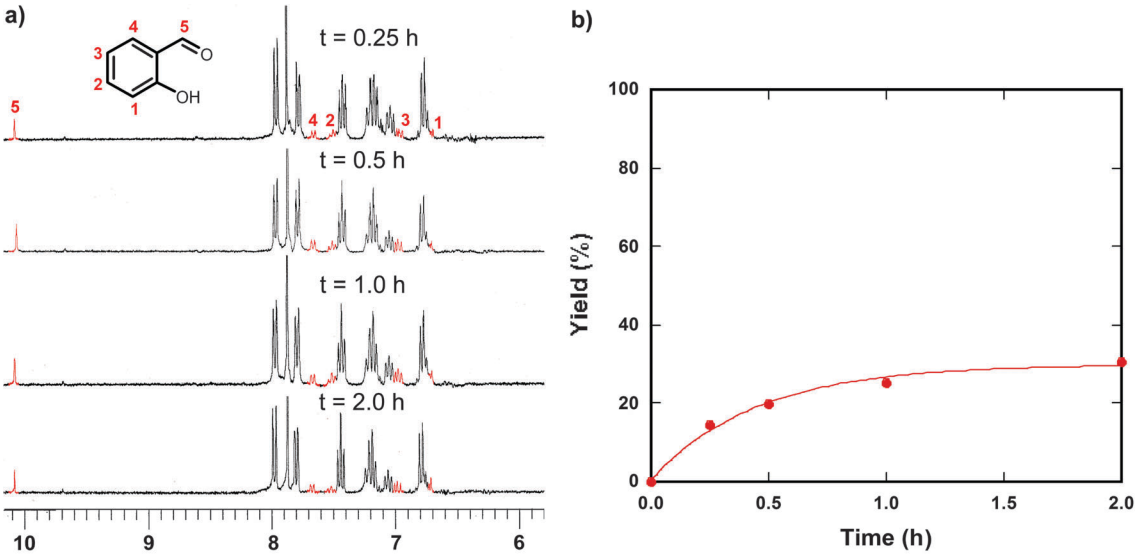


Fig. 1 (a) ^{1}H NMR spectra of the IBX oxidation of 2-hydroxybenzyl alcohol in the presence of 50 mol% HemiQ[6], with the proton resonances of the aldehyde product highlighted in red; (b) kinetics plot of the IBX oxidation of 2-hydroxybenzyl alcohol to afford 2-hydroxybenzaldehyde in the presence of HemiQ[6].

2-hydroxybenzyl alcohol in the presence of HemiQ[6] is less, which provides only 25.3% aldehyde in 1.0 hour, and the conversion is improved by 30.5% over the next 2.0 hours. The kinetic plots of the oxidation of 2-hydroxybenzyl alcohol in the presence of 50 mol% HemiQ[6] has been displayed in Fig. 1b, which could be described by the following first-order formula (1):

$$C_t = C_0 \times [1 - \exp(-k \times t)] \quad (1)$$

where C_0 is the initial 2-hydroxybenyl alcohol concentration (%) and C_t is the concentration (%) at time t, k is the corresponding reaction rate constant, which has been found as $k = 2.2\ h^{-1}$ in this case. In the presence of 50 mol% HemiQ[6], the alcoholic hydroxyl group of the 3-hydroxybenzyl alcohol has been oxidized by IBX to produce 3-hydroxybenzaldehyde, while the phenolic hydroxyl group has been resistant to oxidation, so no quinone product has been found, as observed from the ^{1}H NMR spectra (Fig. 2a). On the other hand, the reaction achieves 55.3% conversion in 1.0 hour, which is more than double the conversion of 2-hydroxybenzyl alcohol, and the non-linear fitting of the kinetic plots with formula 1 gives a corresponding rate constant of $k = 4.1\ h^{-1}$ (Fig. 2b), which is almost twice that in the case of 2-hydroxybenzyl alcohol. Accordingly, both the above thermodynamic and kinetic evidence suggests that the IBX oxidation of 3-hydroxybenzyl alcohol in the presence of HemiQ[6] is more effective than for 2-hydroxybenzyl alcohol.

As in the above cases, the phenolic hydroxyl group on 4-hydroxybenzyl alcohol could be protected against IBX oxidation by the addition of 50 mol% HemiQ[6], and 4-hydroxybenzaldehyde

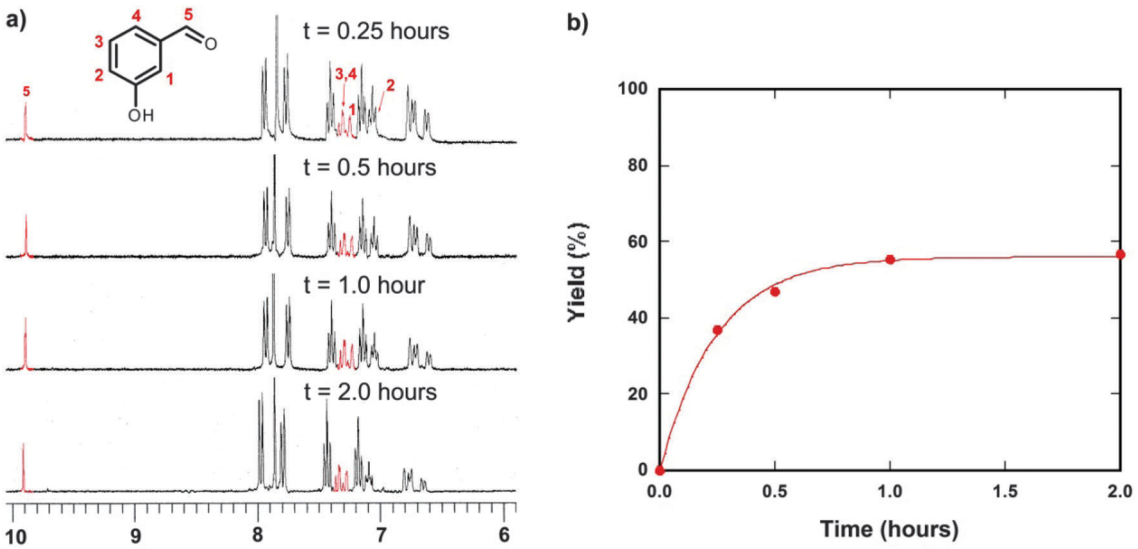


Fig. 2 (a) ^{1}H NMR spectra of the IBX oxidation of 3-hydroxybenzyl alcohol in the presence of 50 mol% HemiQ[6], with the proton resonances of the aldehyde product highlighted in red; (b) kinetics plot of the IBX oxidation of 3-hydroxybenzyl alcohol to afford 3-hydroxybenzaldehyde in the presence of HemiQ[6].

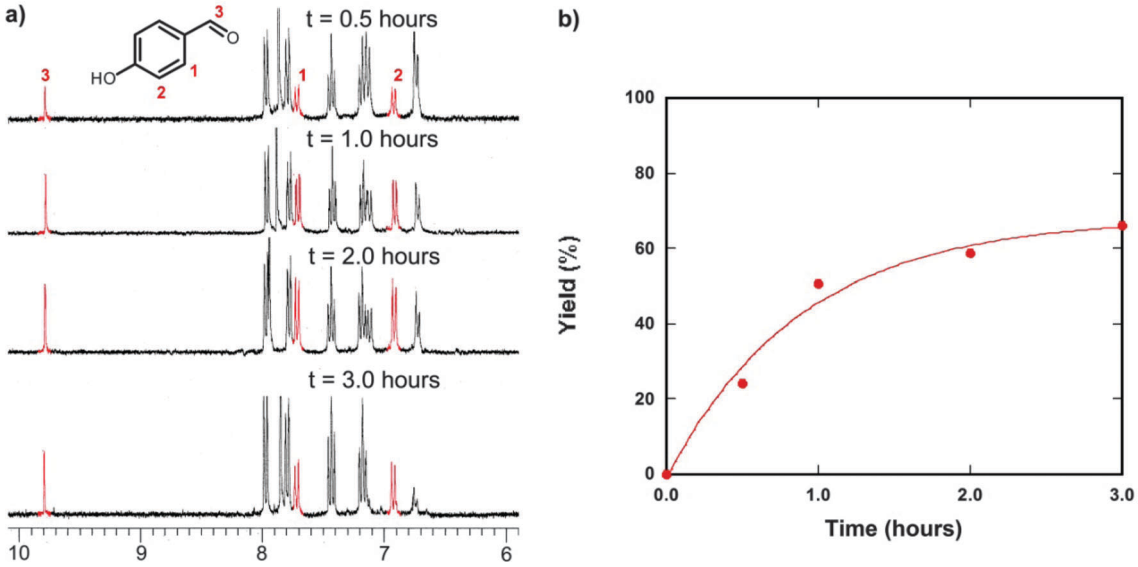


Fig. 3 (a) ^{1}H NMR spectra of the IBX oxidation of 4-hydroxybenzyl alcohol in the presence of 50 mol% HemiQ[6], with the proton resonances of the aldehyde product highlighted in red; (b) kinetics plot of the IBX oxidation of 4-hydroxybenzyl alcohol to afford 4-hydroxybenzaldehyde in the presence of HemiQ[6].

has been found as the only product. The ^{1}H NMR spectrum (Fig. 3a) suggests that the IBX oxidation of this substrate is also more effective than that of 2-hydroxybenzyl alcohol. A conversion of 58.6% has been achieved after 2.0 hours, and a further 7.4% conversion has been achieved after 3.0 hours. The degree of conversion of 4-hydroxybenzyl alcohol at different times could be non-linearly fitted to give a kinetic constant of k = 1.1 h^{-1} with formula 1 (Fig. 3b), which is surprisingly just half of the constant in 2-hydroxylbenzyl alcohol system, so the oxidation of 4-hydroxybenzyl alcohol is the slowest of the studied cases.

The oxidizing activities of the hydroxybenzyl alcohols by IBX in the presence of HemiQ[6] could be comprehended fully from the viewpoints of both thermodynamics and kinetics. 2-Hydroxybenzyl alcohol is the most inert among the bifunctional substrates, with only a 30.5% conversion of 2-hydroxybenzylaldehyde being observed, while the oxidation of 3,4-hydroxybenzyl alcohols provide more products, whose distributions are 56.8% and 66.0%, respectively. It is obvious that the conversion of hydroxybenzyl alcohol depends on the substituent site of the phenolic group on the benzene ring, that is, when the distance between the phenolic hydroxyl group and the alcoholic hydroxyl group is increased, a more effective oxidation at the benzyl alcohol is observed, so the stereo-hindrance effect of HemiQ[6] helps to resist the IBX oxidation of 2-hydroxybenzyl alcohol. However, the oxidation reaction of 4-hydroxybenzyl alcohol has the smallest rate constant of k = 1.1 h^{-1}, and the rate constant of the IBX oxidation of 3-hydroxybenzyl alcohol is the largest (k = 4.1 h^{-1}). According to the results obtained in our previous work,[7b,c] on the electronic effects of substituents on the activity of the IBX oxidation of benzyl alcohols, the *meta*-substituent with an electron-withdrawing group always favours the oxidation due to its strong inductive effect.

To understand the role of HemiQ[6] in this chemo-selective oxidation, the foundations of the host–guest interactions between HemiQ[6] and the hydroxybenzyl alcohols have been investigated. ^{1}H NMR spectroscopy is a common method used to confirm the host–guest interaction models by observation of the changes in the chemical shifts of the guest after addition of the host.[8] In this case, the proton resonances of all of the hydroxybenzyl alcohols do not show any shift in the presence of HemiQ[6] (ESI,† Fig. S1), however, all of resonances of the active protons are fading away with the addition of the host and broadened peaks appear from δ 3.6 ppm–δ 4.2 ppm, which reveals the host–guest interaction between hydroxybenyl alcohols and HemiQ[6] with hydrogen bonds. The formation of supramolecular complexes was also confirmed by the different IR absorptions of the carbonyl groups on binding HemiQ[6] from the those of the free host (ESI,† Fig. S2). UV-vis spectroscopic titration has also been employed to monitor the host–guest interactions. To avoid the solvent absorption of DMSO in this wavelength region, a mixed solvent of chloroform and methanol in the ratio of 1 : 1 has been applied in the UV-vis titrations. The max electronic absorption of 2-hydroxybenzyl alcohol appears at 275 nm, which increases with the increasing concentration of HemiQ[6] (Fig. 4a), and the change in the UV-vis spectra and the variable concentration of the macrocyclic compound could be fitted to give a 1 : 1 interaction model with K_a = (4.8 ± 1.5) × 10^3 L mol^{-1} (Fig. 4b). For 3-hydroxybenzyl alcohol, the UV-vis absorbance at 275 nm is improved by the addition of HemiQ[6] (Fig. 4c), and the increase in the concentration of HemiQ[6] fits to a 1 : 1 binding model with a moderate binding constant of K_a = (7.4 ± 2.2) × 10^4 L mol^{-1} (Fig. 4d). A similar change in the UV-vis spectrum has also been observed in the host–guest interaction system of 4-hydroxybenzyl alcohol and HemiQ[6] (Fig. 4e), and the increase in the absorbance band at 277 nm *versus* the increase in the concentration of HemiQ[6] was fitted to a 1 : 1 binding model to obtain an association constant of K_a = (5.5 ± 1.6) × 10^4 L mol^{-1} (Fig. 4f). Accordingly, the interaction of 2-hydroxylbenzyl alcohol

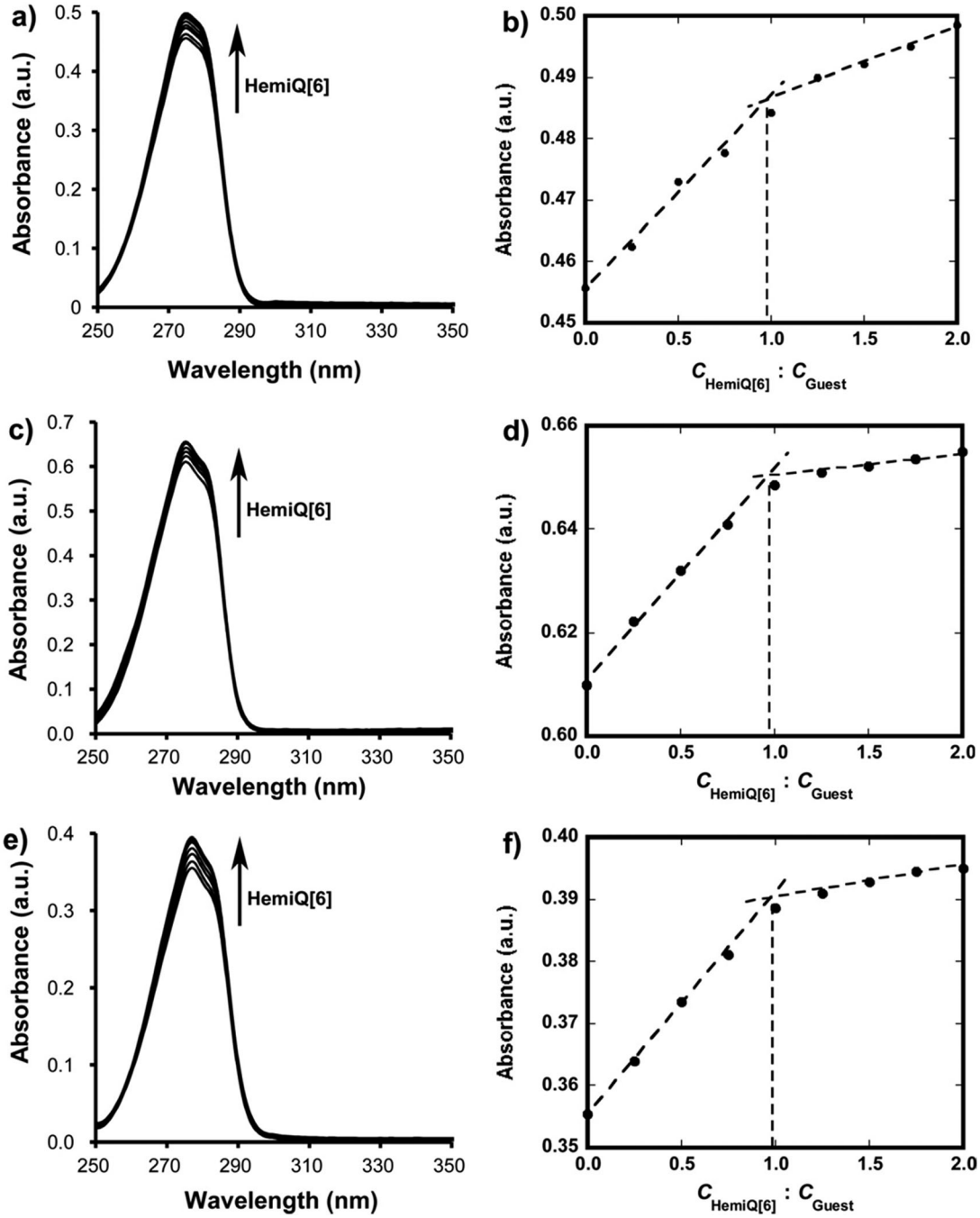


Fig. 4 UV-vis titration of the host–guest interactions between HemiQ[6] and (a) 2-hydroxybenzyl alcohol; (c) 3-hydroxybenzyl alcohol; (e) 4-hydroxybenzyl alcohol. The corresponding absorbance *versus* different ratios of HemiQ[6] to (b) 2-hydroxybenzyl alcohol; (d) 3-hydroxybenzyl alcohol; (f) 4-hydroxybenzyl alcohol.

with HemiQ[6] is weaker than the others, which reveals that a steric hindrance effect is present in the host–guest interaction.

Conclusions

In summary, we have developed a chemo-selective oxidation reaction for bifunctional substrates, hydroxybenzyl alcohols, with the participation of hemicucurbit[6]uril. The IBX oxidations of hydroxybenzyl alcohols provide a mixture of products, both aldehydes and quinones, due to two hydroxyl groups being present on the benzene ring. However, 50 mol% HemiQ[6] is able to protect the phenolic hydroxyl groups against oxidation by IBX, and produces the corresponding aldehydes as the only product. The oxidations with supramolecular protection are affected by both the steric effects and electronic effects of the substrates. The conversion of 2-hydroxyl alcohol is the lowest, as the two hydroxyl groups are very close to each other. The inductive effect of the phenolic

hydroxyl group on 3-hydroxybenzyl alcohol makes the reaction faster than the others. The investigation of the host–guest interactions of HemiQ[6] with hydroxybenzyl alcohols with ^{1}H NMR spectroscopy, IR absorption analysis and UV-vis titration suggests that the hydrogen bonds are formed between HemiQ[6] and the benzyl alcohol guests in an ratio of 1 : 1, through the binding of active hydrogen by the macrocyclic compound.

Experimental

Materials and apparatus

The HemiQ[6] sample was prepared and purified according to a method reported in the literature[12] and was characterized by ^{1}H NMR. HemiQ[6] ($CDCl_3$, δ): 3.40 (s, 24H), 4.67 (s, 12H). IBX was prepared with 2-iodobenzoic acid and oxone.[14] ^{1}H NMR (DMSO-d_6, δ): 7.20 (t, 1H), 7.44 (t, 1H), 7.66 (d, 1H), 7.94 (d, 1H). Mp: 230–233 °C with explosive decomposition. Hydroxybenzyl alcohols and hydroxybenzyl aldehydes were obtained commercially (Tokyo Kasei Kogyo Co., Ltd) and used without further purification.

The ^{1}H NMR spectra were recorded at 25 °C on a JEOL JNM-Al00 spectrometer in a mixture of $CDCl_3$ and DMSO-d_6. UV-vis absorption spectra were recorded on an Perkin-Elmer Lambda 19 UV/Vis/NIR instrument at 25 °C.

IBX oxidation of hydroxybenzyl alcohols in the absence of HemiQ[6]

Hydroxybenzyl alcohols (0.01 mmol) and IBX (0.01 mmol) were added to a mixture (0.6 mL) of $CDCl_3$ and DMSO-d_6 (2 : 1, v/v) in a sealed bottle. The reactions were carried out at 30 °C for 1.0 hour, and then the solutions examined with ^{1}H NMR directly.

IBX oxidation of hydroxybenzyl alcohols in the presence of HemiQ[6]

Hydroxybenzyl alcohols (0.01 mmol), HemiQ[6] (0.005 mmol) and IBX (0.01 mmol) were added to a mixture (0.6 mL) of $CDCl_3$ and DMSO-d_6 (2 : 1, v/v) in a sealed bottle. The reaction was carried out at 30 °C, and monitored by ^{1}H NMR over time.

UV-vis titration of the host–guest interactions

Hydroxybenzyl alcohol solutions were prepared in a mixture of $CHCl_3$ and CH_3OH (1 : 1) with a concentration of 2.5×10^{-4} mol L^{-1}, this solution was combined with HemiQ[6] to give guest–HemiQ[6] ratios of 0, 4 : 1, 2 : 1, 1 : 1, and 1 : 2 and so on.

Acknowledgements

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