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β-Cyclodextrin–micelle mixed systems as a reaction medium. Denitrosation of *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide

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ABSTRACT: The kinetics of the acid hydrolysis of *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide (MNTS) were studied in media containing different cationic micellar aggregates (lauryltrimethylammonium bromide, tetradecyltrimethylammonium bromide and cetyltrimethylammonium chloride) and *β*-cyclodextrin (*β*-CD). The results were interpreted in terms of the pseudo-phase model. The model takes into account the formation of both *β*-CD–surfactant and *β*-CD–MNTS complexes. The presence of *β*-CD has no effect on existing micelles but raises the cmc. Complexation of surfactant by *β*-CD makes the cmc dependent on *β*-CD concentration because the cmc is now the sum of the concentrations of free and complexed surfactant when micelles begin to form. At surfactant concentrations above the cmc, competition between the micellization and complexation processes leads to the existence of a significant concentration of free cyclodextrin. Copyright © 2000 John Wiley & Sons, Ltd.

KEYWORDS: cationic micelles; cyclodextrins; acid denitrosation; pseudophase model; *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide

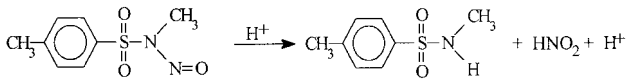
INTRODUCTION

Micellar systems and related association colloids have the ability to alter chemical reactivity.[1] Reaction rates and equilibria in micellar media are affected by solubilization of reactants, changes in local concentrations due to compartmentalization of reaction media and changes in physico-chemical properties of the medium. The influence of micellar systems on chemical reactivity is usually analysed in terms of the pseudo-phase model.[2] In particular, micellar effects upon the reactivity of *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide (MNTS) has been extensively studied.[3]

Cyclodextrins (CDs) are cyclic oligosaccharides consisting of glucose units linked by α-1,4 glucoside bonds.[4] They possess a toroidal or hollow, truncated cone shape with a non-polar, hydrophobic interior and two hydrophilic rims formed by primary (narrower rim) and secondary (wider rim) alcohol groups. CDs form inclusion complexes with molecules that fit into their cavities.[5] Their ability to modulate reactivity depends on their capacity to complex organic substances, i.e. molecules with an appropriate size and shape form inclusion complexes with cyclodextrins. Changes in physico-chemical properties and reactivities result from such host–guest interactions.[6] The effects of inclusion complexes on reactivity vary widely and depend on the guest, the CD and the reaction.

Adding a CD to a micellar system alters its physico-chemical properties because the oligosaccharide complexes surfactant monomers.[7] Complex formation increases the concentration of surfactant required for micellization,[8] so that the critical micelle concentration (cmc) of a micellar system in the presence of a CD is equal to the combined concentrations of surfactant monomers complexed to the CD and free monomer.

In this work, we studied the influence of *β*-CD on the behaviour of aqueous systems containing a cationic surfactant, lauryltrimethylammonium bromide (LTABr), tetradecyltrimethylammonium bromide (TTABr) and cetyltrimethylammonium chloride (CTACl), by determining the kinetics, in these media, of the acid denitrosation of MNTS (Scheme 1).



Scheme 1

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EXPERIMENTAL

All chemicals were of the highest commercially available purity (Aldrich or Sigma) and none required further purification. The low solubility of MNTS in water required the use of acetonitrile as a solvent in a proportion never exceeding 1% (v/v) in the reaction mixture. β-CD solutions were made taking into account that commercial β-CD has an H_2O content of 8 mol mol^{-1}.

The reactions were followed by recording the decrease in absorbance at 250 nm due to the disappearance of MNTS in a Hewlett-Packard model 8453 spectrophotometer with a cell holder thermostated at 25 ± 0.1 °C. The MNTS concentration was always 5×10^{-5} M and $[H^+] = 0.109$ M; under these conditions all the β-CD will be in the neutral form [p$K_a = 12.2$ (Ref. 4]. The experimental procedure has been described in detail elsewhere.[3b]

All kinetic experiments were performed with MNTS concentrations much lower than that of HCl. The absorbance–time data for all kinetic experiments were fitted by first-order integrated equations, and the values of the pseudo-first-order rate constants, k_0, were reproducible to within 3%.

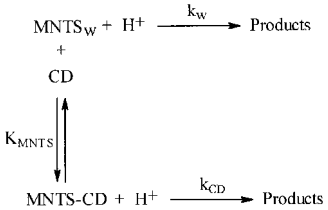
RESULTS AND DISCUSSION

Acid denitrosation of MNTS in the presence of β-CD

Kinetic results in the presence of CDs are often interpreted on the basis of the similarity between the special CD behaviour and enzyme catalysis.[6a] The apolar interior of the β-CD cavity provides a solubilization site for the MNTS, with reversible formation of a 1:1 inclusion complex between β-CD and MNTS[6d] (Scheme 2). From Scheme 2, the variation of k_0 with [CD] is represented by the equation

$$k_0 = \frac{(k_w + k_{CD}K_{MNTS}[CD])[H^+]}{1 + K_{MNTS}[CD]} \qquad (1)$$

where K_{MNTS} is the association constant of MNTS to neutral β-CD, k_w is the rate constant for the acid



Scheme 2

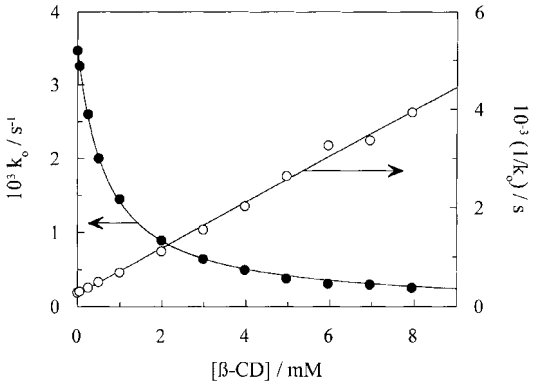


Figure 1. Influence of [β-CD] on k_0, the pseudo-first-order rate constant for acid denitrosation of MNTS. [HCl] = 0.109 M. The curve is the result of fitting Eqn. (2) to the experimental data (●). Reciprocal plot of k_0 as a function of [β-CD] (○); the line represent the fit to Eqn. (3)

hydrolysis of MNTS in aqueous medium and [CD] the concentration of free β-CD.

Because the MNTS concentration is at least 10 times less than that of CD, $[CD_f] \approx [CD_T]$. Figure 1 shows a plot of k_0 and $1/k_0$ as a function of β-CD concentration. The linear dependence of $1/k_0$ on [β-CD] indicates that the percentage of the reaction that goes through the complex is small and is difficult to obtain accurate values for the rate constant for the complex. We assume the absence of reaction between H^+ and the inclusion complex MNTS-CD, $k_{CD} \approx 0$. These considerations imply that Eqn. (1) can be transformed into the following expression:

$$k_0 = \frac{k_w[H^+]}{1 + K_{MNTS}[CD]} \qquad (2)$$

This equation can be linearized as

$$\frac{1}{k_0} = \frac{1}{k_w[H^+]} + \frac{K_{MNTS}[CD]}{k_w[H^+]} \qquad (3)$$

The good fit between Eqn. (2) and the experimental results (Fig. 1) and the agreement between the resulting estimate of $k_w = (3.10 \pm 0.08) \times 10^{-2}$ l mol^{-1} s^{-1} and those obtained in water without β-CD (0.031 l mol^{-1} s^{-1})[3c] corroborate the validity of Scheme 2 and our assumptions and lead us to estimate a value of 1500 ± 50 l mol^{-1} for K_{MNTS}, which will be used in what follows.

Acid denitrosation of MNTS in the presence of β-CD–micelle Mixtures

In the absence of CD, micelles of cationic surfactants inhibit the acid hydrolysis of MNTS.[3c] In this work, the influence of alkyltrimethylammonium halides (LTABr, TTABr and CTACl) concentrations on k_0 in the presence

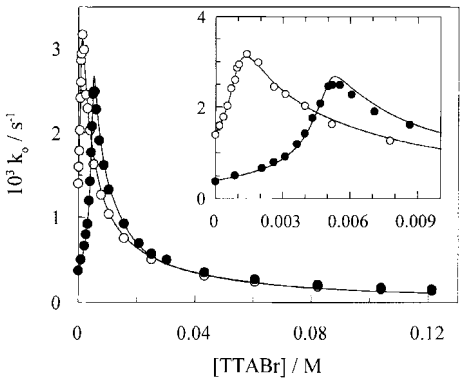


Figure 2. Influence of [TTABr] on k_0, the pseudo-first-order rate constant for acid denitrosation of MNTS, in the presence of β-CD concentrations of (○) 1.00×10^{-3} and (●) 4.97×10^{-3} M. Curves are the results of fitting Eqn. (7) to the experimental data as described in the text

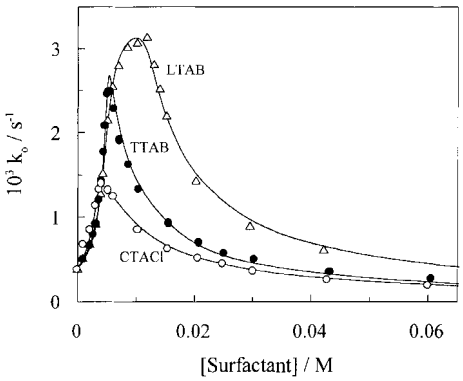
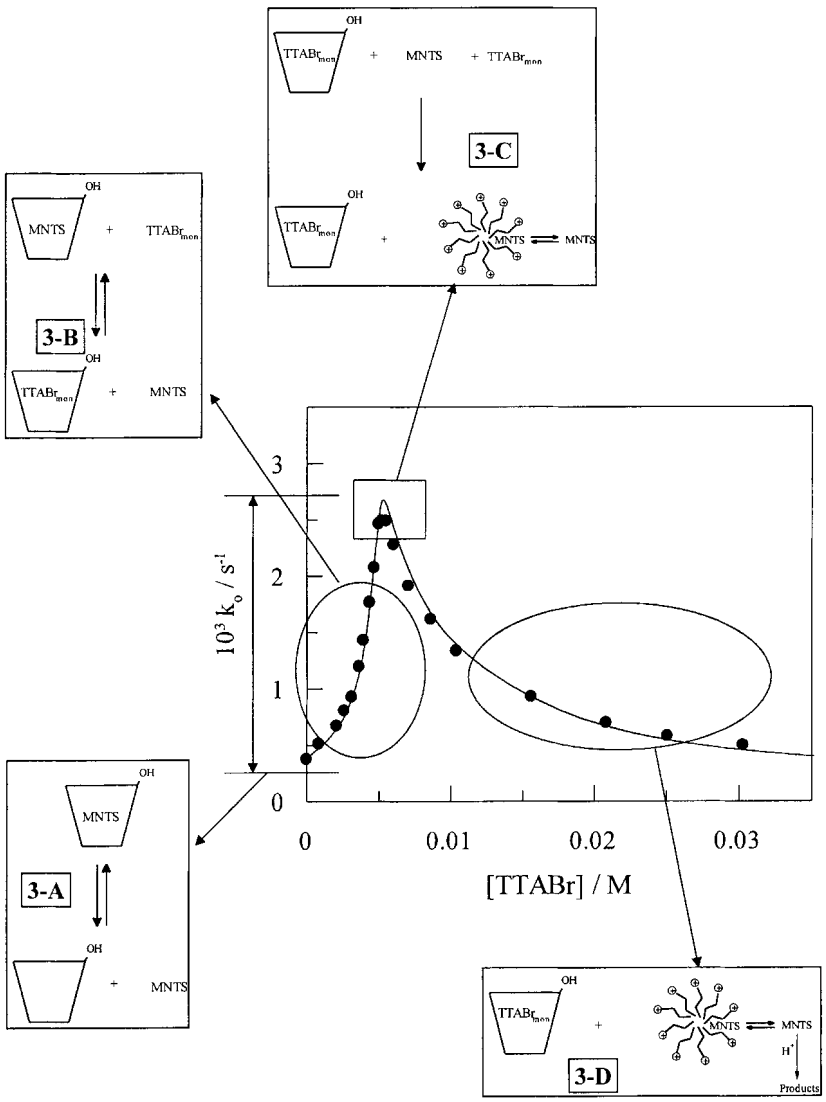
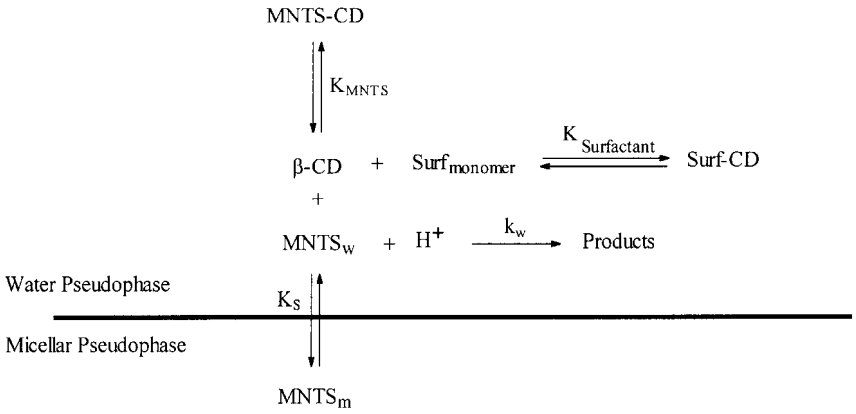


Figure 3. Influence of [surfactant] on k_0, the pseudo-first-order rate constant for acid denitrosation of MNTS, in the presence of [β-CD] = 4.97×10^{-3} M: (△) LTABr; (●) TTABr; (○) CTACl. Curves are the results of fitting Eqn. (7) to the experimental data as described in the text



Scheme 3



Scheme 4

of β-CD was determined by varying the surfactant concentration between pre-micellization and post-micellization values in series of experiments at constant β-CD concentration. In each series (Fig. 2 shows the results of two of them), k_0 increases with surfactant concentration up to a maximum and then drops as it does in the absence of β-CD.[3c] An increase in β-CD concentration decreases the peak value of k_0 and increases the surfactant concentration at which it occurs.

Figure 3 shows the influence of surfactant (LTABr, TTABr, CTACl) concentration on k_0 for the acid hydrolysis of MNTS in the presence of $[CD] = 4.97 \times 10^{-3}$ M. Decreasing the chain length of the surfactant increases the maximum in k_0 vs [surfactant] profile and the surfactant concentration required to reach the maximum.

The experimental behaviour can be explained qualitatively by considering the different competing complexation/micellization processes. The value of k_0 extrapolated to zero surfactant concentration is significantly lower than that observed in pure water, [Scheme 3(A)], because of the formation of MNTS–β-CD host–guest complexes which decrease the free MNTS concentration in the aqueous phase. Hence the k_0 values for each CD concentration correspond to the values obtained in the previous section for experiments in the absence of surfactant.

At surfactant concentrations below the cmc, alkyltrimethylammonium halide addition to the reaction medium produces complexation of surfactant monomers with β-CD, with displacement of MNTS to the aqueous medium [Scheme 3(B)]. Increasing the concentration of free MNTS increases k_0 until the concentration of uncomplexed surfactant is high enough for micelles to form. Once micellization starts, the typical inhibitory effect of cationic micelles on acid hydrolysis of hydrophobic substrates is observed.[3c]

In view of the behaviour of surfactants in the absence of other additives, it may be assumed that surfactant's monomer concentration remains constant when the total surfactant concentration is increased beyond the point at which micelles begin to form.[2] In micelle + β-CD mixed systems, both the free β-CD and the free monomer concentration are assumed to remain constant after micellization. This assumption is reasonable because the surfactant monomer concentration above the cmc is essentially constant and therefore the concentration of surfactant–β-CD complex is constant.[9] The addition of a

Table 1. Results of fitting Eqn. (3) to the experimental data for the acid denitrosation of MNTS in βCD–cationic surfactant mixed systems

Surfactant[a]	[CD] (M)	cmc_{app} (M)	$[CD]_{free}$ (M)	cmc_{real} (M)	K_s/l mol^{-1}	k_w/l mol^{-1} s^{-1}	$K_{Surfactant}$/l mol^{-1}
LTABr	0[b]	—	—	0.010	132	3.10×10^{-2}	—
	1.00×10^{-3}	8.00×10^{-3}	6.30×10^{-6}	7.01×10^{-3}	146 ± 5	$(3.08 \pm 0.03) \times 10^{-2}$	(22500 ± 2500)
	4.97×10^{-3}	1.14×10^{-2}	3.39×10^{-5}	6.46×10^{-3}	134 ± 6	$(3.06 \pm 0.02) \times 10^{-2}$	(22500 ± 2500)
TTABr	0[b]	—	—	1.00×10^{-3}	270	3.10×10^{-2}	—
	1.00×10^{-3}	1.40×10^{-3}	2.65×10^{-5}	4.27×10^{-4}	251 ± 7	$(2.96 \pm 0.04) \times 10^{-2}$	(80000 ± 5000)
	4.97×10^{-3}	5.28×10^{-3}	1.31×10^{-4}	4.41×10^{-4}	260 ± 14	$(3.09 \pm 0.02) \times 10^{-2}$	(80000 ± 5000)
CTACl	0[b]	—	—	4.00×10^{-4}	310	3.10×10^{-2}	—
	1.00×10^{-3}	9.25×10^{-4}	1.23×10^{-4}	4.80×10^{-5}	303 ± 18	$(3.46 \pm 0.06) \times 10^{-2}$	(175000 ± 10000)
	4.97×10^{-3}	4.00×10^{-3}	9.84×10^{-4}	4.40×10^{-5}	290 ± 50	$(3.12 \pm 0.05) \times 10^{-2}$	(175000 ± 10000)

[a] $K_{MNTS} = 1500 \pm 50$ l mol^{-1}
[b] Taken from Ref.[3c].

third component (MNTS) to the β-CD–micelle mixed systems requires accounting for its complexation equilibria with β-CD and micelles. When micelles form, MNTS also associates with them. Simple electrostatic considerations require that the H^+ concentration be much lower at the micellar surface than in bulk water. The effect of MNTS association with the micelles produces a decrease in the concentration of MNTS in the aqueous phase and slows the reaction [Scheme 3(C)].

Above the micellization point, the variation in k_0 is primarily caused by increasing association of MNTS with micelles [see Scheme 3(D)]. We equate the surfactant concentration at which k_o peaks as the point at which micellization begins and define its value of surfactant concentration as the β-CD-dependent critical micellization concentration, cmc_{app}. Note that, above the micellization point, just as the conventional cmc of a surfactant solution with no other additives satisfies the equation $[surfactant]_t = [D_n] + cmc$, where $[D_n]$ is the micellized surfactant concentration, so cmc_{app} must satisfy the equation $[surfactant]_t = [D_n] + cmc_{app}$; this follows from the fact that at the micellization point $cmc_{app} = [surfactant–\beta\text{-CD}] + [surfactant_{monomer}]$ and that $[surfactant–\beta\text{-CD}]$ and $[surfactant_{monomer}]$ are constant when the surfactant concentration is varied above the micellization point (when $[surfactant_{monomer}] = cmc_{real}$).

The above behaviour may be explained on the basis of the pseudo-phase model shown in Scheme 4, in which distribution of the reagents in the two pseudo-phases is considered. The global reaction rate is assumed to be exclusively the reaction at the aqueous pseudo-phase due to electrostatic considerations.

According to Scheme 4, the total β-CD concentration can be expressed as

$$[CD_T] = \lfloor CD_f \rfloor + [MNTS - CD] + [surfactant - CD] \quad (4)$$

and the total surfactant concentration can be expressed as the free monomers, surfactant–β-CD complex and micellized surfactant:

$$[surfactant_T] = [surfactant_{monomer}] + [surfactant - CD] + [D_n] \quad (5)$$

In this way the total MNTS concentration will be given by the sum of MNTS concentration in the aqueous pseudo-phase, MNTS–β-CD complex concentration and MNTS concentration in the micellar pseudo-phase:

$$[MNTS_T] = [MNTS_w] + [MNTS - CD] + [MNTS_m] \quad (6)$$

Scheme 4 allows us to obtain the following equation for the pseudo-first-order rate constant as a function of the free β-CD and micellized surfactant concentration ($[D_n]$):

$$k_o = \frac{k_w[H^+]}{1 + K_{MNTS}[CD_f] + K_S[D_n]} \quad (7)$$

The free β-CD concentration can be obtained as a function of total β-CD concentration, total surfactant concentration and total MNTS concentration, from the following third-order equation:

$$a[CD_f]^3 + b[CD_f]^2 + c[CD_f] = [CD_T] \quad (8)$$

where

$$a = K_{surfactant}K_{MNTS} \quad (9)$$

$$b = \{K_{surfactant} + K_{MNTS} + K_{MNTS}K_{surfactant}([surfactant_T] - [CD_T] + [MNTS_T])\} \quad (10)$$

$$c = \{1 + K_{surfactant}([surfactant_T] - [CD_T]) + K_{MNTS}([MNTS_T] - [CD_T])\} \quad (11)$$

for $K_{surfactant}$ (binding constant of surfactant monomer to β-CD), K_s (binding constant of MNTS to micelles) and K_{MNTS} (binding constant of MNTS to β-CD) the conventional definitions were used.[6d]

The validity of Scheme 4 was tested by fitting Eqn. (7) to the experimental k_o–[surfactant] profile by means of a two-tier optimization process in which the optimized variables were $K_{surfactant}$, k_w and K_S (comparison between optimized values of k_w of K_S with published values[3c] served as a test of the quality of the fit); for K_{MNTS}, the value obtained in the previous section was used. For each of a number of systematically varied $K_{surfactant}$ ($K_{surfactant}$ was stepped by 500 l mol^{-1}), values, Eqn. (8) was solved for [surfactant] between 0 and cmc_{app}, and the resulting values of $[CD_f]$ were used to fit Eqn. (7) to the experimental data by standard optimization of k_w and K_s {In all cases, Eqn. (8) had exactly one real root, which as required lay between 0 and [CD]}. The value of $K_{surfactant}$ for which optimization of k_w and K_s afforded the least root-mean-square deviation from the experimental data was taken as optimal. The results are listed in Table 1 and shown as curves in Figs 2 and 3.

The rate constant at the maximum in the k_o vs [surfactant] curves (Fig. 2) decreases with increasing [CD]. The dependence of the maximum k_o values on [CD] is attributed to the fact that as the total β-CD concentration in the medium increases, so does that of free β-CD and hence its inhibitory effect on the reaction rate. The observed increase in the maximum value of the k_o vs [surfactant] curves (Fig. 3) at a constant [CD] with decrease in the chain length of the surfactant is then attributed to a decrease in the concentration of free β-CD.

The optimized values of k_w and K_s are essentially independent of [CD] and agree satisfactorily with the values obtained in the absence of CD, respectively.[3c] This supports the model and, in particular, the assumption that the properties of the micelles themselves are not affected by the presence of β-CD in the medium. The model is further supported by the finding that for all β-CD concentrations the optimized value of $K_{surfactant}$ for each alkyltrimethylammonium halide was the same.

CONCLUSIONS

Investigation of the kinetics of the acid denitrosation of MNTS in aqueous mixtures of β-CD and surfactants has shed light on the influence of β-CD on the behaviour of the surfactant. β-CD has no effect on the properties of surfactant micelles once these have formed (in particular, it does not alter K_S). The increase in cmc_{app} with increase in [CD] is due to complexation of the surfactant by β-CD, which reduces the concentration of surfactant that is free to form micelles. At total surfactant concentrations higher than the cmc_{app}, competition between the micellization and complexation processes results in the presence of an appreciable concentration of uncomplexed β-CD, which is the same for all total surfactant concentrations above cmc_{app}. The difference between cmc_{app} and total β-CD concentration does not show the monomer concentration present in the medium (cmc_{real}). In fact, evidence has been presented in the literature about cmc_{app} values lower than the total CD concentration.[10] The results in Table 1 show that free monomer concentration in equilibrium (cmc_{real}) depends on β-CD, in agreement with recent results[11] that indicate that the presence of CD induces surfactant aggregation below the cmc.

We must underline the differences in the properties of the CD cavity in acidic medium (neutral β-CD) and basic medium (ionized β-CD^-). In comparison with the results obtained for the basic hydrolysis of MNTS and NPA (nitrophenyl acetate) in CD–surfactant mixed systems,[6d,9] the binding constant of both MNTS and surfactant monomer complexes with neutral β-CD are shown to be higher than those formed with ionized β-CD^-, 4.0 times for MNTS binding constant and 2.5 times for TTABr binding constant. This is in agreement with recent results that indicate the different association behaviour between neutral and ionized β-CD.[6c]

Acknowledgements

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