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Characterization of Alkane Diol-CD Complexes. Acid Denitrosation of *N*-Methyl-*N*-Nitroso-*p*-Toluenesulphonamide as a Chemical Probe

CELIA CABALEIRO-LAGO[1], LUIS GARCÍA-RÍO[2], PABLO HERVÉS[1], JUAN C. MEJUTO[1] and JORGE PÉREZ-JUSTE[1,*]
[1]*Departamento de Química Física, Universidad de Vigo, 36200 Vigo, Spain;* [2]*Departamento de Química Física, Universidad de Santiago de Compostela, 15706 Santiago de Compostela, Spain*

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Abstract

A study was carried out on the acid denitrosation of *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide (MNTS) in mixed systems made up of linear (geminal and terminal) alkyl diols and β-cyclodextrin (CD). The alkyl diols used allowed us to vary the length of the hydrocarbon chain from 2 to 6 carbon atoms. The observed rate constant, k_{obs}, decreases in the presence of CD. The inhibition profile decreases as the as the number of carbons in the chain is increased. This behaviour can be interpreted as a consequence of a balance between the complexation processes of MNTS and the alkyl diols by the CD. At a constant CD concentration and increase in the diols concentration decreases the concentration of free cyclodextrin available to complex with MNTS molecules and therefore produces an increases in the observed rate constant. The results were interpreted in terms of two different models; trough the presupposition and non-presupposition of a stoichiometry for the CD-diols complex. Both models agreed quite well and allow us to determine the uncomplexed cyclodextrin concentration in each case as well as the stoichiometry of the complexes. The binding constant for both types of alkane diols increase with increasing the number of carbon in the chain. Besides, the binding constant of the α,ω-alkane diols is higher than for the analog α,β-alkane diols. One of the main consequences of this study is that the acid denitrosation of MNTS can be use to obtain the stochiometry of the CD-diol complexes and to monitor the free cyclodextrin concentration.

Introduction

Cyclodextrins are macrocyclic carbohydrates built up from D(+)-glycopyranose units linked together via α-(1–4) bonds [1]. The most studied cyclodextrins are α-, β- and γ-cyclodextrins, which consist in six, seven and eight glucose units, respectively. The most important feature of cyclodextrins is their cavity, because this enables them to form inclusion complexes with a great variety of substrates [2–5]. The ability of cyclodextrins to form inclusion complexes in aqueous solution results from the polarity of the cavity – some studies have suggested a similarity to dioxane while others favor ethanol- [1, 3], but the principal factors seem to be the hydrophobicity of the guest and the appropriateness of its size and shape in relation to that of the cyclodextrin cavity. Cyclodextrin complexes have found applications in different fields, e.g., food technology, pharmaceuticals, cosmetics, catalysis, chiral separations, etc., [1, 6, 7].

Several classes of compounds, that can form inclusion complexes with natural cyclodextrin, has been subjected to systematic studies. These cover almost every class of compounds such aliphatic alcohols [8–14], amines and acids [12, 15], aminoacids [16–19], ketones [20, 21], surfactants [22–31] and other compounds [4]. An especial attention has been given to the impact of a third component on the formation of host-guest complexes of cyclodextrins. The addition of a third component to the reaction medium usually provokes a decrease in the stability of the host-guest complex, due to their complexation competition for the host cavity [14, 25–31]. In other systems the third component forms a ternary complex with an stoichiometry 1:1:1 (substrate:cyclodextrin:third component), even more reactive than the binary complex [13, 32–34].

Our research group have developed a kinetic model to study the effect of surfactants on the substrate-cyclodextrin complexation process [25–31]. The results obtained in these studies allowed us to confirm the existence of an appreciable concentration of uncomplexed or free CD in equilibrium with the micellar system. Contrary to expectations, the percentage of free CD increases along with the length of the hydrocarbon chain of the surfactant [29, 30]. Now we have decided to extent our studies to alkane diols as a third component.

* Author for correspondence. E-mail: juste@uvigo.es

In this article, we study the influence of different alkane diols, both geminal and terminal, (varying its number of carbons in the chain) upon the influence of cyclodextrin on the acid denitrosation of *N*-methyl-*N*-nitroso-*p*-toluenesulphonamide (MNTS). The mechanism of this reaction in water is well known [35], the slow step is the proton transfer from the medium to the substrate (see Scheme 1). This reaction has been studied previously in our group in the presence of micelles [36], vesicles [37] and cyclodextrin-micelle mixed systems [25, 28]. The kinetic model proposed will allow us to obtain the binding constant of the different alkane diols to *β*-cyclodextrins, as well as the concentration of free cyclodextrin through the complexation process. The main implications of this result is we can propose the acid denitrosation of MNTS as a chemical probe for determining the concentration of free cyclodextrin in presence of different third components.

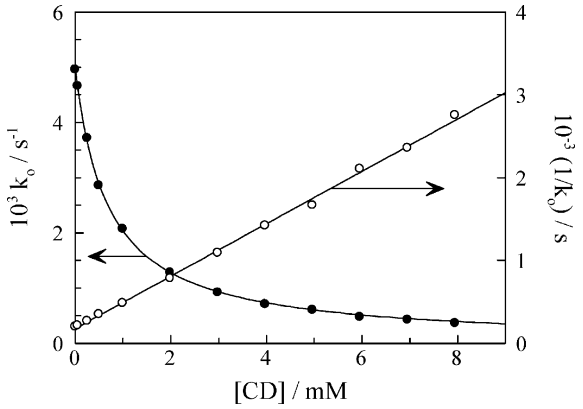
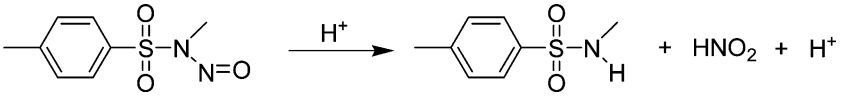


Figure 1. Influence of [CD] on the pseudo-first order rate constant and its inverse for the acid denitrosation of MNTS. The lines represent the best fit of Equation. 1 and 2 respectively, to the experimental data $[H^+] = 0.16$ M, $T = 25$ °C.



Experimental

The alcohols, *N*-methyl-*N*-nitroso-*p*-toluenesulphonamide and *β*-cyclodextrin were supplied by Sigma-Aldrich in the highest available purity and used without further purification. Owing to the low solubility of MNTS in water, its stocks solution were prepared in acetonitrile. The percentage of acetonitrile in the reaction mixtures was always lower than 0.35%. Cyclodextrin solutions were made taking into account that commercial *β*-cyclodextrin has a H_2O content of 8 mol/mol.

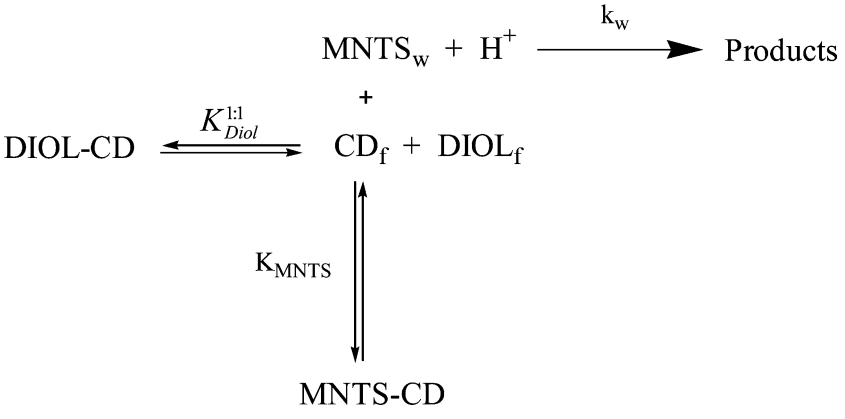
The reaction kinetics were monitored by measuring the disappearance of MNTS at 250 nm, using a HP 8453 spectrophotometer with a cell holder thermostatted at (25.0 ± 0.1) °C. The MNTS concentration was always 1×10^{-5} M and $[H^+] = 0.16$ M; under these conditions all the cyclodextrin will be in the neutral form ($pK_a = 12.2$) [1]. The pseudo-first-order rate constant (k_{obs}) were obtained by the integration method. All the values of k_{obs} were reproducible to within 3%.

Results

Acid denitrosation of MNTS in aqueous medium containing β-Cyclodextrin

The influence of the cyclodextrin concentration on the acid denitrosation of MNTS has been studied and compared with previously results to ensure good consistency in the evaluations of the experimental results. The rate limiting step of the acid denitrosation of MNTS, leading to the formation of *N*-methyl sulphonamide and nitrous acid, is the protonation of the sulphonamide [35]. This acid denitrosation is inhibited by the presence of cyclodextrin.

The rate law for the acid denitrosation of MNTS is $v = k_w [H^+][MNTS]$, and in an aqueous medium, $k_w = [(3.1 \pm 0.1) \times 10^{-2}\ M^{-1}\ s^{-1}]$ [36]. In the presence of *β*-cyclodextrin, the apolar inner cavity of the CD provides a solubilization site for the MNTS with a reversible formation of a non-reactive 1:1 inclusion complex [25], as shown in Scheme 2 and Equation 1. The analysis



of the dependence of k_{obs} with the concentration of cyclodextrin (see Figure 1) gives a value for the association constant of MNTS to the cyclodextrin of $K_{MNTS} = 1500 \pm 50\ M^{-1}$.

$$k_{obs} = \frac{k_w[H^+]}{(1 + K_{MNTS}[CD]_{free})} \quad (1)$$

being $[CD]_{free}$ the concentration of free-cyclodextrin. Because the concentration of MNTS is at less 10 times less than that of CD, we assume that $[CD]_{free} \approx [CD]_{total}$ The supposition of an unreactive 1:1 complex can be demonstrated by the linear dependence of $1/k_{obs}$ on the CD concentration (Equation 2, see Figure 1).

$$\frac{1}{k_{obs}} = \frac{1}{k_w[H^+]}(1 + K_{MNTS}[CD]) \quad (2)$$

Denitrosation of MNTS in α,β-alkane diol/CD mixed systems

The addition of water soluble diols, as a third component, to the reaction medium produces a complexation competition with MNTS for the cyclodextrin cavity. Therefore the stability of the MNTS:CD complex is decreased, allowing us to determine the binding constant of the different diols to the cyclodextrins.

The influence of different linear α,β-alkane diols, ranging from to 2 to 6 carbons in the alkyl chain, in the presence of β-cyclodextrin was determined by varying the cyclodextrin concentration between 0 and 0.01 M in series of experiments in which the alcohol concentration was kept constant. The alcohol concentration was chosen taking into account the solubility of the alcohol in water. In each series (Figure 2 shows the results for six concentrations of 1,2−hexanediol), k_{obs} decreases with increasing the concentration of CD. Increasing the alcohol concentration decreases the inhibition effect of the cyclodextrin. Furthermore, an increase in the diol concentration decreases the value of k_w, due to a lower polarity of the medium [38]. The value of the bimolecular rate constant, k_w, has been calculated for each diol concentration through a k_{obs} vs. $[H^+]$ representation (data not shown). In order to consider any change in the properties of the medium (such this decrease in the dielectric constant) that alters the bimolecular rate constant, k_w, of the reaction, the ratio k_{obs}/k_w vs. [CD] has been represented (Figure 2).

The substrate complexation in surfactant-CD mixed systems seems to depend strongly upon substrate size [39]. The MNTS size makes likely its accommodation inside the CD cavity (see Scheme 2). We have previously shown that an increase in the carbon chain length of surfactants produces a decrease on the MNTS complexation processes [25, 28]. In a similar way, the α,β-alkane diols will also show an effect on this complexation.

According to these ideas the experimental behavior observed can be explained qualitatively considering the different complexation processes. The addition of a constant concentration of diol to the reaction medium produces complexation of diol molecules with CD (CD-DIOL), with displacement of MNTS to the aqueous medium, thereby increasing the concentration of reactive MNTS, $MNTS_w$. An increase in the concentration of diol present in each series will produce a greater complexation with CD and therefore more MNTS molecules will be displaced to the reaction medium, giving to a decrease in the inhibition effect caused by an increase in the CD concentration (see Figure 2). The presence of diols does not affect the non-reactivity of the 1:1 complex, as can be deduced by the linear dependence of $1/k_{obs}$ on CD concentration (see Figure 3).

Figure 4 shows the effect of CD concentration on the rate constant k_{obs}/k_w, for the acid denitrosation of MNTS in the absence of diol and in the presence of 0.2 M of 1,2-propanediol, 1,2-butanediol, 1,2-pentanediol and 1,2-hexanediol. The inhibition effect produced by the cyclodextrin in the presence of 1,2-hexanediol, with six carbons in the chain, is lower than the others because a

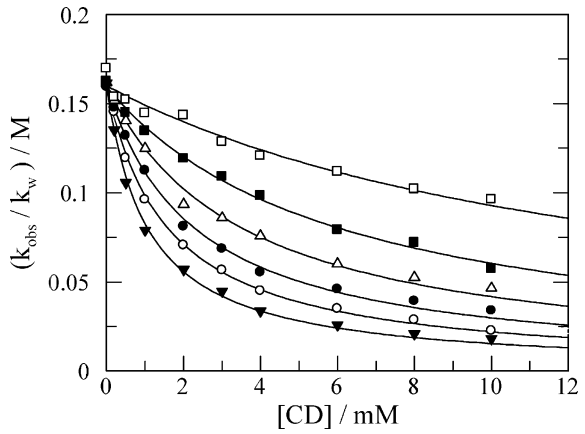


Figure 2. Influence of [CD] on the pseudo-first order rate constant for the acid denitrosation of MNTS in the presence of different 1,2-hexanediol concentrations; (▼) 0.020 M; (○) 0.042 M; (●) 0.081 M; (Δ) 0.13 M; (■) 0.24 M and (□) 0.54 M. [HCl] = 0.16 M, T = 25°C.

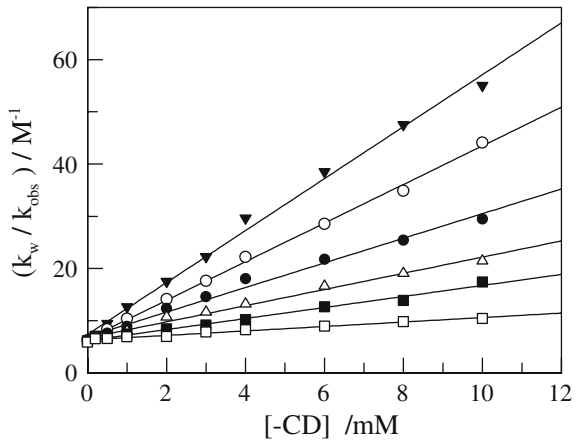


Figure 3. Influence of [CD] on the ratio k_w/k_{obs} for the acid denitrosation of MNTS in the presence of different 1,2-hexanediol concentrations; (▼) 0.020 M; (○) 0.042 M; (●) 0.081 M; (Δ) 0.13 M; (■) 0.24 M and (□) 0.54 M. [HCl] = 0.16 M, T = 25°C.

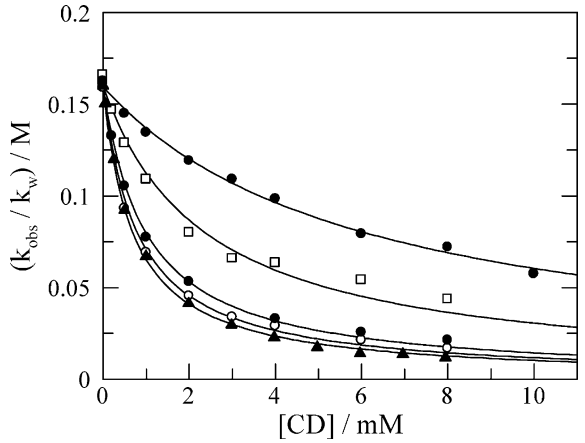


Figure 4. Influence of [CD] on the pseudo-first order rate constant for the acid denitrosation of MNTS in the absence (▲) and the presence of a constant 0.2 M alcohol concentration; (○) 1,2-propanediol; (●)1,2-butanediol; (□)1,2-pentanediol and (■)1,2-hexanediol. [HCl] = 0.16 M, T = 25°C.

higher binding constant of the diol to the cyclodextrin. This is due to hydrophobic and steric effects.

Assuming that the different complexation processes will be govern mainly by hydrophobic and size effects, in the case of the cyclodextrin-micellar surfactant mixed systems and increase in the length of the carbon tail lead to a increase in the association constant of the CD-surfactant complex [28, 30] and also to a change in the stoichiometry of the complex [30]. In our case, at similar concentration, an increase in the number of carbons in the chain of the α,β-alkane diol means a higher value of the association constant between the diol and the β-cyclodextrin. This increase in the association constant of the diol produce a lower inhibition effect as the CD concentration is increased.

Denitrosation of MNTS in α,ω-alkane diol/CD mixed systems

In the case of terminal diols a similar study has been carried out. The influence of CD in the presence of a constant concentration of the α,ω-alkane diol (from 2 to 6 carbons between the two alcohol groups) upon the acid hydrolysis of MNTS was studied. The effect observed is similar to that obtained for the geminal alcohol. As before, an increase in the alcohol concentration produces a greater complexation with cyclodextrins and then a decrease in the inhibition effect of the cyclodextrin (see Supplementary Material). Increasing the carbon tail between the alcohol groups give us, at a constant alcohol concentration, to a decrease in the inhibiton effect of the cyclodextrin due the increase of the association constant of the diol (see Supplementary Material).

Discussion

The above behavior may be explained on the basis of the model shown on Scheme 2, in which the complexation of both, the substrate and the diol, with the CD is taken into account. With these considerations the global reaction rate can be expressed by Equation 1.

For the application of Equation 1 it is necessary *to determine the concentration of uncomplexed CD* (CD_{free}) for each diol concentration. To obtain this and considering the proposed model two methods can be developed; a) Presupposing a stoichiometry for the CD-Diol complex and b) not presupposing any stochiometry for the CD-Diol complex.

Method A: Presupposition of a complex stoichiometry

As in previous studies carried our in our laboratory in presence of micellar surfactant as a third component [25–31]. the concentration of free CD can be obtained by means of simulation, supposing that the complex formed between the diol molecules and the CD present a stoichiometry ratio of 1:1, as well as for the CD-MNTS complex.

The complexation constants for binding of the substrate by CD, K_{MNTS}, and diol molecules by CD, $K^{1:1}_{Diol}$, are expressed as

$$K_{MNTS} = \frac{[MNTS - CD]}{[MNTS]_w [CD]_{free}} \tag{3}$$

$$K^{1:1}_{Diol} = \frac{[CD - DIOL]}{[DIOL]_{free} [CD]_{free}} \tag{4}$$

The mass balances for the total concentrations of cyclodextrin, diol and substrate

$$[CD]_{Total} = [CD]_{free} + [DIOL - CD] + [MNTS - CD] \tag{5}$$

$$[DIOL]_{Total} = [DIOL]_{free} + [DIOL - CD] \tag{6}$$

$$[MNTS]_{Total} = [MNTS]_w + [MNTS - CD] \tag{7}$$

are combined with binding constant to give a third order equation for the concentration of free cyclodextrin.

$$A[CD_L]^3_{free} + B[CD]^2_{free} + C[CD]_{free} - [CD]_{Total} = 0 \tag{8}$$

where

$$A = K^{1:1}_{Diol} K_{MNTS} \tag{9}$$

$$B = K^{1:1}_{Diol} + K_{MNTS} + K^{1:1}_{Diol} K_{MNTS} \left([DIOL]_{Total} + [MNTS]_{Total} - [CD]_{Total} \right) \tag{10}$$

$$C = \left\{ 1 + K^{1:1}_{Diol} \left([DIOL_{Total} - [CD]_{Total} \right) + K_{MNTS} \left([MNTS]_{Total} - [CD_{Total}) \right) \right\} \tag{11}$$

The validity of the proposed model was tested by fitting the Equation 1 to the experimental results by

Table 1. Binding constants of CD-Diol complexes determined using *Method* A and B, see text for details

Diol	Method A		Method B
	K_{MNTS}/M^{-1}	$K^{1:1}_{Diol}/M^{-1,a}$	$K^{1:1}_{Diol}/M^{-1}$
α,β-alkane diols			
Etilenglicol	1623 ± 27	0.25 ± 0.05	0.30 ± 0.09
1,2-propanediol	1550 ± 39	1.00 ± 0.05	0.99 ± 0.18
1,2-butanediol	1616 ± 43	3.60 ± 0.05	3.29 ± 0.61
1,2-pentanediol	1629 ± 68	11.50 ± 0.5	10.77 ± 2.50
1,2-hexanediol	1590 ± 80	33.0 ± 2.0	33.18 ± 4.86
α,ω-alkane diols			
Etilenglicol	1623 ± 27	0.25 ± 0.05	0.30 ± 0.09
1,3-propanediol	1669 ± 15	1.75 ± 0.05	1.78 ± 0.30
1,4-butanediol	1524 ± 75	3.80 ± 0.05	3.85 ± 0.67
1,5-pentanediol	1570 ± 29	16.5 ± 0.5	16.61 ± 1.08
1,6-hexanediol	1590 ± 110	50.0 ± 2.0	48.37 ± 6.42

[a]The error denotes the systematic variation in $K^{1:1}_{Diol}$ during the fitting, see text for details.

means of an optimization process in which the optimized parameters were $K^{1:1}_{Diol}$ and K_{MNTS}; for K_{MNTS} the value obtained in the previous section in the absence of alcohol was used. The association constant $K^{1:1}_{Diol}$ was systematically varied (the stepped range was varied depending of the diol, see Table 1). For each $K^{1:1}_{Diol}$ value, Equation 8 was solved for all the cyclodextrin and diol concentrations, and the resulting value of $[CD]_{free}$ were used to fit Equation 1 to the experimental data by standard optimization of K_{MNTS}. The value of $K^{1:1}_{Diol}$ for which optimization of K_{MNTS} afforded the least root-mean-square deviation from the experimental data was taken as optimal. The results for the α,β and α,ω-alkane diols are listed in Table 1. The obtained optimized values for K_{MNTS} agree, within the error, with the value obtained in the absence of diols, showing the validity of the fitting process.

Considering each [CD] and [diol] pair of values and solving Equation 8 the value of $[CD]_{free}$ for each k_{obs} can be obtained. In such a way, the pair of values k_{obs} vs. $[CD]_{free}$ (see Figure 5) eliminate the effect due to the diol, i. e. the third component effect on the acid hydrolysis of MNTS in the presence of CDs. The Figure 5 shows the best fit of Equation 1 to all alcohol and cyclodextrin concentrations for the 1,5-pentanediol. The validity of the proposed method can be checked if we compare the values of free cyclodextrin and k_{obs} for each alcohol concentration with the values in the absence of alcohol. Figure 5 shows the concordance of the method for 1,5-pentanediol. Similar representations can be obtained for the other diols studied in this work (see supplementary material).

If the effect of a third component on the acid hydrolysis of MNTS in the presence of CD can be eliminated, it can be concluded that this reaction can be employed as a chemical probe to obtained the value of $[CD]_{free}$ in equilibrium with any other substrate acting as a third component.

Method B: Non Presupposition of a complex stoichiometry

As opposed to method A, this method of calculating free cyclodextrin, $[CD]_{free}$, has the advantage of not presupposing any stoichiometry for the CD-diol complex. The experimental values of k_{obs} obtained from the study of the influence of the CD concentration in the acid denitrosation of MNTS in the absence of diols, leads to an inhibition profile (Equation 1). Equation 1 can be rearranged (Equation 12) to obtain the values of free cyclodextrin from the experiments carried out in the presence of diols through the used of k_w and K_{MNTS} determined previously, without use $K^{1:1}_{Diol}$.

$$[CD]_{free} = \left(\frac{k_w[H^+]}{k_{obs}} - 1\right)\frac{1}{K_{MNTS}} \qquad (12)$$

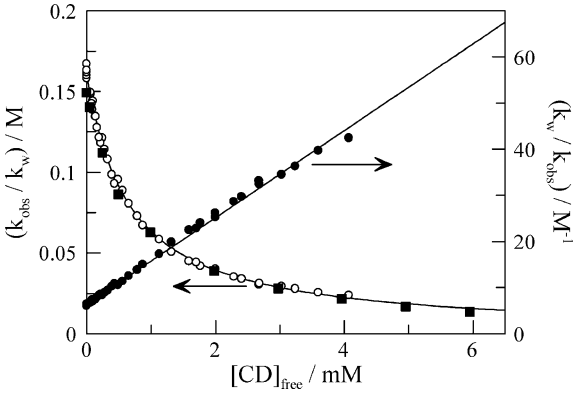


Figure 5. Variation of the k_{obs}/k_w ratio with the concentration of free cyclodextrin obtained from Equation 8 in the presence of 1,5-pentanediol, $K^{1:1}_{Diol}$ = 16.5 M^{-1}, [HCl]= 0.16 M. The curve represent the fit of Equation 1 to the experimental data (○), the closed squares (■) corresponds to reaction in the absence of alcohol. Reciprocal plot of k_{obs} as a function of the free cyclodextrin (●); the line represents the fit to Equation 2.

Table 2. Concentration of free cyclodextrin and binding constant of 1,6-hexanediol to CD for the different alcohol and CD concentrations, see text for details[a]

$[CD]_{Total}$/mM	[DIOL]/M	$[CD]_{free}$/mM	$K^{1:1}_{Diol}/M^{-1}$	$[CD]_{Total}$/mM	[DIOL]/M	$[CD]_{free}$/mM	$K^{1:1}_{Diol}/M^{-1}$
0.2	0.041	0.07	48.96	0.2	0.150	–	–
0.5	0.041	0.15	58.14	0.5	0.150	0.06	50.82
1	0.041	0.35	45.91	1	0.150	0.14	42.15
2	0.041	0.69	48.37	2	0.150	0.26	45.38
4	0.041	1.29	54.84	4	0.150	0.53	44.98
6	0.041	1.89	59.04	6	0.150	0.77	46.86
8	0.041	2.49	62.47	8	0.150	0.99	49.66
0.2	0.055	–	–	0.2	0.246	0.01	55.71
0.5	0.055	0.14	45.23	0.5	0.246	0.05	37.70
1	0.055	0.31	41.88	1	0.246	0.09	39.77
2	0.055	0.61	42.33	2	0.246	0.18	42.29
4	0.055	1.10	50.92	4	0.246	0.34	44.00
6	0.054	1.54	57.09	6	0.246	0.52	44.22
8	0.055	2.05	59.25	8	0.246	0.67	46.08
0.2	0.082	0.05	41.46	$\overline{K^{1:1}_{Diol}}$ =48.37 ± 6.42			
0.5	0.082	0.11	43.74				
1	0.082	0.19	52.37				
2	0.082	0.41	48.39				
4	0.082	0.82	49.29				
6	0.082	1.19	52.54				
8	0.082	1.50	57.59				

[a]The point with low and high cyclodextrin concentration presented, as expected, a higher experimental error determining the concentration of free cyclodextrin.

considering that we are under pseudo-first order conditions ($[MNTS] \approx 1 \times 10^{-5}$ M) the concentration of cyclodextrin complexed with the MNTS can be neglected. Proposing now the formation of a 1:1 complex between the diol and the CD, the mass balance for the total concentration of CD and diol can be rewritten as

$$[CD]_{Total} = [CD]_{free} + [CD - DIOL] \quad (13)$$

$$[DIOL]_{Total} = [DIOL]_{free} + [CD - DIOL] \quad (14)$$

and the binding constant of diol molecules to CD, Equation 4, can be rewritten as:

$$K^{1:1}_{Diol} = \frac{[CD]_{Total} - [CD]_{free}}{[CD]_{free}\left([DIOL]_{Total} - \left([CD]_{Total} - [CD]_{free}\right)\right)} \quad (15)$$

the unknown value of $[CD]_{free}$ can be obtained through Equation 12, in such a way that the association constant of diol to CD can be calculated punctually for each point. It is interesting to point out the best conditions where this method will reflects the better results; since at low diol concentration the difference between $[CD]_{total}$ and $[CD]_{free}$ will be small and with higher error. On the other hand, at high diol and cyclodextrin concentrations the value of $[CD]_{free}$ will carry a higher error.

The constant in the value of $K^{1:1}_{Diol}$ obtained with the different diols concentrations and varying the CD concentration shows us the validity of the method. In Table 2 are shown the values of the free CD concentrations and $K^{1:1}_{Diol}$ obtained from Equations 11 and 14 for 1,6-hexanediol. Similar tables for the others diols have been obtained (see Supplementary Material) and the values of $K^{1:1}_{Diol}$ for the other diols are listed in Table 1.

In Table 1 are shown the $K^{1:1}_{Diol}$ obtained from *Method A* that gave us the best linear fit of Equation 1 to the experimental data and the average $K^{1:1}_{Diol}$ obtained from *Method B* for all CD and alcohol concentrations in each case. The agreement between both methods shows us the validity of the proposed mechanism and the two methods of analysis. The coherence between the two

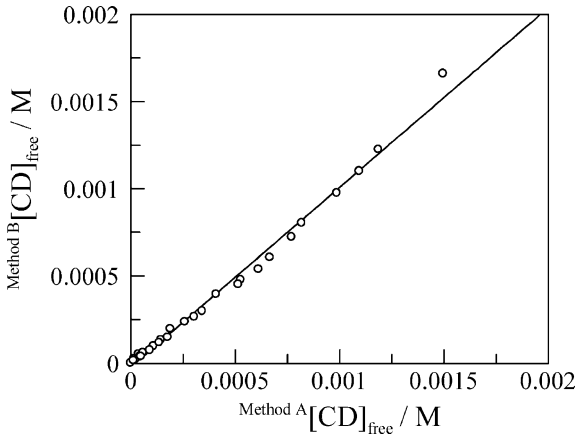


Figure 6. Concentration of free cyclodextrin obtained by Method B vs. the concentration of free cyclodextrin obtained for Method A for each cyclodextrin concentration in the presence of 1,6-hexanediol. The line represent the linear fit to the data.

proposed methods will be also determined by the concordance in the obtained values for the concentration of free cyclodextrin. In Figure 6 are shown the concentration of free cyclodextrin obtained by both methods for each cyclodextrin concentration in the presence of 1,6-hexanediol. The slope of the plot close to one (1.03 ± 0.02) shows us the agreement between the methods. For the other diols used in this work all slopes are also close to the unity (see supplementary material). The validity of both methods allows to obtain the value of the free cyclodextrin concentration in equilibrium with MNTS and the diol without presupposing any stoichiometry of the CD-diol complex.

As the number of carbons increases there is an increase in the binding constant of the alcohol to the CD for both the geminal and terminal alcohols (see Table 1). The correlation between the stability of the complexes, denote as $K^{1:1}_{\text{Diol}}$, with the molecular size can be expressed in different ways. This dependence with number of carbons can be linear or curve as has been showed for surfactants [40, 41], and alkanols [42, 43]. Figure 7 shows a linear correlation between the $\log K^{1:1}_{\text{Diol}}$ and the number of carbons in the chain for both type of diols. An increase in the number of carbons (an increase in its hydrophobicity) shows an increase in the stability of the complex. Similar results has been obtained for linear alkanols [14].

The binding constant for the alkane diols are lower than for the corresponding mono-alcohol [14]. (for example, $K^{1:1}$ = 11.5, 16.5 and 90 M^{-1} for 1,2-pentanediol, 1,5-pentanediol and pentanol respectively), suggesting that the presence of a second alcohol group in the diols gives a greater hydrophilic character. Therefore, an increase in the hydrophilic character of a substrate implies less stable complexes with cyclodextrins and lower binding constants.

Initially the trend in the binding constant is parallel to the decrease of solubility of the diol in water as the number of carbons is increased, i.e. an increase in the hydrophobicity means an increase in the binding constant. The binding constant of the α,ω-alkane diols is higher than for the analog α,β-alkane diols. As expected considering that the interactions can be qualitatively understood in terms of van der Waals forces and hydrophobic effects. In the case of the α,β-alkane diols we can consider $-CH_2OHCH_2OH$ as the polar head group of the molecule oriented towards the outer part of the cavity and the hydrophobic tail towards the inner part of the cavity. In the case of the α,ω-alkane diols, it is expected that both hydroxyl groups will be oriented to the ends of the cavity, and the flexible hydrocarbon moiety in the central part of the cavity. A X-ray diffraction study on the 1,4-butanediol-CD crystal complex showed that the diol molecule is accommodated in the inner cavity of the CD as previously described [44].

Independently of the orientation adopted, the position of the –OH groups at both end of the alkyl chain allows the molecule to adopt a conformation where their interactions are more favorable. However, the "rigidity" of the "polar head" constituted by the geminal diols ($-CH_2OHCH_2OH$), as well as its higher hydrophilic character compare to the $-CH_2OH$ group of a α,ω-alkane diol makes the complexation process between the CD and the terminal diol less favorable, what implies lower association constants, $K^{1:1}_{\text{Diol}}$, for the α,ω-alkane diol compared with the analog α,ß-alkane diol.

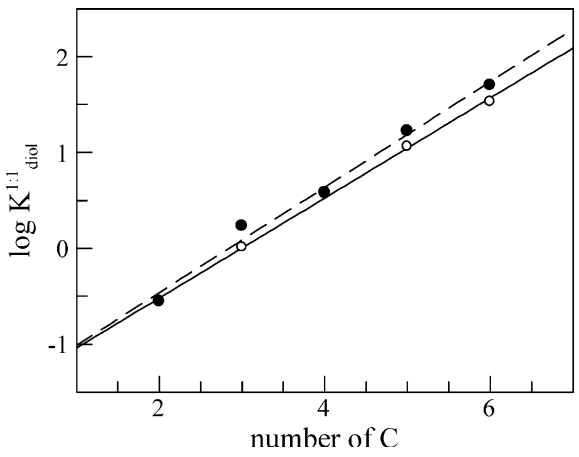


Figure 7. Variation of log with the number of carbons in the chain; (○) α,ω-alkane diols and (●) α,β-alkane diols. The line represent the best linear fit to the data.

Conclusions

The study of acid denitrosation of MNTS in presence of cyclodextrins allowed us to propose a kinetic model which let us to obtain the binding constants of the different alkane diols to β-cyclodextrins, as well as the concentration of free cyclodextrin through the complexation process.

The diol molecules act as a third component through a complexation competition with MNTS molecules for the cavity of the cyclodextrin. This leads to a decrease in the stability of the CD-MNTS complex. Then, the effect of the diols, as a third component, is a decrease in the inhibition effect of the cyclodextrin on the reaction.

Two methods has been proposed to obtain the results: one presupposing a stoichiometry for the CD-Diol complex and the other not presupposing any stoichiometry. The agreement between both methods shows the validity of the proposed kinetic model and the two methods of analysis avoiding the presupposition of a stoichiometry for the complex CD-diol the concentration of free cyclodextrin in equilibrium with MNTS and the diol.

The binding constant for both types of alkane diols increase with increasing the number of carbon in the chain. Besides, the binding constant of the α,ω-alkane diols is higher than for the analog α,β-alkane diols and

always lower than for the corresponding mono-alcohol, as expected by hydrophobic and steric effects.

The main conclusion of this study is we can propose the acid denitrosation of MNTS as a chemical probe for determining the concentration of free cyclodextrin in presence of different third components.

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