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Denitrosation of N-Nitrososulfonamide as Chemical Probe for Determination of Binding Constants to Cyclodextrins

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The influence of β-CD concentration on the acid hydrolysis of N-methyl-N-nitroso-p-toluenesulfonamide (MNTS) has been studied in the presence and absence of different alcohol concentrations. The rate of the denitrosation reaction in bulk water decrease as the β-CD concentration increases due to MNTS complexation in the CD cavity and the reaction taking place exclusively outside the cyclodextrin. Changes in this inhibition due to the presence of β-CD allow us to obtain the binding constants of different alcohols to the cyclodextrin. These binding constants are in very good agreement with those determined in the bibliography by other methods.

Keywords: Cyclodextrin; Nitroso compounds; Kinetic; Binding constants; Alcohol; Chemical probe

INTRODUCTION

Cyclodextrins (CDs) are naturally occurring cyclic oligosaccharides built up from 6, 7, or 8 glucopyranose units and are thus called α-, β-, or γ-cyclodextrins. They have a central hydrophobic cavity, with which they can bind hydrophobic or amphipathic molecules. It is well documented that cyclodextrins form inclusion complexes with a variety of inorganic and organic molecules in aqueous solution [1,2]. The formation of host-guest complexes occurs through desolvation of the species. Nevertheless, the stability of the complex is related to the amount of water, which may be released by the cyclodextrin upon the encapsulation of the guest molecule [3].

Different techniques such as NMR [4–7], surface tension [8], potentiometry [9–11], sound velocity [10,12], etc. were used to determine the host–guest binding constant (*K*). From the bulk thermodynamic properties (calorimetry [13–15], density [10], and heat capacity [16,17]), *K* and the change in the property for the host–guest complex formation were simultaneously estimated.

N-Methyl-N-nitroso-*p*-toluenesulphonamide (MNTS) has proved to be a highly interesting substrate with regard to the behaviour in basic or neutral media from both biochemical [18,19] and chemical [20] points of view. The mechanism for acid [21] and alkaline [22] hydrolysis of MNTS in water are well known (Scheme 1). In an acid medium, the slow step is the proton transfer from the medium to the substrate, whereas in an alkaline medium it is the nucleophilic attack of HO^- on the sulphur atom [21].

In this work, we present a kinetic based method in order to obtain cyclodextrin-guest binding constants, through the variation in the apparent binding constant of MNTS to the cyclodextrin by the presence of a guest. The association constants will be obtain analysing the influence of the cyclodextrin and alcohol concentrations on the variation of the observed rate constant for the acid denitrosation of MNTS.

RESULTS AND DISCUSSION

Absence of Additives

The acid denitrosation and basic hydrolysis of MNTS in the presence of cyclodextrin has been already studied [23–26]. The apolar interior of the ß-CD cavity provides a solubilization site for the MNTS, with reversible formation of a 1:1 inclusion complex between ß-CD and MNTS (Scheme 2). The linear

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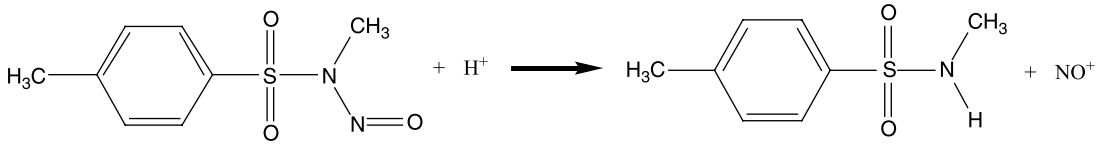


SCHEME 1

dependence of $1/k_{obs}$ as function of the ß-CD concentration, see Fig. 1, indicates that the percentage of the reaction that goes through the complexes can be neglected. From Scheme 2A, the variation of k_{obs} with [ß-CD] is represented by the equation

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

k_w being the bimolecular rate constant, K_{MNTS} the binding constant between the CD and MNTS and [β-CD_f] the concentration of free cyclodextrin that can be assume to [β-CD_{total}] since the study is developed under pseudofirst order conditions on MNTS. The equation can be linearised as follows

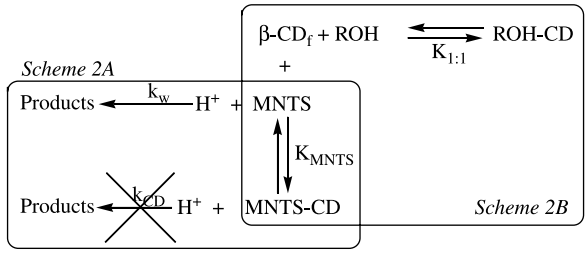
$$\frac{1}{k_{obs}} = \frac{1}{k_w[H^+]} + \frac{K_{MNTS}[\beta - CD]}{k_w[H^+]} \quad (2)$$

the good fit between Equation (1) and the experimental results in the absence of alcohol and the agreement between the resulting estimated value of $k_w = (3.10 \pm 0.08) \times 10^{-2}\,M^{-1}\,s^{-1}$ and that obtained in water without cyclodextrin ($0.031\,M^{-1}\,s^{-1}$) [23].

INFLUENCE OF ALCOHOLS

The influence of ß-cyclodextrin on k_{obs} in the presence of alcohols was determined by varying the cyclodextrin concentration, typically between 0 and 8 mM in a series of experiments at a constant alcohol concentration. Different linear (methanol, ethanol, 1-propanol, 1-butanol, 1-hexanol) and branched (2-propanol, 2-butanol, isopropanol) alcohols have been studied. Fig. 1 shows the variation of k_{obs}/k_w with the [ß-CD] for five different constant concentrations of 2-propanol (ranging from 0.043 to 0.818 M). It should be noted that the ratio k_{obs}/k_w has been considered to take into account the variation of k_w with the change in dielectric constant of the medium as the percentage of alcohol increases [22].

In each case, as the cyclodextrin concentration increases the value k_{obs}/k_w decreases due to the formation of a non-reactive 1:1 complex between the ß-CD and MNTS. The inhibition profile depends strongly in the concentration of alcohol present, an increase in the alcohol concentration produces a less steepest inhibition profile (see Fig. 1B) as a consequence of the formation of a 1:1 complex between cyclodextrin and an alcohol molecule, $K_{1:1}^{ROH}$, and less cyclodextrin molecules will be available to complex MNTS molecules and therefore the inhibition effect is lower as the alcohol concentration increases (see Scheme 2B). Fig. 2 shows the effect of [ß-CD] on the relationship k_{obs} / k_w in the absence and in the presence of a constant concentration (0.055 M) of different linear alkyl chain alcohols (1-propanol, 1-butanol and 1-hexanol). As expected, as the



SCHEME 2

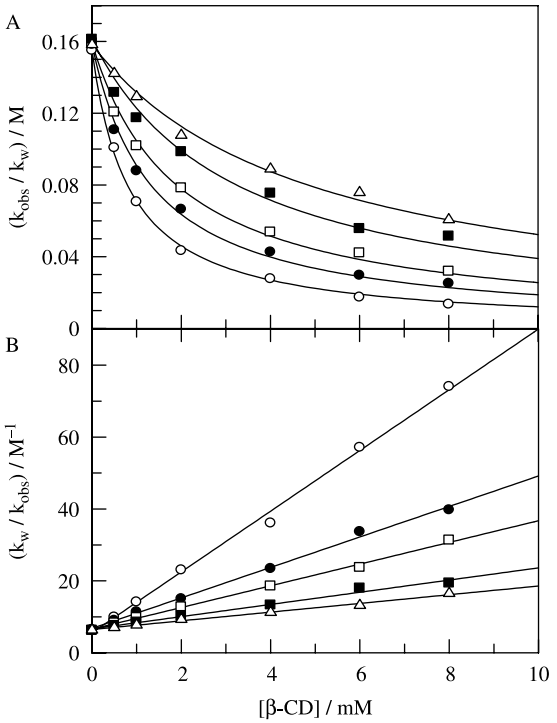


FIGURE 1 (A) Influence of the ß-CD concentration on k_{obs}/k_w for the acid denitrosation of MNTS in the presence of various 2-propanol concentrations: (○) 0.043 M, (●) 0.129 M, (□) 0.215 M, (■) 0.516 M, (△) 0.818 M. The curves where obtained by fitting Equation (1) to the experimental results. (B) Reciprocal plot of k_w / k_{obs} as a function of ß-CD; the line represent the fit to Equation (2).

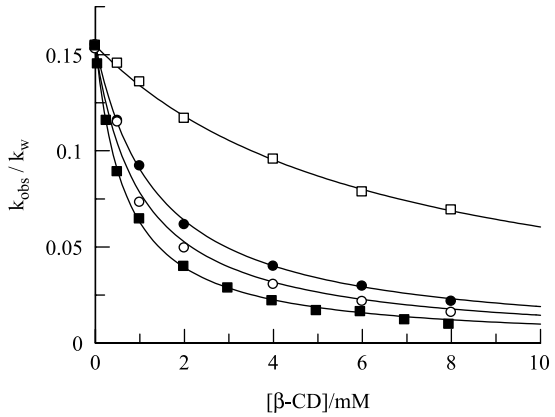


FIGURE 2 Influence of the ß-CD concentration on k_{obs}/k_w for the acid denitrosation of MNTS in the absence (■) and in the presence of 0.055 M of alcohol; (○) propanol, (●) butanol and (□) hexanol. The curves where obtained by fitting Equation (1) to the experimental data.

number of carbons in the alcohol chain increases the inhibition profile due to the CD decreases as a consequence of a stronger competition with MNTS molecules for the CD cavity.

Scheme 2 shows the proposed mechanism to explain the experimental results obtained, involving two competitive equilibriums between the CD and MNTS and alcohol molecules respectively. The obtained expression for the variation of the observed rate constant with the cyclodextrin concentration is similar to that obtained in the absence of alcohol (Equation 1), therefore the second competitive equilibrium alters the free cyclodextrin concentration. Taking into account the different mass balances the free cyclodextrin concentration can be obtain trough a third order equation on free cyclodextrin as was already proposed [27,28], but the knowledge of K_{MNTS} and an iteration of the $K_{1:1}^{ROH}$ value is needed.

In this work, we propose to analyse the experimental data trough the mechanism proposed in Scheme 2, this means to consider the free cyclodextrin concentration equal to the total cyclodextrin concentration. Therefore, only the *apparent* association constant between CD and MNTS, K_{MNTS}^{app}, will be affected with increasing the alcohol concentration. The linear dependence of k_w/k_{obs} with the cyclodextrin concentration shown in Fig. 1B confirms the validity of the model since the presence of alcohol only produces a decrease in the inhibition effect of the [CD] but do not alter the formation of a non-reactive 1:1 complex between MNTS and the ß-CD.

The fit of Equation (1) to the experimental data for the influence of [ß-CD] on k_{obs} in the presence of different constant concentration of alcohol will provide a value for K_{MNTS}^{app} for each alcohol concentration. This value will depend on the concentration of alcohol presence and as expected it will decrease as the alcohol concentration

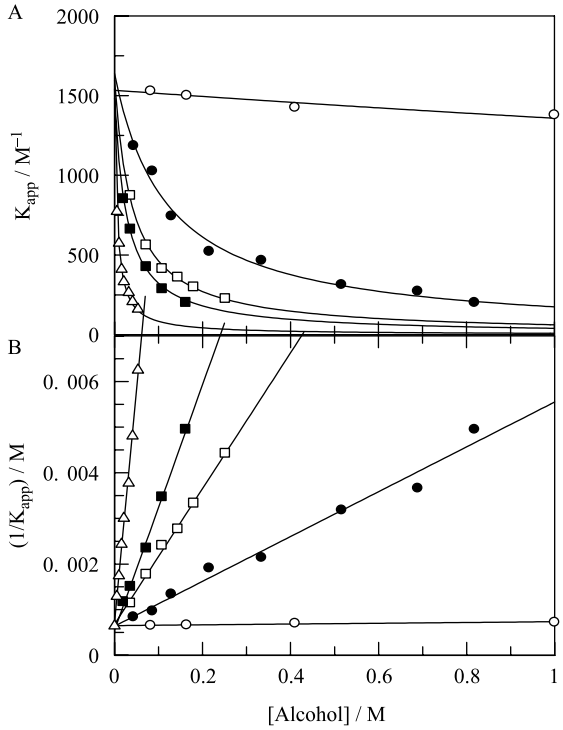


FIGURE 3 (A) Influence of [alcohol] on K_{app}^{MNTS}, the apparent association constant of MNTS to ß-CD: (○) methanol, (●) 2-propanol, (□) 2-butanol, (■) isobutanol, (△) hexanol. The curves where obtained by fitting Equation (6) to the experimental results. (B) Reciprocal plot of K_{app}^{MNTS} versus the alcohol concentration, the lines represent the linear fit to the data.

increases. Fig. 3 shows the variation of this apparent association constant with the alcohol concentration for five different alcohols, as the number of carbons in the chain increases (and therefore its hydrophobicity) the decrease in the value of K_{MNTS}^{app} is more pronounced due to a stronger competition of the alcohol molecules for the CD cavity.

Considering schemes 2A and 2B it will be possible to obtain an expression for the dependence of K_{MNTS}^{app} with the *real* association constant of MNTS to CD, K_{MNTS}, the association constant of the alcohol to ß-CD and the alcohol concentration. From Scheme 2 K_{MNTS}^{app} can be defined as

$$K_{MNTS}^{app} = \frac{[MNTS - CD]}{[MNTS_w][CD_f^*]} \tag{3}$$

where $[CD_f^*]$ is the concentration of free cyclodextrin, initially in the absence of a second guest (such as the alcohol) it can be considered equal to $[CD_t]$ (the total concentration of CD). Due to the presence of alcohol $[CD_f^*]$ should be considered as the sum of the *real* free cyclodextrin, CD_f, plus the cyclodextrin bind to alcohol molecules, ROH-CD,

$$[CD_f^*] = [CD_f] + [ROH - CD] \tag{4}$$

combining Equations (3) and (4) we obtain the following expression to relate the variation of the

TABLE I Association constants of CD-MNTS and CD-alcohol complexes determined using inhibition kinetics and the kinetics of the acid denitrosation of MNTS

Alcohol[a]	[b]K_{MNTS} / M^{-1}	$K_{1:1}$ / M^{-1}	Literature
Methanol	1534 ± 20	1.3 ± 0.1	0.32
Ethanol	1528 ± 58	4.5 ± 0.9	0.93
1-Propanol	1517 ± 39	9.4 ± 0.5	3.7–5.5
2-Propanol	1509 ± 28	8.7 ± 0.8	3.8–7.9
1-Butanol	1504 ± 19	22.4 ± 2.0	16.6–27
2-Butanol	1507 ± 22	20.1 ± 0.9	12.9–20.0
Isobutanol	1480 ± 40	35.8 ± 3.8	27.9–41.7
1-Hexanol	1497 ± 16	147.3 ± 9.8	206–280

[a] Literature values for ß-CD and alcohols binding constants are given as the range of the most reasonable values to be found in [1,2,29].
[b] The value in the absence of alcohol is 1500 ± 50 M^{-1} [23].

apparent association constant of MNTS to CD with the *real* one as a function of the free [CD] and [ROH-CD] (Scheme 2B),

$$K_{MNTS}^{app} = \frac{K_{MNTS}}{1 + \frac{[ROH-CD]}{[CD_f]}} \quad (5)$$

the presupposition of a 1:1 complex between the alkyl chain alcohol and the CD allows us to obtain an expression

$$K_{MNTS}^{app} = \frac{K_{MNTS}}{1 + K_{1:1}^{ROH}[ROH_f]} \quad (6)$$

where $K_{1:1}^{ROH}$is the association constant for a 1:1 complex between an alcohol molecule and the CD and [ROH_f] the concentration of free alcohol concentration in each point. Considering the relatively low values for $K_{1:1}^{ROH}$ it is possible to consider that [ROH_f] is equal to the total alcohol concentration, [ROH_t], when the ratio [ROH_t]/[CD_t] > 5 is satisfied. The validity of this approach as well as the proposed model can be deduced from the good fit of Equation (6) to the experimental data shown in Fig. 3A. Furthermore, Equation (6) can be linearized showing a linear dependence of the reciprocal value of K_{MNTS}^{app} with the alcohol concentration, Fig. 3B confirms this linear dependence. The values of $K_{1:1}^{ROH}$ and K_{MNTS} obtained from the fit of eq. 6 to the experimental data are listed in Table I, the values obtained for $K_{1:1}^{ROH}$ are similar to those reported in the literature and obtained trough other methods. An additional evidence for the validity of the method is related with the coherent values obtained for K_{MNTS} with the different alcohol studied with the value determined in the absence of alcohol [23].

In conclusion we present here a simple kinetic method to obtain the association constant of different substrates to cyclodextrins.[†] The method is based on the variation of the apparent association constant of MNTS to CD with the presence of a second guest that competes for the cavity of the cyclodextrin.

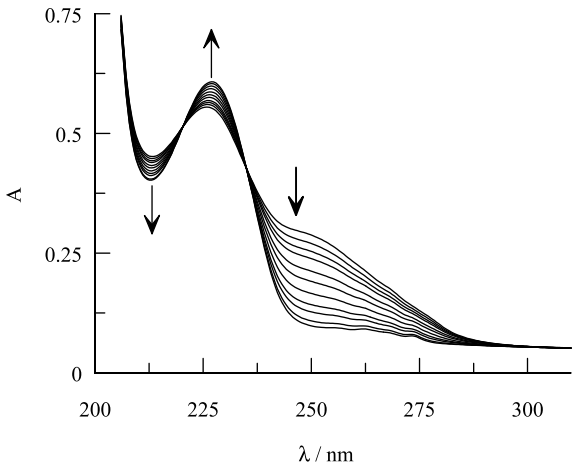


FIGURE 4 Reaction Spetra for the acid hydrolysis of MNTS in the presence of β-cyclodextrin ([MNTS] = 3.33×10^{-5} M, [HCl] = 0.158 M, [β-CD] = 4.03×10^{-3} M), Reaction time: 90 min.

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 (see Fig. 4) in a Hewlett-Packard model 8453 spectrophotometer with a cell holder thermostated at (25.0 ± 0.1)°C. The MNTS concentration was always 5.00×10^{-5} M and [HCl] = 0.109 M; under these conditions all the β-CD will be in the neutral form ($pK_a = 12.2$) [30]. 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_{obs}, were reproducible to within 3%.

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[†]During the deduction of kinetic models several assumptions and approximations were made: (1) the complex between MNTS and β-CD is not hydrolysed; (2) the stoichiometry of complexes of β-CD with MNTS and ROH is 1:1 alone; (3) the concentration of free β-CD is equal to the total concentration of β-CD; (4) The concentration of free ROH is equal to the total concentration of ROH. These assumptions and approximations are reasonable under our reaction conditions. A Change in the reaction used as probe must imply the revision of these assumptions.

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