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Aminocyclodextrins to facilitate the deprotonation of 4-*tert*-butyl-α-nitrotoluene

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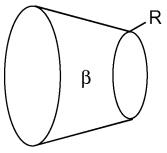
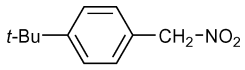
6^A-Amino-6^A-deoxy-β-cyclodextrin enhances the rate of the deprotonation of 4-*tert*-butyl-α-nitrotoluene. The rate constants for reaction of the cyclodextrin-bound species, $k_{inc} = 4 \times 10^{-3}$, 9×10^{-3} and 19×10^{-3} s^{-1}, at pH 6.0, 6.5 and 7.0, respectively, in 0.1 mol dm^{-3} aqueous phosphate buffer containing 1% methanol at 298 K. These rate constants correspond to a rate acceleration (k_{inc}/k_{un}) of *ca.* 10 times at each pH. Under the same conditions, 6^A-dimethylamino-6^A-deoxy-β-cyclodextrin and 6^A-(2-aminoethylamino)-6^A-deoxy-β-cyclodextrin are more effective; at pH 6.0, 6.5 and 7.0, for the former, $k_{inc} = 3 \times 10^{-2}$, 7×10^{-2} and 12×10^{-2} s^{-1}, whilst for the latter, $k_{inc} = 4 \times 10^{-2}$, 5×10^{-2} and 9×10^{-2} s^{-1}, respectively. Each cyclodextrin also decreases the pK_a of the nitrotoluene, from 6.8 in free solution, to 6.2 when bound. The accelerated deprotonation by 6^A-amino-6^A-deoxy-β-cyclodextrin is reflected in the enhanced rates of hydrogen–deuterium exchange of the nitrotoluene in deuterium oxide, and in the conjugate addition of the nitrotoluene to methyl vinyl ketone in aqueous solution.

Introduction

Natural and modified cyclodextrins have been studied extensively as catalysts and enzyme mimics.[1] The modified cyclodextrins have incorporated a wide range of functional groups, including a variety of basic residues.[2,3] For example, Breslow *et al.*[3] have shown that imidazole-substituted cyclodextrins can be exploited as either acid or base catalysts, and in particular cases they have used bisimidazole-substituted cyclodextrins for concerted acid–base catalysis. The objective of the present work was to explore the effects of the simple amino-substituted cyclodextrins 6^A-amino-6^A-deoxy-β-cyclodextrin (**1a**), 6^A-dimethylamino-6^A-deoxy-β-cyclodextrin (**1b**) and 6^A-(2-aminoethylamino)-6^A-deoxy-β-cyclodextrin (**1c**) on the deprotonation of 4-*tert*-butyl-α-nitrotoluene (**2**). Nitroalkanes, such as this deprotonate under neutral or mildly basic conditions,[4] and the product nitronates are versatile intermediates in organic synthesis;[5,6] they undergo nitroaldol (Henry) reactions with aldehydes and ketones,[7] and Michael additions with electron-deficient olefins.[6,8] However, the rates of deprotonation of nitroalkanes are anomalously slow for acid–base reactions.[9] For example, the half-life for reaction of the nitrotoluene **2** at pH 7.0 and 298 K is *ca.* 8 min, so this process is an obvious target for rate enhancement.



1a R = NH_2
1b R = NMe_2
1c R = $NHCH_2CH_2NH_2$



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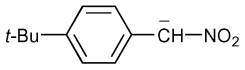

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Results and discussion

The nitrotoluene **2** was chosen as the substrate because it was expected to readily include into the cavity of the modified cyclodextrins **1a**–**c**. It was also expected to deprotonate at near neutral pH to give the chromophoric nitronate anion **3**. In the event, it was prepared by treatment of the corresponding bromide with silver nitrite,[10] and found to have a pK_a of 6.8. The nitronate **3** had λ_{max} 300 nm (ε 22,000 mol^{-1} dm^3 cm^{-1}), at which wavelength the nitroalkane **2** displayed negligible absorption. At pH 6.0, 6.5 and 7.0, in 0.1 mol dm^{-3} aqueous phosphate buffer containing 1% methanol at 298 K, the nitrotoluene **2** deprotonated with pseudo-first order rate constants of 4×10^{-4}, 9×10^{-4} and 15×10^{-4} s^{-1}, respectively. The modified cyclodextrins **1a**–**c** were prepared as reported.[11,12] The pK_a of the protonated dimethylaminocyclodextrin **1b** was measured to be 8.6, while those of the conjugate acids of the aminocyclodextrin **1a** and the aminoethylaminocyclodextrin **1c** have been reported as 8.9, and 5.7 and 9.4, respectively.[11]

The complexation of the nitrotoluene **2** by β-cyclodextrin and the modified cyclodextrins **1a**–**c** was studied using ^{1}H NMR spectroscopy, at 298 K in deuterium oxide containing 1% d_4-methanol and 0.1 mol dm^{-3} phosphate buffer, adjusted to pD 4.4, 8.4 and 11.4 with either sodium deuteroxide or deuterium chloride. These pD values were chosen to encompass the various stages of protonation and deprotonation of the cyclodextrins **1a**–**c** and the nitrotoluene **2** in aqueous solutions, based on the pK_a values described above. The samples contained 0.2 mmol dm^{-3} of the nitrotoluene **2** and ranged in cyclodextrin concentration from 0.0–1.5 mmol dm^{-3}. With each cyclodextrin and at each pD, the chemical shift due to the signal of the *tert*-butyl group of the nitrotoluene **2** moved downfield with increasing cyclodextrin concentration (Fig. 1). Curve fitting of these data showed that the association constants (eqn. 1) of the host–guest complexes of the nitrotoluene **2** with β-cyclodextrin and the modified cyclodextrins **1a**–**c** are greater than 10000 dm^3 mol^{-1}, irrespective of the charged state of either the nitrotoluene **2** or the hosts. It is reasonable to expect that the corresponding values in water would be similar and, on the basis of that and eqn. 1, to assume that the nitrotoluene **2** is effectively, completely complexed in aqueous solutions containing 0.1 mmol dm^{-3} of the nitrotoluene **2** and at least 10 mmol dm^{-3} of either β-cyclodextrin or one of the modified cyclodextrins **1a**–**c**. These conditions were therefore used to measure the extents and rates of deprotonation of the nitrotoluene **2** in the host–guest complexes.

$$K\ (dm^3\ mol^{-1}) = [complex]/[host]\cdot[guest] \quad (1)$$

Accordingly, pK_as of 6.7, 6.2, 6.2 and 6.2 were measured for the nitrotoluene **2** included in the annulus of β-cyclodextrin and

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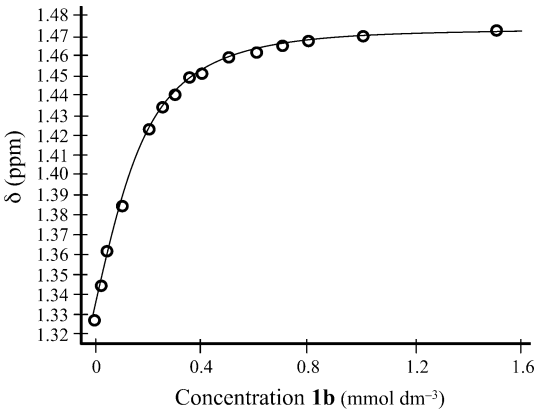


Fig. 1 The change in chemical shift of the signals due to the *tert*-butyl group of **2** (0.2 mmol dm^{-3}) plotted as a function of increasing cyclodextrin concentration for 6^{A}-dimethylamino-6^{A}-deoxy-β-cyclodextrin (**1b**) (0.0–1.5 mmol dm^{-3}) in 0.1 mol dm^{-3} phosphate buffer, at pD 4.4, containing 1% d_4-methanol at 298 K.

the modified cyclodextrins **1a**–**c**, respectively. At pH 6.0, 6.5 and 7.0, in 0.1 mol dm^{-3} aqueous phosphate buffer containing 1% methanol at 298 K, the pseudo-first order rate constants for deprotonation of the nitrotoluene **2** included in the cavity of β-cyclodextrin (k_{inc}) were found to be 3×10^{-4}, 8×10^{-4} and 14×10^{-4} s^{-1}, respectively, while the corresponding values for the modified cyclodextrins **1a**–**c** were 4×10^{-3}, 9×10^{-3} and 19×10^{-3} s^{-1}, 3×10^{-2}, 7×10^{-2} and 12×10^{-2} s^{-1}, and 4×10^{-2}, 5×10^{-2} and 9×10^{-2} s^{-1}. Very similar rate constants were obtained when either higher or lower cyclodextrin concentrations were used, confirming the expectation that the nitrotoluene **2** is fully complexed and that the measurements reflect the rates of deprotonation of the complexed species. When ethanolamine was used instead of a cyclodextrin, the pK_a of the nitrotoluene **2** was 6.9 and the observed pseudo-first order rate constants for deprotonation of the nitrotoluene **2** (k_{obs}) at pH 6.0, 6.5 and 7.0 were 4×10^{-4}, 9×10^{-4} and 15×10^{-4} s^{-1}, respectively.

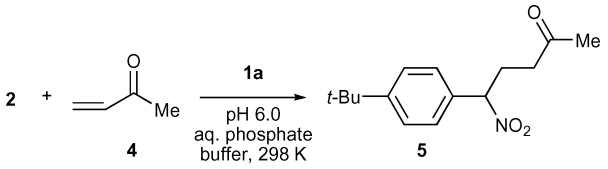
Neither β-cyclodextrin nor ethanolamine increases the rate of deprotonation of the nitrotoluene **2**. By comparison, the aminocyclodextrin **1a** accelerates the rate of deprotonation by approximately 10 times at each pH studied. The deprotonation rate increases with increasing pH, presumably because the active form of the cyclodextrin **1a** is the free base and, since the pK_a of the protonated form of the cyclodextrin **1a** is 8.9, the concentration of the base also increases when going from pH 6.0 to 7.0. The dimethylaminocyclodextrin **1b** is more effective, increasing the rate of deprotonation of the nitrotoluene **2** by approximately 75 times at each pH studied. The greater effect of this cyclodextrin is probably due, at least in part, to its lower pK_a value, and the consequently higher concentration of the free base form at pH 6.0–7.0. The ethylenediamine **1c** is also more efficient than the aminocyclodextrin **1a**, but the rate of deprotonation by this species does not show the same increase with increasing pH as observed with the aminocyclodextrins **1a** and **1b**. In this case it is likely that both the monoprotonated and the free base form of the cyclodextrin **1c** promote reaction, and the pH dependence on the rate of deprotonation of the nitrotoluene **2** reflects the concentrations of these species.

The extent of deprotonation of the nitrotoluene **2** at equilibrium at a given pH, as reflected in the pK_a, is little affected by either β-cyclodextrin or ethanolamine. However, each of the modified cyclodextrins **1a**–**c** increases the extent of deprotonation and reduces the pK_a by approximately 0.6. The pK_as of other acids, such as benzoic acids, are known to be altered on inclusion in cyclodextrins.[13] In those cases the effect is attributable to inclusion of uncharged, more hydrophobic species in preference to the corresponding anions. As a consequence the pK_as are increased. Presumably, the peculiar effect observed with the nitrotoluene **2** and the cyclodextrins **1a**–**c**, to decrease the guest pK_a, reflects the ability of the cyclodextrins' protonated amino groups to form ion-pairs with, and therefore stabilise, the included nitronate **3**.

The pK_a of the nitrotoluene **2** reflects the ratio of the rate of its deprotonation and the rate of protonation of the corresponding nitronate **3**. Since each of the cyclodextrins **1a**–**c** reduces this pK_a by 0.6, it follows that the ratio is altered by a factor of approximately 4. Given that the cyclodextrins **1a**–**c** increase the rate of deprotonation by factors ranging from 10–100, they must also increase the rate of protonation of the nitronate **3** by 2–25 times. It seems likely that this effect is due to the proximity of the cyclodextrins' protonated amino groups to deliver a proton to the nitronate **3**.

Based on the observations above, the cyclodextrins **1a**–**c** should increase the rate of deuteration of the nitrotoluene **2** in deuterium oxide. To investigate this, solutions of the nitrotoluene **2** (1 mmol dm^{-3}) with either β-cyclodextrin or the aminocyclodextrin **1a** (5 mmol dm^{-3}), in deuterium oxide containing 10% d_4-methanol and 0.1 mol dm^{-3} phosphate buffer, at 298 K and pD 6.4, were monitored using ^{1}H NMR spectroscopy. Under these conditions, the pseudo-first order rate constants for hydrogen–deuterium exchange of the acidic methylene protons of the nitrotoluene **2** were observed to be 1.0×10^{-4} s^{-1} with β-cyclodextrin and 23×10^{-4} s^{-1} with the amine **1a**. It was not practical to examine the reaction in the absence of a cyclodextrin, due to the limited aqueous solubility of the nitrotoluene **2** unless complexed.

The utility of the cyclodextrins **1a–c** increasing the rate and extent of deprotonation of the nitroalkane **2** depends on the nitronate **3** being accessible for further reactions. To examine this, reaction of the nitronate **3** with methyl vinyl ketone (**4**) to give the adduct **5** was investigated (Scheme 1). Mixtures of the nitrotoluene **2** (5 mmol dm^{-3}) and methyl vinyl ketone (5 mmol dm^{-3}), and either β-cyclodextrin or the aminocyclodextrin **1a** (25 mmol dm^{-3}), in 0.1 mol dm^{-3} pH 6.0 aqueous phosphate buffer containing 1% methanol, were left stirring at 298 K. Again, it was not possible to examine the reaction in the absence of a cyclodextrin due to the low aqueous solubility of the nitrotoluene **2**. Under these conditions, after 24 h the yield of the adduct **5** was 68% when the reaction was carried out in the presence of the aminocyclodextrin **1a**, but only small quantities (<10%) were recovered from the mixture containing β-cyclodextrin.



Scheme 1

In summary, this work demonstrates that an aminocyclodextrin can increase both the rate and extent of deprotonation of a nitroalkane without interfering with the reactions of the resultant nitronate. In the formal sense, the cyclodextrins are thus behaving as catalysts, since they exert their effects without being altered, but in a practical sense they are only effective when used in excess rather than catalytic amounts. In addition to the effects on deprotonation, this work shows the advantage of using cyclodextrins to increase the aqueous solubility of organic compounds, facilitating the use of this solvent for chemical transformations. The more general application of these results will depend on the identification of alternative molecular hosts that are compatible with a wide range of nitroalkanes, but the basic principles of this form of catalysis have been established.

Experimental

General

^{1}H and ^{13}C NMR spectra were recorded on Varian Gemini 300 and Varian Inova 500 spectrometers. Electron impact mass spectra were recorded on a Micromass VG AutoSpec mass spectrometer, operating with an ionisation potential of 70 eV. UV spectra were recorded using a Shimadzu UV-2101PC UV-vis scanning spectrophotometer coupled to a Shimadzu CPS temperature controller or a stopped-flow spectrometer (Model SF. 17MV). The Australian National University Microanalytical Service performed the elemental analyses. Melting points were determined on a Kofler hot-stage melting point apparatus under a Reichert microscope.

4-*tert*-Butylbenzyl bromide and methyl vinyl ketone (**4**) were purchased from Sigma-Aldrich Chemical Co. β-Cyclodextrin was the generous gift of Nihon Shokuhin Kako Co. It was recrystallised from water and dried *in vacuo* over P_2O_5 to constant weight before use. The modified cyclodextrins **1a**–**c** were prepared as previously reported.[11,12] Water was deionised and then purified with a Milli-Q™ reagent system to ensure a resistivity of <15 MΩ cm. Phosphate buffer solutions were prepared using an Orion PerpHecT® Meter, Model 320. The pK_a of the protonated dimethylaminocyclodextrin **1b** was measured to be 8.6, using the procedure reported previously for determination of the pK_as of the aminocyclodextrin **1a** and the aminoethylaminocyclodextrin **1c**.[11]

4-*tert*-Butyl-α-nitrotoluene (2)

4-*tert*-Butylbenzyl bromide (11.4 g, 50 mmol) was added dropwise over 1 h to a slurry of $AgNO_2$ (10.0 g, 65 mmol) and CaH_2 (0.1 g, 2.4 mmol) in diethyl ether (60 cm^3) maintained at 0 °C. The mixture was stirred for a further 26 h at 0 °C, after which it was filtered and the filter cake washed with diethyl ether (3 × 50 cm^3). The combined filtrates were concentrated under reduced pressure to give a crude oil comprising the nitrotoluene **2** and the related nitrite ester in a ratio of 43 : 57. Chromatography of the oil on silica gel, eluting with ethyl acetate–hexane (1 : 9, v : v), gave the nitrotoluene **2** as a colourless crystalline solid (3.4 g, 35%): mp 27–28 °C; (Found: C, 68.67; H, 7.54; N, 7.00%. $C_{11}H_{15}NO_2$ requires C, 68.37; H, 7.82; N, 7.25%); δ_H (300 MHz, $CDCl_3$) 7.45 (d, 2H, *J* 8.7), 7.39 (d, 2H, *J* 8.7), 5.42 (s, 2H), 1.33 (s, 9H); δ_C (75 MHz, $CDCl_3$) 153.1, 129.6, 126.7, 126.0, 79.8, 34.8, 31.3; *m*/*z* (EI) 193 (0.3%, M$^{+\bullet}$), 178 (3), 147 (100), 132 (51) and 91 (55).

Determination of the association constants, *K*, of the complexes of the nitrotoluene 2 with β-cyclodextrin and the aminocyclodextrins 1a–c in D_2O at pD 4.4, 8.4 and 11.4

Solutions of the nitrotoluene **2** (0.2 mmol dm^{-3}) and either β-cyclodextrin or one of the aminocyclodextrins **1a**–**c** (0–7.5 mol. equiv.) in phosphate buffer (0.1 mol dm^{-3}) were made up in D_2O containing 1% d_4-methanol, and adjusted to pD 4.4, 8.4 or 11.4 with either NaOD–D_2O or DCl–D_2O. They were then analysed at 298 K using ^{1}H NMR spectroscopy (500 MHz). The changes in the chemical shift of the resonance due to the *tert*-butyl protons of the nitrotoluene **2** were recorded and plotted as a function of cyclodextrin concentration (Fig. 1), and curves were fitted to the data according to eqn. 1 and 2 by applying non-linear regression analysis using Mac-Curvefit v1.2®. This gave the values for the association constants, *K*, that are summarised in Table 1.

$$\delta_{observed} = \frac{[guest] \cdot \delta_{free} + [complex] \cdot \delta_{complexed}}{[guest] + [complex]} \qquad (2)$$

Table 1 Association constants *K* of the complexes formed between 4-*tert*-butyl-α-nitrotoluene (**2**) and either β-cyclodextrin or one of the aminocyclodextrins **1a**–**c** in 0.1 mol dm^{-3} phosphate buffer, at pD 11.4 (A), 8.4 (B) and 4.4 (C), containing 1% d_4-methanol at 298 K

	$K \times 10^{-4}$/dm^3 mol^{-1}		
Cyclodextrin	A	B	C
β-Cyclodextrin	2.6 ± 0.6	1.2 ± 0.3	4.4 ± 0.9
1a	2.0 ± 0.3	2.0 ± 0.2	1.1 ± 0.1
1b	3.0 ± 0.8	4.6 ± 0.8	2.2 ± 0.3
1c	2.9 ± 0.4	4.1 ± 0.6	1.0 ± 0.1

Determination of the pK_a of the nitrotoluene 2 alone and in the presence of either ethanolamine, β-cyclodextrin or one of the aminocyclodextrins 1a–c

Solutions of the nitrotoluene **2** (0.1 mmol dm^{-3}), alone or in the presence of either ethanolamine, β-cyclodextrin or one of the aminocyclodextrins **1a**–**c** (10.0 mmol dm^{-3}), were made up in aqueous phosphate buffer (0.1 mol dm^{-3}) containing 1% d_4-methanol, and adjusted to the chosen pH values using either NaOH–H_2O or NaH_2PO_4–H_2O. Their UV spectra were then recorded at 298 K. At high pH values, the spectra of the solutions are attributable to the nitronate **3**, which was therefore determined to have a λ_{max} at 300 nm, with ε = 22,000 mol^{-1} dm^3 cm^{-1}. At low pH values the spectra of the solutions, which then contain the nitrotoluene **2**, showed negligible absorbance at this wavelength. At high and low pH values, the spectra are not significantly affected by either ethanolamine or any of the cyclodextrins. The absorbance of the solutions at 300 nm was recorded and plotted as a function of pH (Fig. 2). From these curves, pK_a values were determined, from the pH at which the absorbance at 300 nm was half that of a solution of high pH. On this basis, the pK_a of the nitrotoluene **2**, alone and in the presence of either ethanolamine, β-cyclodextrin or one of the aminocyclodextrins **1a**–**c**, was determined to be 6.8 ± 0.1, 6.9 ± 0.1, 6.7 ± 0.1, 6.2 ± 0.1, 6.2 ± 0.1 and 6.2 ± 0.1, respectively.

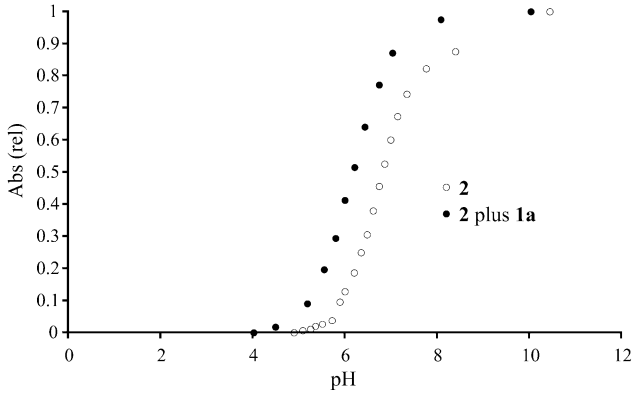


Fig. 2 Relative absorbance, at 300 nm plotted as a function of pH, for series of solutions of the nitroalkane **2** (0.1 mmol dm^{-3}) at different pH values, in 0.1 mol dm^{-3} phosphate containing 1% methanol at 298 K, in the presence and in the absence of the amine **1a** (10 mmol dm^{-3}).

Determination of the pseudo-first order rate constants for deprotonation of the nitrotoluene 2 in aqueous solution, alone and in the presence of either ethanolamine, β-cyclodextrin or one of the aminocyclodextrins 1a–c, at pH 6.0, 6.5 and 7.0

Solutions of the nitrotoluene **2** (0.1 mmol dm^{-3}), alone and in the presence of either ethanolamine, β-cyclodextrin or one of the aminocyclodextrins **1a**–**c** (10.0 mmol dm^{-3}), were made up in aqueous phosphate buffer (0.1 mol dm^{-3}) containing 1% d_4-methanol, and adjusted to either pH 6.0, 6.5 or 7.0 using either NaOH–H_2O or NaH_2PO_4–H_2O. Their absorbance was then

Table 2 Pseudo-first order rate constants for the deprotonation of the nitrotoluene **2** (0.1 mmol dm^{-3}), at pH 6.0, 6.5 and 7.0, in 0.1 mol dm^{-3} phosphate buffer containing 1% methanol at 298 K, alone and in the presence of either ethanolamine, β-cyclodextrin or one of the aminocyclodextrins **1a**–**c** (10 mmol dm^{-3})

		$k_{obs} \times 10^2/s^{-1}$				
pH	$k_{un} \times 10^2/s^{-1}$	Ethanolamine	β-Cyclodextrin	**1a**	**1b**	**1c**
6.0	0.04	0.04	0.03	0.4	3	4
6.5	0.09	0.09	0.08	0.9	7	5
7.0	0.15	0.15	0.14	1.9	12	9

recorded as a function of time at 298 K, using either conventional or stopped-flow UV spectrophotometry, at 300 and 325 nm, respectively, to monitor appearance of the nitronate **3**. The rates of deprotonation of the nitrotoluene **2** determined in this manner from the initial rates of reaction are summarised in Table 2. These values are the average of at least three determinations, and the results of individual experiments varied by less than 10%.

3-(4-*tert*-Butylphenyl)-3-nitropropyl methyl ketone (5)

Method 1. A solution of diisopropylamine (10 mg, 0.1 mmol), methyl vinyl ketone (**4**) (73 mg, 1.0 mmol) and 4-*tert*-butyl-α-nitrotoluene (**2**) (200 mg, 1.0 mmol) in acetonitrile (1 cm^3) was stirred at 298 K for 24 h, before being poured into aqueous HCl (0.1 mol dm^{-3}, 5 cm^3). The aqueous solution was extracted with diethyl ether (3 × 15 cm^3), and the combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue on silica, eluting with ethyl acetate–hexane (1 : 9, v : v) afforded 3-(4-*tert*-butylphenyl)-3-nitropropyl methyl ketone (**5**) as a colourless solid (120 mg, 46%): mp 61–62 °C; (Found: C, 68.13; H, 8.12; N, 5.06%. $C_{15}H_{21}NO_3$ requires C, 68.42; H, 8.04; N, 5.32%); δ_H (300 MHz, $CDCl_3$) 7.42 (d, 2H, *J* 8.7), 7.37 (d, 2H, *J* 8.7), 5.51 (dd, 1H, *J* 9.1, *J* 5.8), 2.68 (m, 1H), 2.50 (t, 2H, *J* 7.0), 2.38 (m, 1H), 2.14 (s, 3H), 1.31 (s, 9H); δ_C (75 MHz, $CDCl_3$) 206.1, 153.0, 131.0, 127.3, 125.9, 89.9, 39.3, 34.8, 31.3, 30.1, 27.6; *m*/*z* (EI) 263 (0.01%, $M^{+\bullet}$), 248 (25), 233 (52), 217 (82), 143 (84) and 57 (100).

Method 2. Methyl vinyl ketone (**4**) (35 mg, 0.50 mmol), 4-*tert*-butyl-α-nitrotoluene (**2**) (10 mg, 0.052 mmol) and 6^A-amino-6^A-deoxy-β-cyclodextrin (**1a**) (285 mg, 0.25 mmol) were dissolved in phosphate buffer (pH 6.0, 0.1 mol dm^{-3}, 10 cm^3) containing 1% methanol, and the mixture was stirred at 298 K for 24 h, before being poured into aqueous HCl (0.1 mol dm^{-3}, 5 cm^3). The aqueous solution was extracted with diethyl ether (3 × 15 cm^3), and the combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue on silica, eluting with ethyl acetate–hexane (1 : 9, v : v), afforded 3-(4-*tert*-butylphenyl)-3-nitropropyl methyl ketone (**5**) as a colourless solid (9.3 mg, 68%).

When the reaction was repeated using β-cyclodextrin instead of the aminocyclodextrin **1a**, only traces of the adduct **5** were evident in the ^1H NMR spectrum of the crude product mixture. Based on the ratio of the nitrotoluene **2** to the adduct **5**, the yield was determined to be <10%.

Acknowledgements

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References

1 (*a*) R. Breslow and S. D. Dong, *Chem. Rev.*, 1998, **98**, 1997; (*b*) C. J. Easton and S. F. Lincoln, *Modified Cyclodextrins: Scaffolds and Templates for Supramolecular Chemistry*, Imperial College Press, London, 1999; (*c*) L. Barr, P. G. Dumanski, C. J. Easton, J. B. Harper, K. Lee, S. F. Lincoln, A. G. Meyer and J. S. Simpson, *J. Inclusion Phenom. Macrocyclic Chem.*, 2004, **50**, 19; (*d*) C. J. Easton, S. F. Lincoln, L. Barr and H. Onagi, *Chem. Eur. J.*, 2004, **10**, 3120.
2 (*a*) A. C. Hengge, A. E. Tobin and W. W. Cleland, *J. Am. Chem. Soc*, 1995, **117**, 5919; (*b*) K. K. Park, B.-K. Kang and J. W. Park, *Bull. Korean Chem. Soc.*, 1995, **16**, 672; (*c*) C. J. Easton, S. Kassara, S. F. Lincoln and B. L. May, *Aust. J. Chem.*, 1995, **48**, 269; (*d*) C. G. Ferguson and G. R. J. Thatcher, *Org. Lett.*, 1999, **1**, 829; (*e*) M.-M. Luo, R.-G. Xie, P.-F. Xia, L. Tao, D.-Q. Yuan and H.-M. Zhao, *J. Phys. Org. Chem.*, 2001, **14**, 515; (*f*) L. Barr, C. J. Easton, K. Lee, S. F. Lincoln and J. S. Simpson, *Tetrahedron Lett.*, 2002, **43**, 7797; (*g*) A. Fragoso, R. Cao and M. Baños, *Tetrahedron Lett.*, 2004, **45**, 4069.
3 (*a*) R. Breslow and A. Graff, *J. Am. Chem. Soc.*, 1993, **115**, 10988; (*b*) R. Breslow, *J. Mol. Catal.*, 1994, **91**, 161; (*c*) R. Breslow and C. Schmuck, *J. Am. Chem. Soc.*, 1996, **118**, 6601; (*d*) R. Breslow, J. Desper and Y. Huang, *Tetrahedron Lett.*, 1996, **37**, 2541.
4 (*a*) R. G. Pearson and R. L. Dillon, *J. Am. Chem. Soc.*, 1953, **75**, 2439; (*b*) A. T. Nielsen, in *The Chemistry of the Nitro and Nitroso Groups*, ed. H. Feuer, Wiley-Interscience, New York, 1969, ch. 7, pp. 349–486.
5 (*a*) H. Adams, J. C. Anderson, S. Peace and A. M. K. Pennell, *J. Org. Chem.*, 1998, **63**, 9932; (*b*) R. Nouguier, V. Béraud, P. Vanelle and M. P. Crozet, *Tetrahedron Lett.*, 1999, **40**, 5013; (*c*) R. Ballini, D. Fiorini and A. Palmieri, *Tetrahedron Lett.*, 2004, **45**, 7027.
6 R. Ballini, L. Barboni and G. Giarlo, *J. Org. Chem.*, 2003, **68**, 9173.
7 (*a*) R. Ballini and G. Bosica, *J. Org. Chem.*, 1997, **62**, 425; (*b*) P. B. Kisanga and J. G. Verkade, *J. Org. Chem.*, 1999, **64**, 4298; (*c*) D. A. Evans, D. Seidel, M. Rueping, H. W. Lam, J. T. Shaw and C. W. Downey, *J. Am. Chem. Soc.*, 2003, **125**, 12692.
8 (*a*) R. Ballini, P. Marziali and A. Mozzicafreddo, *J. Org. Chem.*, 1996, **61**, 3209; (*b*) N. Halland, R. G. Hazell and K. A. Jørgensen, *J. Org. Chem.*, 2002, **67**, 8331; (*c*) N. Ono, A. Kamimura, H. Miyake, I. Hamamoto and A. Kaji, *J. Org. Chem.*, 1985, **50**, 3692.
9 (*a*) F. G. Bordwell and W. J. Boyle, Jr., *J. Am. Chem. Soc.*, 1972, **94**, 3907; (*b*) A. J. Kresge, *Can. J. Chem.*, 1974, **52**, 1897.
10 N. Kornblum, R. A. Smiley, R. K. Blackwood and D. C. Iffland, *J. Am. Chem. Soc.*, 1955, **77**, 6269.
11 B. L. May, S. D. Kean, C. J. Easton and S. F. Lincoln, *J. Chem. Soc., Perkin Trans. 1*, 1997, 3157.
12 K. Hamasaki, H. Ikeda, A. Nakamura, A. Ueno, F. Toda, I. Suzuki and T. Osa, *J. Am. Chem. Soc.*, 1993, **115**, 5035.
13 (*a*) K. A. Connors and J. M. Lipari, *J. Pharm. Sci.*, 1976, **65**, 379; (*b*) K. A. Connors and T. W. Rosanske, *J. Pharm. Sci.*, 1980, **69**, 173; (*c*) T. Aoyagi, A. Nakamura, H. Ikeda, T. Ikeda, H. Mihara and A. Ueno, *Anal. Chem.*, 1997, **69**, 659.