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The role of β-cyclodextrin in mediating regioselective dimethylaminomethylation of phenol

Wen-Hai Wu, Jiang Duan, Ting Wei, Hai-Yang Tu**, Ai-Dong Zhang*

Key Laboratory of Pesticide & Chemical Biology of Ministry of Education, College of Chemistry, Central China Normal University, Wuhan 430079, PR China

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ABSTRACT

Regioselective reactions with supramolecular control are of great interest. Herein, the *para*-regioselectivity in the Mannich reaction of phenol with formaldehyde and dimethylamine was achieved with the use of β-cyclodextrin (β-CD), giving 4-(*N*,*N*-dimethylaminomethyl)phenol (*p*-AP) as major product. ^{1}H NMR and ITC measurements of the binding of β-CD with the reactants and the products *o*- and *p*-AP revealed a new mechanism, in which β-CD includes *p*-AP instead of phenol to control the reaction regioselectivity. This product-inclusion mechanism is remarkably different to the known reactant-inclusion process.

1. Introduction

Supramolecularly controlled regioselective reactions have been widely exploited for the synthesis of a variety of compounds that are unable or difficult to be synthesized using common methods. A number of host molecules such as crown ethers,[1] cucurbiturils,[2] and cyclodextrins (CDs)[3] are known to have this role to mediate regioselective reactions through forming supramolecular inclusion complexes by hydrogen bonding, electrostatic, van der Waals and π-π interactions, as well as steric, shape-complementary and hydrophilic/hydrophobic effects.[4] The inclusion complex is able to block some reaction sites of the substrate, or stabilize the transition state or the intermediate, leading to control of a chemio-, regio-, stereo- and/or enantio-selective reaction toward a desired direction.[5,6] CDs are among the most important supramolecular hosts and many of their mediated regioselective reactions are known.[7–9] For example, Breslow et al.[10] utilized α-CD to include anisole, realizing the *para*-selective synthesis of 4-chloroanisole in the reaction with HOCl. Hirai et al.[11] succeeded in introducing carboxyl to the *para*-site of benzoic acid selectively to yield terephthalic acid through the reaction of benzoic acid with CCl_4 and copper under the presence of β-CD. The mechanism of this reaction was accounted in terms of ^{1}H NMR measurements[11] that the inclusion complex formation of β-CD with benzoic acid and thereby the blocking of the *ortho*/*meta* sites was essential to achieve the perfect regioselectivity. γ-CD, which has a larger cavity, was reported to include both cinnamic acid and coumarin, forming a 1:1:1 ternary inclusion complex that kept nearby the C=C bonds of the two partners and afforded a heterodimerization instead of homodimerization product under light irradiation.[12]

Phenol is a kind of electron-rich aromatic compound with high reactivity toward electrophiles. Due to the strong *ortho*/*para* orientation of phenolic hydroxyl, the reaction of phenol tends to give products with non-selective *ortho*- and *para*-substitution. A few works regarding the *para*-selective reaction of phenol have been reported using supramolecular methods. For instance, Komiyama et al. realized the synthesis of 4-hydroxy benzaldehyde and 4-hydroxybenzoate with high *para*-selectivity via β-CD controlled formylation[13] and carboxylation[14] of phenol. β-CD was also usable in achieving the *para*-Reimer-Tiemann reaction of phenol to give 4-hydroxybenzaldehyde with high regioselectivity under light irradiation.[15] Further, with the presence of β-CD, a mild and efficient protocol was developed for the *para*-selective bromination of substituted phenols with Br_2/CCl_4 in aqueous or methanol medium.[16] Although solid evidence was still needed, these reports proposed the reactions occurring through a mechanism where the encapsulation of phenol by β-CD to block the *ortho*-

* Corresponding author.
** Corresponding author.
E-mail addresses: haiytu@mail.ccnu.edu.cn (H.-Y. Tu), adzhang@mail.ccnu.edu.cn (A.-D. Zhang).

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sites was the necessary process to give the desired *para*-substituted products.

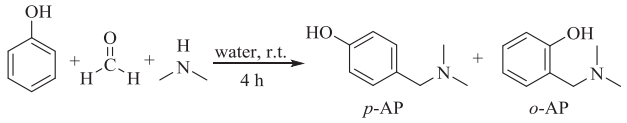
The three-component Mannich reaction of phenol, formaldehyde and amine could be performed in a one-pot manner but always produces a mixture of *ortho/para* mono- or multi-substituted products.[17,18] To overcome this difficulty, two variations of Mannich reaction for synthesis of *ortho*-substituted products were reported; one was the *ortho*-selective reaction of phenol to give 2-(*N*,*N*-dimethylaminomethyl)phenol (*o*-AP) with 81% regioselectivity through use of the Eschenmoser salt[19]; the other was the ruthenium catalytic dehydrogenation of methanol as C1 source to react with dimethylamine and phenol to yield *o*-AP.[20] However, the *para*-selective Mannich reaction of phenol with formaldehyde and dimethylamine to give 4-dimethylamino methylphenol (*p*-AP) has thus far not been reported. In this work, we demonstrated that, among various CDs, β-CD was able to achieve the *para*-regioselectivity of the Mannich reaction. Furthermore, the role of β-CD was explored in-depth with ^{1}H NMR and ITC measurements, and the results revealed a process that is remarkably different to the existing mechanism.

2. Results and discussion

2.1. Effect of cyclodextrins on the Mannich reaction

At the beginning of this work, the Mannich reaction of phenol with formaldehyde and dimethylamine in the absence and presence of various CDs serving as a supramolecular host was performed and monitored with ^{1}H NMR. When the reaction was conducted in the absence of any CD, a low phenol conversion rate of 77% and a non-regioselective formation of *p*-AP/*o*-AP in ratio of 53/47 were observed (Table 1, Entry 1). In the presence of equimolar α-CD, the conversion rate was improved whereas the product ratio had no obvious alteration (Entry 2). When equimolar β- or γ-CD was used, both the conversion rate and the product ratio were improved significantly. With use of β-CD the conversion rate and the product ratio were raised up to 92% and 75/25, respectively (Entry 3), while the corresponding rate and ratio were 90% and 63/37 in the presence of γ-CD (Entry 4), indicating β-CD was the best host molecule in this *para*-selective reaction. The inferior effects of α- and γ-CD might come from their unsuitable cavity sizes.[21] In addition, the employed amount of β-CD was optimized. A half equiv of β-CD led the reaction to the decease of both the conversion rate (83%) and the selectivity ratio (65/35) (Entry 5). At a 1.5-fold excess of β-CD, the rate was improved to 95% and the ratio of *p*-AP/*o*-AP to 89/11 (Entry 6). Further increasing the amount of β-CD did not result in a more profound improvement (Entry 7).

Table 1
Conversion rate of phenol and selectivity toward *p*-/*o*-AP.[a]



Entry	CD	Phenol/CD	Conversion (%)[b]	*p*-AP/*o*-AP[c]
1	none	–	77	53/47
2	α-CD	1: 1	83	54/46
3	β-CD	1: 1	92	75/25
4	γ-CD	1: 1	90	63/37
5	β-CD	1: 0.5	83	65/35
6	β-CD	1: 1.5	95	89/11
7	β-CD	1: 2	96	90/10

[a] Reaction conditions: a molar ratio of 1:1:1 was used for phenol, formaldehyde and dimethylamine.
[b] Conversion rate was calculated based on the recovered amount of phenol.
[c] Product ratio was calculated based on the ^{1}H NMR signal intensities of methylene in *p*-AP and *o*-AP.

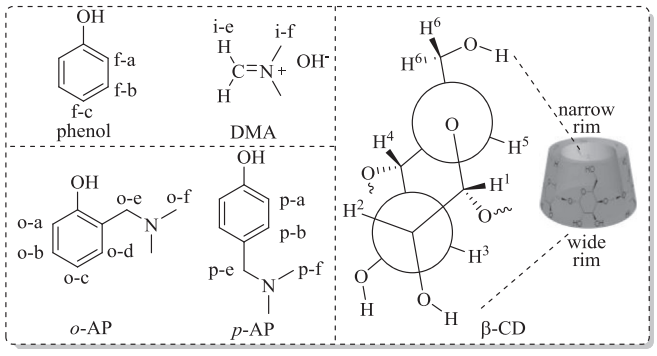
The above results show that the use of β-CD as a mediator enabled the *para*-selective *N*,*N*-dimethylaminomethylation of phenol for the first time. To highlight the feasibility of this supramolecular method, a practical 10-fold scale-up synthesis of *p*-AP, in conjunction with a simplified purification procedure, was done and described in the experiment section. It remains unclear, however, whether the achievement of *para*-regioselectivity in this reaction is a result of the known mechanism that the β-CD cavity includes the reactant phenol to alter the reaction regioselectivity.[22]

2.2. ^{1}H NMR measurements

To gain insight into the mechanism, a supramolecular ^{1}H NMR method[23] was used to investigate the interactions of β-CD with the reactant phenol, the intermediate *N*,*N*-dimethyliminium (DMA) generated from the reaction of formaldehyde and dimethylamine, and the products *p*- and *o*-AP. The criterion of this method is the proton signal upfield shift of a guest molecule when included in the cavity of β-CD host, due to the shielding effect to the applied magnetic field.[23] Scheme 1 depicts the structures and proton labels of phenol, DMA, and the products, as well as one glucose unit of β-CD with numbered protons H^1-H^6 and their relative positions to the β-CD cavity.

According to the molecular model and the literature,[24] β-CD consists of seven α-D-glucose units with 1,4-linkage to form a cone-type structure, where protons H^5 and H^3 locate inside the cone with the former close to the narrow rim (the primary hydroxyl rim) and the latter to the wide rim (the secondary hydroxyl rim); while the protons H^1, H^2, H^4 and H^6 reside outside the cavity. Since H_2O was the medium in the Mannich reaction, D_2O was used for the ^{1}H NMR measurements, and therefore, the active proton signals of phenol, the products and β-CD were invisible due to the DH exchange. The chemical shift variations (Δδ, ppm) of the inner protons H^3 and H^5 can be used as a measure to evaluate the host-guest binding strength and the inclusion depth and orientation of the guest in the cavity.[25] The Δδ for phenol, DMA, *o*-AP, *p*-AP and β-CD in their individual complexation states are summarized in Table 2, and their ^{1}H NMR spectra sets shown in Figs. 1–4.

The interaction of phenol with β-CD was first examined. For phenol, small upfield shifts of H^{f-a} (−0.01 ppm), H^{f-b} (−0.02 ppm) and H^{f-c} (−0.03 ppm) are observed (Fig. 1 and Table 2), indicating that phenol receives a negligible shielding effect from β-CD and does not insert into the cavity. Relatively, H^{f-c} has a larger Δδ,



Scheme 1. Structures and proton labels of phenol, DMA, the products and one glucose unit in Newman projection of the β-CD model.

Table 2
Proton chemical shift variations in complexation (Δδ, ppm).[a]

Phenol/β-CD		DMA/β-CD	
Phenol	β-CD	DMA	β-CD
H^{f-a} (−0.01)	H^1 (−0.02)		H^1 (−0.01)
H^{f-b} (−0.02)	H^2 (−0.03)		H^2 (−0.02)
H^{f-c} (−0.03)	H^3 (−0.05)		H^3 (−0.03)
	H^4 (−0.04)		H^4 (−0.02)
	H^5 (−0.11)	H^{i-e} (+0.02)	H^5 (−0.03)
	H^6 (−0.02)	H^{i-f} (+0.03)	H^6 (−0.02)
o-AP/β-CD		*p*-AP/β-CD	
o-AP	β-CD	*p*-AP	β-CD
H^{o-a} (+0.11)	H^1 (−0.01)	H^{p-a} (+0.03)	H^1 (−0.04)
H^{o-b} (+0.01)	H^2 (−0.02)	H^{p-b} (−0.08)	H^2 (−0.03)
H^{o-c} (+0.10)	H^3 (−0.03)		H^3 (−0.13)
H^{o-d} (−0.03)	H^4 (−0.01)		H^4 (−0.02)
H^{o-e} (−0.27)	H^5 (−0.05)	H^{p-e} (−0.14)	H^5 (−0.20)
H^{o-f} (−0.15)	H^6 (−0.01)	H^{p-f} (−0.20)	H^6 (−0.04)

[a] Signs "+" and "−" indicate downfield and upfield shift, respectively.

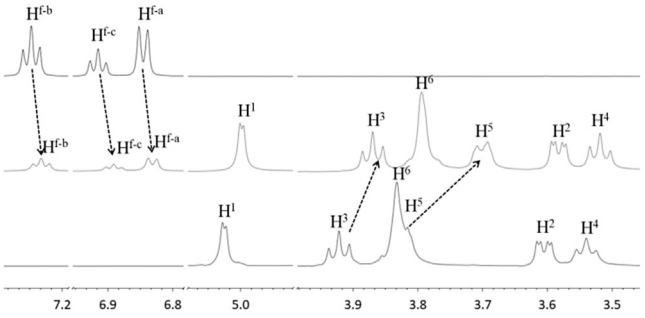


Fig. 1. ^{1}H NMR spectra set of phenol (top), phenol/β-CD mixture (middle) and β-CD (bottom) in D_2O at 0.1 mmol.

meaning that it is near to the shielding region of the cavity. As for β-CD, the inner protons H^3 (−0.05 ppm) and H^5 (−0.11 ppm) have upfield shifts with the latter more significant. Because H^5 locates at the narrow rim, its large upfield shift would be a result caused by the anisotropic magnetic field shielding of phenol.[26] Using circular dichroism spectroscopy in combination with molecular mechanical calculation, Marconi et al.[27] demonstrated that phenol resides slantingly near the narrow rim, in line with our observation. This binding conformation may take use of the hydrogen bonding between the hydroxyl group of phenol and the primary hydroxyl group of β-CD,[28] impeding the entry of the phenol ring into the β-CD cavity.

The intermediate DMA in complexation shows a completely different shift direction in proton signals (Fig. 2 and Table 2), such that the small downfield shifts of protons H^{i-e} (+0.02 ppm) and H^{i-f} (+0.03 ppm) are observed, as an indicative of the DMA residing in the deshielding region outside β-CD. Meanwhile, the β-CD inner protons H^3 (−0.03 ppm) and H^5 (−0.03 ppm) have negligible Δδ, further suggesting that DMA does not enter the β-CD cavity. This may be a result of the highly hydrophilic nature of ionic DMA that is repulsive to the hydrophobic attraction of β-CD cavity.

Fig. 3 shows the ^{1}H NMR spectra set of *o*-AP, *o*-AP/β-CD mixture and β-CD. The aromatic H^{o-a} (+0.11 ppm) and H^{o-c} (+0.10 ppm) in *o*-AP exhibit relatively large downfield shifts; whereas H^{o-b} (+0.01 ppm) has a negligible downfield Δδ and H^{o-d} (−0.03 ppm) a slight upfield Δδ. More significantly, the methylene H^{o-e} (−0.27 ppm) and the methyl H^{o-f} (−0.15 ppm) of *N*,*N*-dimethylaminomethyl have large upfield Δδ. The ^{1}H NMR data manifest that the different parts of the *o*-AP molecule suffer different interactions from the induced magnetic field of β-CD. Thus a scenario can be created, where phenyl resides at the interface of the shielding/deshielding regions near the narrow rim of β-CD cone while *N*,*N*-dimethyl aminomethyl locates inside the β-CD cavity. On the other hand, the host β-CD displays small upfield Δδs for H^3 (−0.03 ppm) and H^5 (−0.05 ppm) in the cavity, presumably due to the minor effect from the aromatic ring of *o*-AP; while the relatively larger upfield Δδ for H^5 means that *o*-AP enters the β-CD cavity through the narrow rim.

The ^{1}H NMR spectra set of the product *p*-AP, the *p*-AP/β-CD mixture and β-CD is shown in Fig. 4. The phenolic hydroxyl-*ortho*

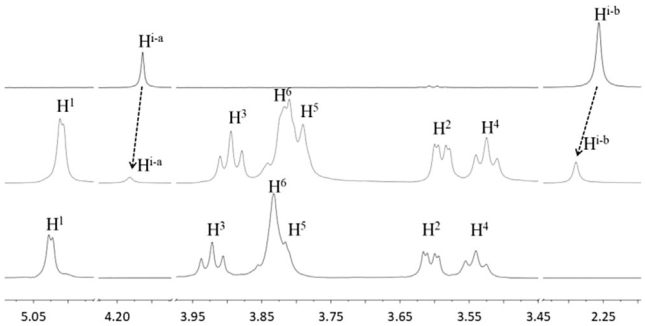


Fig. 2. ^{1}H NMR spectra set of DMA (top), DMA/β-CD mixture (middle) and β-CD (bottom) in D_2O at 0.1 mmol.

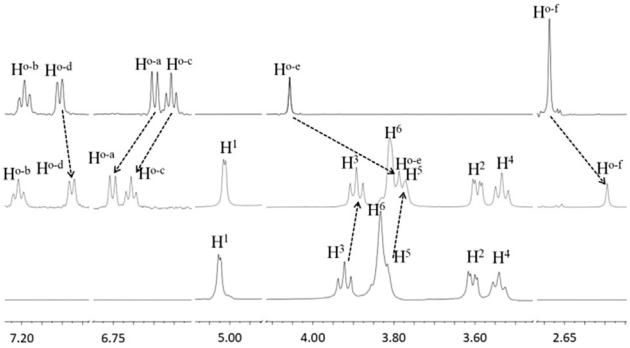


Fig. 3. ^{1}H NMR spectra set of *o*-AP (top), *o*-AP/β-CD (middle) and β-CD (bottom) in D_2O at 0.1 mmol.

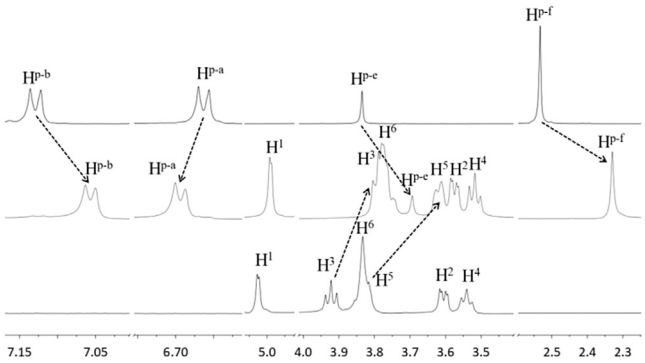


Fig. 4. ^{1}H NMR spectra set of *p*-AP (top), *p*-AP/β-CD (middle) and β-CD (bottom) in D_2O at 0.1 mmol.

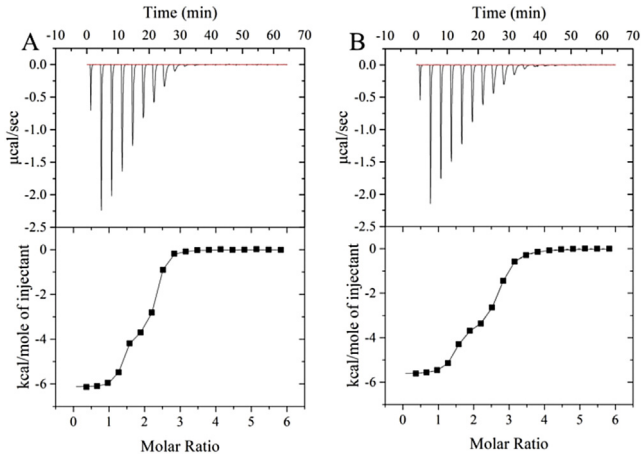


Fig. 5. ITC data in 298 K for *p*-AP (**A**) and *o*-AP (**B**) to complex with β-CD.

H^{p-a} (+0.03 ppm) and hydroxyl-*meta* H^{p-b} (−0.08 ppm) of *p*-AP shift oppositely to downfield and upfield, suggesting the phenolic hydroxyl group may point outside the β-CD cavity with the phenyl ring residing in a half-insertion state because of the small positive Δδ of H^{p-a}. Moreover, the methylene H^{p-e} (−0.14 ppm) and the methyl H^{p-f} (−0.20 ppm) of *p*-AP exhibit large upfield Δδs, thus *N*,*N*-dimethylaminomethyl should be inside the β-CD cavity with methyl H^{p-f} more deeply inserted. As for β-CD, the wide rim H^3 (−0.13 ppm) and the narrow rim H^5 (−0.20 ppm) in the cavity shift upfield remarkably, most likely attributed to the impact of the strong aromatic induced magnetic field of *p*-AP in the cavity. In addition, the larger Δδ for H^5 suggests the phenyl of *p*-AP locating near to the narrow rim of β-CD cone.

According to the results from ^{1}H NMR data, phenol may not enter into the β-CD cavity but lies slantingly near the narrow rim as an outer-sphere complex[29] through the hydrophobic and hydrogen bonding effects. By contrast, both the products *o*-AP and *p*-AP enter the cavity and form inclusion complexes with β-CD, though in different binding modes. Another point worthy of mention is that the entry of the products into the cavity most likely occurs upon the product formation, implying the β-CD cavity is not the reaction place. Thus we postulated that the β-CD mediated *para*-selective aminomethylation of phenol takes place not through the complexation of β-CD with phenol and blocking the *ortho*-reaction sites, but instead through a binding process involving the formation of the inclusion complexes of β-CD with the individual products. Since *p*-AP inserts more deeply inside the β-CD cavity than *o*-AP, there should be a thermodynamically controlled process favouring the reaction toward the direction of *para*-selectivity.

2.3. ITC and UV absorption analyses

To obtain more information about the effect of β-CD on the reaction regioselectivity, isothermal titration calorimetry (ITC) measurements were performed to determine the changes of enthalpy (ΔH), entropy (ΔS) and Gibbs free energy (ΔG) with titration of β-CD by phenol, *p*-AP and *o*-AP, respectively and simultaneously, to obtain the binding constants (*K*). The exotherm of complexation of phenol with β-CD was nearly a horizontal line, demonstrating a rather weak interaction and giving no reasonable thermodynamic parameters (data not shown). The exotherms of complexation of *p*-AP (Fig. 5A) and *o*-AP (Fig. 5B) with β-CD show typical exothermic "S" shapes, a consequence of the inclusion complex formation of *p*-AP/β-CD and *o*-AP/β-CD. The exotherm was best fitted using a complexation number of 2 for *p*-AP or *o*-AP over β-CD, suggesting the binding was a two-step process when excess of a guest was used in the titration. Since the first step binding was dominant in ΔG and *K* (2 orders higher in both cases for *p*-AP and *o*-AP, Supporting Information), the thermodynamic parameters (Table 3) derived from the first step binding are used for further discussion. The values of ΔH_1, ΔS_1, ΔG_1 and K_1 for *p*-AP/β-CD are −25.68 ± 0.08 KJ/mol, 0.066 KJ/mol·K, −45.35 ± 0.08 KJ/mol and 8.26 ± 1.08 × 10^7 M^{-1}, respectively. In contrast, the *o*-AP/β-CD generates the respective thermodynamic parameters as −23.57 ± 0.08 KJ/mol, 0.062 KJ/mol·K, −42.05 ± 0.08 KJ/mol and 2.28 ± 0.29 × 10^7 M^{-1}, respectively. As a result, the ΔH_1 of *p*-AP/β-CD is 2.11 KJ/mol lower and the ΔS_1 0.004 KJ/mol·K higher than that of *o*-AP/β-CD, leading to the binding constant of *p*-AP/β-CD 3.6-fold higher.

The differences in thermodynamic parameters reflect that *p*-AP binds with β-CD more tightly than *o*-AP, consistent with the results speculated from the ^{1}H NMR data. This binding preference of β-CD with *p*-AP other than *o*-AP in the competitive aminomethylation of phenol comes from the larger ΔG_1 lowering (−45.35 vs −42.05 KJ/mol, Table 3), thereby disrupting the non-selectivity as in the case of without β-CD and leading to the formation of *p*-AP as major product.

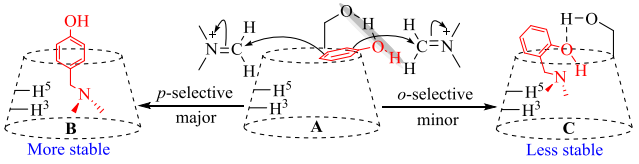
The bindings of *p*-AP and *o*-AP with β-CD were also examined using UV–vis absorption spectroscopy. The measurements were done by keeping the concentration of *p*-AP or *o*-AP at 50 μM while varying the molar ratio of β-CD to the guest in the range from 0 to 0.7 with 0.1 intervals. The inclusion of *p*-AP and *o*-AP with β-CD resulted in the increase of absorption and both the complexes gave maximum absorptions at the guest/β-CD molar ratio of 1:0.5 with λ_{max} 272 and 275 nm, respectively (Supporting Information), meaning that the binding ratio was 2:1 for both *p*-AP and *o*-AP over β-CD. This binding ratio is consistent with the result obtained in the exotherm fitting of ITC measurements, where the exotherms were best fitted using a complexation number of 2. Interestingly, both the bindings did not result in λmax shift, but the binding of *p*-AP with β-CD produced a 4.3-fold enhancement in the maximum absorption at the ratio of 2:1; while a 1.4-fold increase was found for *o*-AP, a consequence of distinct binding strengths.[30]

2.4. Mechanism discussion

On the basis of the above results from ^{1}H NMR and ITC, a plausible mechanism can be outlined for the β-CD mediated *para*-regioselective dimethylaminomethylation of phenol as shown in Scheme 2. First, phenol poses slantingly near the narrow rim of β-CD cone via the hydrophobic and hydrogen bonding interactions to

Table 3
Thermodynamic parameters obtained from ITC measurement.

Inclusion complex	ΔH_1 (KJ/mol)	ΔS_1 (KJ/mol·K)	ΔG_1 (KJ/mol)	$K_1 \times 10^7$ (M^{-1})
p-AP-β-CD	−25.68 ± 0.08	0.066	−45.35 ± 0.08	8.26 ± 1.08
o-AP-β-CD	−23.57 ± 0.08	0.062	−42.05 ± 0.08	2.28 ± 0.29



Scheme 2. Plausible mechanism for the β-CD mediated *para*-selective aminomethylation.

form an outer-sphere complex (Scheme 2A). The intermediate *N*,*N*-dimethyliminium, which resides in the proton-deshielding region outside β-CD, undergoes an electrophilic addition either via the attack at the *para*-site of phenol to generate *p*-AP and subsequently forming a inclusion complex with β-CD (Scheme 2B), or via the attack at the *ortho*-site of phenol to give *o*-AP and followed by the formation of *o*-AP/β-CD (Scheme 2C). The positions and orientations of *p*-AP and *o*-AP in β-CD are drawn accordingly in line with this process. In addition, there may exist somewhat hydrogen bonding between the phenolic hydroxyl group of *o*-AP and the primary hydroxyl group at the narrow rim of β-CD, which is presumably formed upon interaction with β-CD by disrupting the intramolecular cyclic hydrogen bond between the hydroxyl and the amino nitrogen in *o*-AP. This result can be inferred from the large methylene chemical shift variation from δ4.06 to δ3.79 ppm when free *o*-AP binds with β-CD, and the resulting value of δ3.79 ppm approximates the methylene chemical shift of δ3.83 ppm of free *p*-AP, where no intramolecular hydrogen bonding exists. Furthermore, this intermolecular hydrogen bonding may prevent *o*-AP from entering into the cavity, resulting in a binding conformation different to the deep complexation of *p*-AP/β-CD.

The proposed binding conformations are in agreement with the ^{1}H NMR data to a large extent, except for that of the dimethylaminomethyl group. In principle, the more deep insertion of a gust molecule inside the β-CD cavity, the larger upfield proton Δδs should be resulted.[31,32] The methyl Δδs of *p*- and *o*-AP are consistent with this expectation ($H^{p\text{-}f}$ (−0.20 ppm) vs H^{o-f} (−0.15 ppm)); however, the methylene Δδs ($H^{p\text{-}e}$ (−0.14 ppm) vs H^{o-e} (−0.27 ppm)) deviate from this expectation largely. We could attribute the deviation to a consequence of the transformation of the intramolecular hydrogen bonding to the intermolecular one as mentioned above, due to the former induces a larger downfield shift to the methylene group of *o*-AP. Another remaining concern is that the stoichiometry of β-CD in the optimal reaction conditions needed to be or more than 1.5-fold over that of phenol to give the high regioselectivity. This might be ascribed to fact that the binding of β-CD with *p*-AP is a thermodynamic process, thus a higher amount of β-CD would favor the reaction toward the desired direction.

It is worthy of mention that the plausible mechanism depicted in Scheme 2, in which β-CD includes more efficiently the product *p*-AP to realize the *para*-selectivity, is significantly different to the known role of β-CD on supramolecular chemistry based syntheses. For example, the *para*-photo-Reimer-Tiemann reaction of phenol to yield 4-hydroxy benzaldehyde under light irradiation was reported to involve the complexation of β-CD with phenol and block the *ortho*-site other than to affect the product.[15]

3. Conclusions

In summary, we investigated the effect of various cyclodextrins on the three-component Mannich reaction of phenol with formaldehyde and dimethylamine, and demonstrated the use of β-CD is most effective to give *p*-AP as major product. By utilizing ^{1}H NMR and ITC measurements, we probed in-depth the role of β-CD, and proposed the inclusion conformations of phenol/β-CD, *o*-AP/β-CD and *p*-AP/β-CD. Based on these conformations, the β-CD mediated *para*-regioselective dimethylaminomethylation of phenol could be reasonably explained, that is, the preferential formation of the complex *p*-AP/β-CD resulted in the change of the reaction pathway to the desired direction. This product-inclusion process is complementary to the known substrate-inclusion mechanism and may have an important role in developing regioselective reactions by supramolecular chemistry.

4. Experimental section

4.1. Synthesis

One solution was firstly prepared by dissolving 2 mmol phenol and a certain amount of one CD (α-, β- or γ-CD) in 15 ml water and stirring for 30 min. Another solution, involving the formation of the intermediate *N*,*N*-dimethyliminium (DMA), was prepared by mixing 37% aqueous solution of formaldehyde (0.16 g, 2 mmol) and 33% aqueous solution of dimethylamine (0.27 g, 2 mmol) in 10 ml water. Then the DMA solution was added dropwise to the phenol solution with magnetic stirring, and the reaction was monitored by TLC. After stirring for 4 h, the reaction was complete, and the solution was acidified to pH 2 with 2 M HCl and extracted with ethyl acetate (3 × 10 ml). The organic extracts were combined, dried with anhydrous sodium sulfate, concentrated in vacuum to give unreacted phenol, whose amount was used to calculate the conversion rate. The aqueous phase was basified to pH 9–10 with 2 M NaOH and extracted with ethyl acetate (3 × 10 ml). The combined organic phase was dried with anhydrous sodium sulfate, concentrated in vacuum to give a product mixture, which was used for the ^{1}H NMR analysis of the composition of *o*-AP and *p*-AP. The mixture was also subjected to purification with flash chromatography on silica gel with EtOAc/petroleum ether (volumetric ratio 1:1) as the first eluent to obtain *o*-AP, then with EtOAc/CH_3OH (volumetric ratio 1:1) as the second eluent to afford *p*-AP.

4.2. Simplified purification procedure

An alternative simplified purification procedure was developed to obtain the pure compounds *o*-AP and *p*-AP without use of column chromatography. Briefly, after the reaction mentioned above, the reaction mixture was first acidified to pH 2 with 2 M HCl and extracted with ethyl acetate (3 × 10 ml) to remove the unreacted phenol. Next, the aqueous phase was basified to about pH 7 using 2 M NaOH and extracted with ethyl acetate (3 × 10 ml) to give an organic phase which contained the product *o*-AP. Finally, the aqueous phase was further basified to about pH 8–9 and extracted with ethyl acetate (3 × 10 ml) to give another organic phase containing p-AP. Both the organic phases were dried with anhydrous

sodium sulfate, concentrated in vacuum to afford the products *o*-AP and *p*-AP, respectively, with adequate purity as determined by ^{1}H NMR.

4.3. Scale-up synthesis of p-AP

The optimal reaction conditions and the simplified procedure were employed for the scale-up synthesis of *p*-AP with a 10-fold amplification. Thus 2.4 grams of the pure product *p*-AP in 90% yield was obtained after recrystallization from acetonitrile.

4.4. ^{1}H NMR measurements

^{1}H NMR spectra of pure *o*-AP, *p*-AP and the product mixture in DMSO obtained in the synthesis procedure were recorded on Varian NMR System 600 MHz and used to calculate the composition of *o*- and *p*-AP in the mixture. For the ^{1}H NMR analyses of the β-CD complexes, the interactive ^{1}H NMR spectra of β-CD with phenol, DMA, *p*-AP, and *o*-AP were recorded using the samples prepared by ultrasonically dissolving 0.1 mmol of the substances separately in D_2O containing 0.1 mmol β-CD.

4.5. ITC measurements

ITC experiments were carried out on a Microcal VPITC apparatus at 25 °C with the reference power set at 10 μcal s^{-1}. The aqueous solutions of phenol, *o*-AP or *p*-AP at 1 mM were used separately to titrate 0.1 mM aqueous β-CD in the sample cell under stirring continuously at 310 rpm. For each titration, consecutive 15–20 injections with 15 μL each were made at 5-min intervals and data were recorded. Data were analyzed using the ITC associated software.

4.6. UV–vis titration

UV–vis titration measurements were performed with a UV-3600 spectrophotometer (Shimadzu, Japan) at room temperature. The concentration of *p*-AP or *o*-AP was maintained constant at 50 μM while the molar ratio of β-CD to the guest was varied in the range from 0 to 0.7 with 0.1 intervals. The spectra were acquired by scanning from 200 to 500 nm.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.tet.2017.12.007.

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