Cyclodextrin catalysis in the basic hydrolysis of alkyl nitrites

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The influence of β-cyclodextrin (β-CD) on the hydrolysis reaction of a variety of structural types of alkyl nitrites (RONO) is studied in acid and in basic aqueous solutions. Acid-catalysed hydrolysis of alkyl nitrites is inhibited by the presence of β-cyclodextrin. The results are accounted for by assuming the formation of host–guest complexes between β-cyclodextrin and alkyl nitrite, which are unreactive or much less reactive than the uncomplexed RONO. We propose that the result is a consequence of the orientation of the alkyl nitrite in the cavity of CD. The degree of inhibition increases with the greater inclusion of the alkyl nitrite in the CD cavity. The kinetic data are quantitatively analyzed to afford the stability constants of the host–guest complexes. On the contrary, the presence of β-cyclodextrin strongly increases the rate of hydrolysis of alkyl nitrites in a basic medium, that is at a pH value higher than the pK_a of β-cyclodextrin. This feature suggests the formation of a reactive complex between the alkyl nitrite and β-cyclodextrin, whose ionized CD hydroxy group promotes a nucleophilic attack in the rate-limiting step. This behaviour is consistent with a higher reactivity towards alkyl nitrites of an ionized CD hydroxy group as compared with the OH^-; the contrary occurs in the case of esters, whose cleavage by cyclodextrins in basic aqueous media has been studied extensively over the last several years.

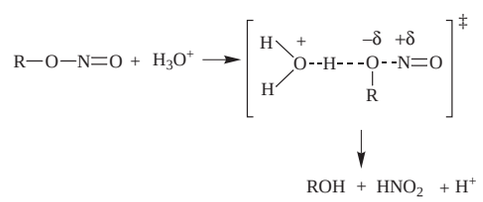
Introduction

Cyclodextrins (CDs) are α-(1,4)-linked glucopyranose rings forming truncated cone-shaped compounds with a hydrophobic interior. The number of the D-(+)-glucopyranose units, *e.g.* six for α-CD, seven for β-CD and eight for γ-CD, defines the width of the central cavity and the flexibility of the compound. The narrow rim of the truncated cone bears the primary OH-groups, while the wider rim bears the secondary OH-groups.[1–3]

Cyclodextrins are widely used as hosts to form inclusion complexes with small- and medium-sized organic molecules. Stabilization of the complex is achieved by van der Waals forces, hydrogen bonding, decrease of strain energy and release of high-energy water from the cavity. Changes in spectroscopic and physico-chemical properties, as well as reactivities, result from such host–guest interactions.[4–6] Chemical reactions pertaining to the included guest may take place, and the effects of inclusion on the reactivity vary widely depending on the guest, the CD and the reaction. In some cases, the rate of reaction is greatly reduced, which has led to the use of CDs as stabilizers; but of more interest are the situations in which CDs accelerate reactions. In other cases, the CD host merely provides a confined environment for a reaction that is less polar than the bulk solvent; moreover, the CD may even participate directly in the reaction.[6–9]

In this investigation we have studied the effects of β-CD in the acid and basic hydrolysis of some alkyl nitrites, whose general structure might be represented as R–O–N=O. Alkyl nitrites are *O*-nitroso compounds, which can be easily synthesized from aqueous sulfuric acid solutions of sodium nitrite and their corresponding alcohols. These compounds are exceedingly insoluble in water due to their strong hydrophobic character resulting from the low polarizability of the nitroso group, which makes solvation by water difficult. On the other hand, the N-atom of an alkyl nitrite is an electrophilic center and is prone to nucleophilic attack, whereas the alcoholic O-atom behaves as a nucleophilic center. Since an alkyl nitrite is a relatively poor electrophile, the process becomes an 'orbital controlled reaction'. And while the reaction of alkyl nitrites (soft electrophiles) with amines (soft nucleophiles) is relatively fast, the attack of the OH^- (a typical hard nucleophile) on an alkyl nitrite is a very slow process. Therefore, the alkaline hydrolysis of alkyl nitrites is a slow process; however, the acid hydrolysis is quite fast, faster even than that of the corresponding ester, for example.

The results of the study of the acid hydrolysis of several alkyl nitrites in an aqueous medium suggest that the reaction takes place through a concerted mechanism that involves both proton transfer and the breaking of the O–N bond, the latter being facilitated by the presence of electron withdrawing groups.[10,11] The determined solvent deuterium isotope effects, together with the value of the Brønsted exponent, α, found for the general acid catalysis, conform perfectly with the postulated transition state of these systems, in which a concerted process with an imbalanced transition state occurs, having an important negative charge develop on the O-atom prior to the proton transfer (see Scheme 1).



Scheme 1

This system constitutes an easy, simple reaction where the substrate is protonated in the rate-controlling step of the reaction, either by H^+ or the acid form of a weak acid, HA. Then, the complete reaction rate equation is that stated in eqn. (1), or,

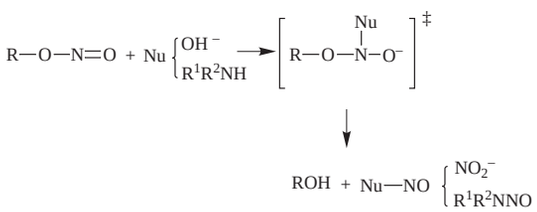
$$\text{rate} = (k_H[H^+] + k_{HA}[HA])[\text{RONO}] \quad (1)$$

in terms of the total concentration of the buffer, that in eqn. (2), where K_a is the acidity constant of the weak acid.

$$k_o = \left(k_H + \frac{k_{HA}[\text{Buffer}]}{K_a + [H^+]}\right)[H^+] \quad (2)$$

The hydrolysis of the alkyl nitrites in an alkaline medium is also a concerted process[12,13] and does not proceed *via* an

addition–elimination pathway, which is the well-known $B_{AC}2$ mechanism for the hydrolysis of carboxylic esters.[14] The fact that nitrogen is more electronegative than carbon and has a lone pair probably explains the significant differences between the chemistry of alkyl nitrites and that of carboxylic esters: carboxyl chemistry is dominated by the formation of tetrahedral intermediates, whereas the N=O group has been thought to be transferred intact (see Scheme 2).



Scheme 2

The nucleophilic reactivity of OH^- in the hydrolysis of carboxylic esters is remarkably greater than that for alkyl nitrites; however, the nucleophilic reactivity of amine in the aminolysis of esters is remarkably lower than that for alkyl nitrites.[12] Therefore, amine is a better nucleophile than OH^- in reactions with alkyl nitrites, but is much weaker in reactions with carboxylic esters.[15–17] These observations are rationalized in terms of an unfavourable lone pair–lone pair interaction between the nucleophiles and the nitroso N-atom in the reaction with OH^-, while no such repulsion takes place in the reaction with amines.

Experimental

Alkyl nitrites were synthesized by treating the corresponding alcohol with sodium nitrite in aqueous sulfuric acid,[18] were purified by fractional distillation and were stored at low temperature over molecular sieves to prevent their hydrolysis. β-CD was purchased from Aldrich and was used without further purification. All other reagents were supplied by Merck and were used as received. Sodium hydroxide was standardized against primary standard potassium acid phthalate. All solutions were prepared with doubly-distilled water obtained from a permanganate solution.

In studying the acid hydrolysis, the kinetics of the faster reactions were monitored by using a Hi-Tech SF-61 stopped flow apparatus, and those of the slower reactions, with a Kontron-Uvikon (model 941) UV–VIS double beam spectrophotometer, provided with a multiple cell carrier thermostatted by circulating water. The kinetics of the basic hydrolysis reaction were studied by conventional spectrophotometry. Either in the acid or basic hydrolysis, the consumption of alkyl nitrites was followed by recording the decreasing absorbance in the 240–250 nm region. The kinetics of the reaction with pyrrolidine were studied by recording the increase in absorbance due to the formation of *N*-nitrosopyrrolidine. All the experiments were performed at 25 °C.

Stock solutions of the alkyl nitrites were prepared in dioxane. When their hydrolysis was studied by conventional spectrophotometry, the reaction was initiated with the addition of 50 μl of a solution of alkyl nitrite in dioxane to the rest of the reaction mixture. The percentage of dioxane in the final reaction mixture was less than 1.7% by volume. When the reaction was studied by stopped-flow a small amount of the alkyl nitrite solution in dioxane was dissolved in weakly basic carbonate buffer (2×10^{-3} mol dm^{-3} of pH 10.25) in which alkyl nitrites are stable, and was loaded into one syringe; the appropriate quantity of hydrochloric acid was loaded into the other. The percentage of dioxane in the final reaction mixture never exceeded 1% by volume. Both syringes contained the same CD concentration.

The concentration of alkyl nitrite used was $(1–4) \times 10^{-4}$ mol dm^{-3}. Kinetic experiments were carried out under pseudo-first-order conditions, with the acid (or base) concentration at least 20 times greater than the [alkyl nitrite]. In each case the integrated method was followed, fitting the experimental absorbance–time data to the first-order integrated equation and obtaining satisfactory correlation coefficients (>0.999) and residuals. In what follows, k_o denotes the observed pseudo-first-order rate constant, whose values were usually reproducible to within 2%.

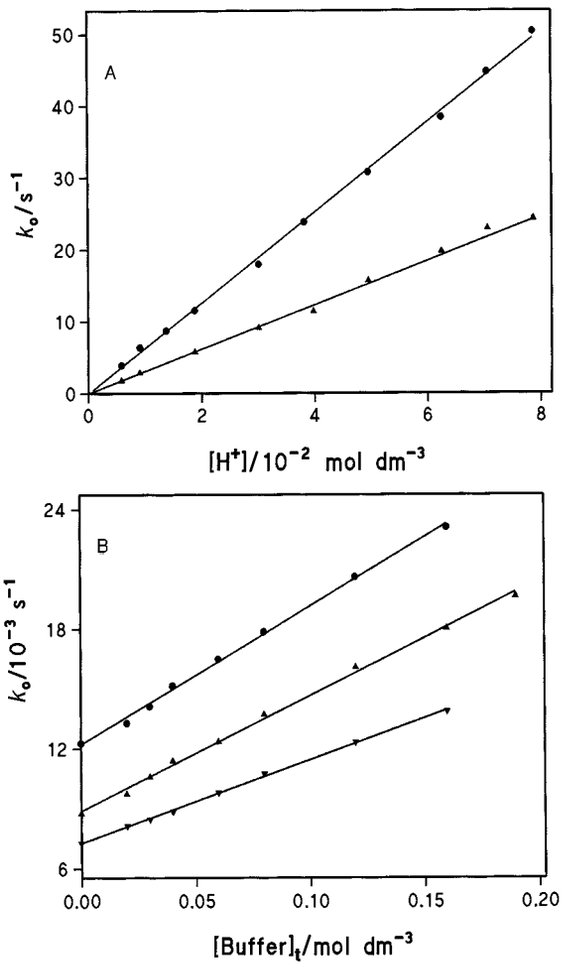


Fig. 1 A, Influence of $[H^+]$ on the pseudo-first-order rate constant of the acid hydrolysis of *tert*-butyl nitrite at β-cyclodextrin concentration of (●) 2.52×10^{-3} and (▲) 9.24×10^{-3} mol dm^{-3}; B, influence of the concentration of acetic acid–acetate buffer of pH 4.89 in the acid hydrolysis of (●) *tert*-butyl nitrite, (▼) *tert*-butyl nitrite at [β-CD] = 5.4×10^{-3} mol dm^{-3} and of (▲) 1-phenylethyl nitrite

Results and discussion

Acid hydrolysis

We analyzed the influence of β-CD on the acid hydrolysis of some alkyl nitrites of varied structure. The influence of the acidity in the presence of β-CD was examined by varying the $[H^+]$ (controlled with HCl) in the range of $(6–80) \times 10^{-3}$ mol dm^{-3} at two fixed values of β-CD concentration (2.5 and 9.2) $\times 10^{-3}$ mol dm^{-3}. In each case the observed rate constant increased with $[H^+]$, describing, as expected, a straight line, *i.e.* $k_o = k_H[H^+]$, meaning that the presence of β-CD does not induce changes in the mechanism of the reaction. Fig. 1A shows the results corresponding to the acid hydrolysis of *tert*-butyl nitrite.

Fig. 1B shows the results of the influence of the concentration of the acetic acid–acetate buffer of pH 4.89 on the observed rate constant of the acid hydrolysis of *tert*-butyl and 1-phenylethyl nitrites determined in the absence and presence

Table 1 Experimental conditions, bimolecular rate constants and stability constants of the complex formed between alkyl nitrite and β-cyclodextrin, obtained in the kinetic study of the influence of the acidity, or buffer concentration, on k_o of the acid hydrolysis of alkyl nitrites

[β-CD]/mol dm^{-3}	[H$^+$]/mol dm^{-3}	Intercept/s^{-1}	Slope/mol^{-1} dm^3 s^{-1}	k_H/mol^{-1} dm^3 s^{-1}	k_{HA}/mol^{-1} dm^3 s^{-1}	K_c^N/mol^{-1} dm^3
tert-Butyl nitrite						
0	Variable/HCl	—	953[a]–916[b]	934	—	—
2.5×10^{-3}	Variable/HCl	—	629 ± 8	895[c]	—	169
9.2×10^{-3}	Variable/HCl	—	311 ± 4	795[c]	—	169
Variable	0.014/HCl	—	—	—	—	169 ± 3
0	1.29×10^{-5}/buffer	$(12.2 \pm 0.2) \times 10^{-3}$	$(6.9 \pm 0.2) \times 10^{-2}$	946	0.165	—
5.4×10^{-3}	1.29×10^{-5}/buffer	$(7.3 \pm 0.1) \times 10^{-3}$	$(4.2 \pm 0.7) \times 10^{-2}$	566[d]	0.100[e]	143
1-Phenylethyl nitrite						
0	1.29×10^{-5}/buffer	$(8.9 \pm 0.1) \times 10^{-3}$	$(5.8 \pm 0.1) \times 10^{-2}$	687	0.138	—

[a] Ref. 10. [b] Ref. 11. [c] Calculated as: slope × (1 + K_c^N[β-CD]). [d] Value corresponding to ($k_H + k_H^c K_c^N$[β-CD])/(1 + K_c^N[β-CD]). [e] Value of ($k_{HA} + k_{HA}^c K_c^N$[β-CD])/(1 + K_c^N[β-CD]), see eqn. (4).

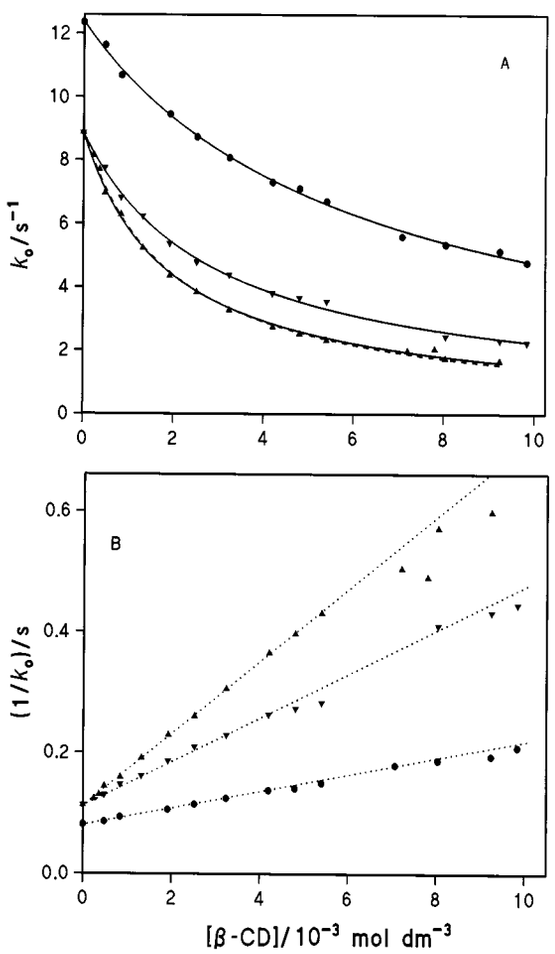


Fig. 2 A, Variation of the pseudo-first-order rate constant for the acid hydrolysis of (●) *tert*-butyl nitrite, (▼) 1-phenylethyl nitrite and (▲) cyclohexyl nitrite, as a function of β-CD concentration at [HCl] = 0.014 mol dm^{-3}; dashed line, assuming no reaction of the complex; B, reciprocal plot of k_o as a function of [β-CD]

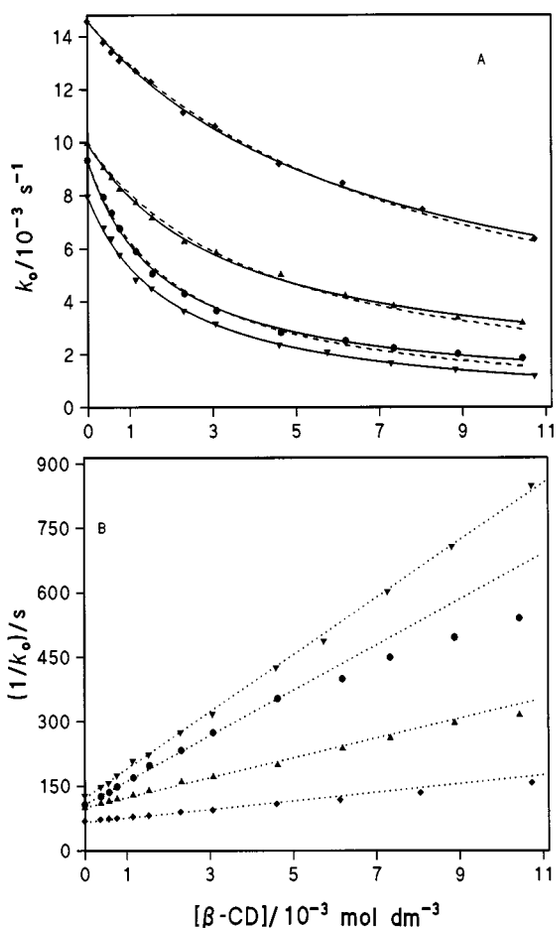


Fig. 3 A, Variation of the pseudo-first-order rate constant for the acid hydrolysis of (◆) *tert*-butyl nitrite, (▼) 1-phenylethyl nitrite, (●) cyclohexyl nitrite and (▲) 1-phenylprop-1-yl nitrite as a function of [β-CD] at acetic acid–acetate buffer of pH 4.89 at 0.030 mol dm^{-3}; dashed lines correspond to the fit of eqn. (4) by assuming no reaction of the complex; B, reciprocal plot of k_o as a function of [β-CD]

of β-CD ([β-CD] = 5.6 × 10^{-3} mol dm^{-3}). (The ionic strength was not kept constant, because the effect at low values is negligible.[10]) In all cases there is moderate catalysis in accordance with eqn. (1), or eqn. (2). The intercepts at the origin of the resulting straight lines yield the values of k_H, whereas from the slopes, the values of k_{HA} can be determined.

Table 1 reports the obtained results. As one can see, the presence of β-CD strongly inhibits the reaction by a factor of nearly 3 at [β-CD] = 9.2×10^{-3} mol dm^{-3} with respect to the value obtained when β-CD is absent.

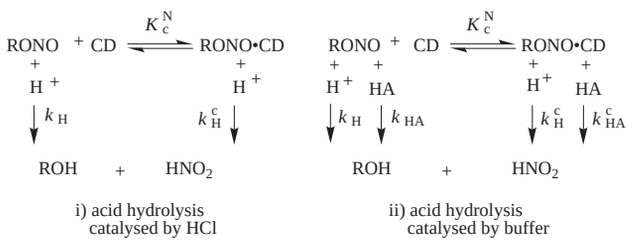
The influence of β-CD was examined at fixed [HCl] equal to 0.014 mol dm^{-3} and at fixed concentration (0.030 mol dm^{-3}) of acetic acid–acetate buffer of pH 4.89. Figs. 2 and 3 show the experimental results for the cases of *tert*-butyl, 1-phenylethyl, cyclohexyl and 1-phenylprop-1-yl nitrites. The addition of CD causes a reduction of k_o throughout the entire range of [β-CD] studied.

The kinetic results obtained for the presence of CDs are often interpreted on the basis of the similarity between the special CD-behaviour and enzyme catalysis. The apolar interior of the CD-cavity provides a solubilization site for the highly hydrophobic alkyl nitrites, forming here a 1:1 inclusion complex between CD and RONO, which are intimately linked but not through covalent bonds (see Scheme 3).

Table 2 Stability constants of the complex RONO·CD, bimolecular rate constants and parameters used in the fit of kinetic data to eqns. (3) or (4) obtained in the acid hydrolysis of alkyl nitrites at 25 °C

R–	$[H^+]$/mol dm^{-3}	k_o^w/s^{-1}	k_H/mol^{-1} dm^3 s^{-1}	k_H^c/mol^{-1} dm^3 s^{-1}	k_{HA}/mol^{-1} dm^3 s^{-1}	k_{HA}^c/mol^{-1} dm^3 s^{-1}	K_c^N/mol^{-1} dm^3
Ph–CH_2CH_2–	0.014	10.2	729	n.s.[a]	—	—	132 ± 2
$(CH_3)_3C$–	0.014	12.4	882	n.s.	—	—	169 ± 3
Ph–CH–CH_3	0.014	9.2	658	~34	—	—	359 ± 7
C_6H_5–	0.014	9.0	641	~11	—	—	528 ± 9
$CH_3(CH_2)_2CH_2$–	0.014	7.1	522	n.s.	—	—	50 ± 2
$CH_3(CH_2)_4CH_2$–	0.014	6.7	479	n.s.	—	—	141 ± 3
$(CH_3)_3C$–	1.29×10^{-5}	1.47×10^{-2}	946	74	0.165	0.0161	147 ± 2
Ph–CH–CH_3	1.29×10^{-5}	1.06×10^{-2}	687	66	0.135	0.0133	282 ± 11
C_6H_5–	1.29×10^{-5}	0.93×10^{-2}	693	~35	0.030	~0.0016	547 ± 21
Ph–$CHCH_2CH_3$	1.29×10^{-5}	0.78×10^{-2}	545	~0	0.061	~0	521 ± 15

[a]n.s. = not significant.



Scheme 3

From Scheme 3, the variation of k_o with [β-CD] may be represented by eqns. (3) and (4), depending on whether the acid

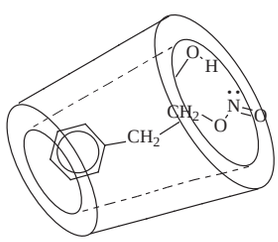
$$k_o = \frac{(k_H + k_H^c K_c^N[\text{β-CD}])[H^+]}{1 + K_c^N[\text{β-CD}]} \quad (3)$$

$$k_o = \frac{(k_H[H^+] + k_{HA}[HA]) + (k_H^c[H^+] + k_{HA}^c[HA])K_c^N[\text{β-CD}]}{1 + K_c^N[\text{β-CD}]} \quad (4)$$

hydrolysis is studied in the presence of HCl or acetic acid–acetate buffer, respectively; with K_c^N being the equilibrium stabilization constant of the complex; k_o^w ($= k_H[H^+]$ or $= (k_H + k_{HA}[HA])[H^+]$ according to the acid used) is the observed rate constant in the absence of β-CD, and [β-CD] represents the free β-CD concentration.

Since the alkyl nitrite concentration is about 10 times less than that of CD, one might consider the total [β-CD] to be free. The values of K_c^N were obtained by fitting the experimental data to eqns. (3) or (4), using experimental values of k_o^w. Figs. 2B and 3B show the reciprocal plots of k_o as a function of β-CD concentration. In some cases, experimental data seem to slightly deviate from the straight line, principally at high host concentration. This feature is indicative of reaction through the complex. Nevertheless, the percentage of the reaction which goes through the complex is small and it makes it difficult to obtain accurate values for the rate constants of the complex, principally in the experiments studied by the stopped-flow technique. The results reported in Table 2 are based on the rate constant–cyclodextrin concentration profiles.

The degree of interaction between CD and the alkyl nitrite is a function of the hydrophobicity of RONO, of the size cavity, of the orientation of RONO and of the nature of the interaction forces between the alkyl nitrite and the cavity interior of CD. Generally, the host–guest bond is not classically apolar because complex formation is associated with favourable enthalpy change and negative (or slightly positive) entropy change. Here, our interpretation of the results works on the assumption that the included RONO is unreactive or much less reactive than the RONO not complexed. The orientation of the substrate in the cavity of the CD is sometimes responsible for its reactivity. It is supposed that charged substituents protrude from the wider side of the cavity because of their high degree of solvation and because of the great energy that would be required to desolvate them and allow them to penetrate the cavity; meanwhile, for uncharged derivatives the atom or group with the highest Hammett σ-value is presumably bound in the narrower end of the cavity because of the favourable host–guest dipole–dipole interaction energy. Working from this basis, in a picture of the complex formed between the alkyl nitrite and β-CD, one would find the nitroso group oriented toward the wider side of the cavity, with the N-atom located close to the CD hydroxy group, and stabilized by hydrogen bonding (see Scheme 4 for the case of 2-phenylethyl nitrite). Given this



Scheme 4 Schematic representation of the inclusion complex

situation, the center of the reaction (the alcoholic O-atom) is deep inside the cavity, that is, largely separated from the other reagent, H^+.

In conclusion, the main effect of the presence of CD in the acid hydrolysis of alkyl nitrites is a separation of the reagents. Corroborating this point are the results shown in Fig. 4, which were obtained by examining the influence of dodecyltrimethylammonium bromide (DTABr) on the acid hydrolysis of 1-phenylethyl and *tert*-butyl nitrites in the presence of 5.7×10^{-3} mol dm^{-3} of β-CD. The reaction was performed at pH 4.89 in the presence of 0.030 mol dm^{-3} of acetic acid–acetate buffer. At concentrations below the critical micelle concentration (cmc), (determined as 0.012 mol dm^{-3} at [HCl] = 0.014 mol dm^{-3}, but in the absence of β-CD, by following the method of benzoylacetone solubilization[19]), DTABr has no effect on the reaction; but in the presence of β-CD, due to the fact that the binding constant of DTABr to CD (K_s = 1450,[20] 2000[21] or 3000[22] mol^{-1} dm^3) is higher than that of alkyl nitrites, an efficient competition for the CD cavity between the substrates appears. Then, an increase in the [DTABr] increases the [RONO] in water, *i.e.* not forming the inclusion complex, and the reaction rate consequently increases until it reaches again the value of k_o measured in the absence of cyclodextrin, *i.e.* when all the complexed RONO was pushed out of the CD-cavity by the surfactant monomers. Also in Fig. 4, a plot of k_o against free CD concentration is displayed. In order to calculate $[\text{β-CD}]_f$ in line with treatments previously described,[23] the equilibrium constant for the inclusion complex between the surfactant and β-CD was taken as 3000 mol^{-1} dm^3 and free β-CD concentra-

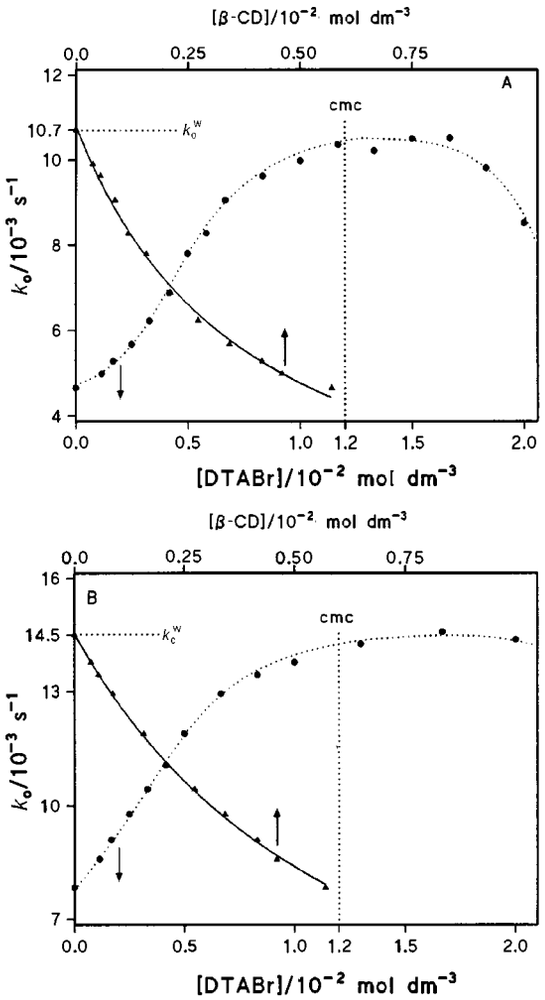


Fig. 4 (●) Influence of DTABr (dodecyltrimethylammonium bromide) concentration on the acid hydrolysis of A, 1-phenylethyl nitrite and B, *tert*-butyl nitrite, at [β-CD] = 5.7×10^{-3} mol dm^{-3} and acetic acid–acetate buffer of 0.030 mol dm^{-3} and pH 4.89; dotted line to guide the eye; (▲) plot of the data against free [β-CD], calculated assuming a value of 3000 mol^{-1} dm^3 for the binding constant of DTABr to β-CD; solid line fit eqn. (4), for parameters see text

tion was determined at each surfactant concentration by solving eqn. (5). Fitting the data thus obtained to eqn. (4), one

$$[\beta\text{-CD}]^2 + [\beta\text{-CD}]\left(\frac{1}{K_s} + [\text{Surfactant}]_t - [\beta\text{-CD}]_t\right) - \frac{[\beta\text{-CD}]_t}{K_s} = 0 \quad (5)$$

determines that $k_o^w = 10.6 \pm 0.5$ s^{-1} and $K_c^N = 286 \pm 6$ mol^{-1} dm^3, in the case of 1-phenylethyl nitrite, and $k_o^w = 14.6 \pm 0.5$ s^{-1} and $K_c^N = 147 \pm 2$ mol^{-1} dm^3, in the case of *tert*-butyl nitrite, which compares quite well with the data in Table 2. (At the low β-CD concentration used in these experiments, we did not consider reaction through the complex in the fitting process.)

Basic hydrolysis

Reaction with OH$^-$. The basic hydrolysis of alkyl nitrites is a slow process. The reaction in water exhibits marked differences[12] from the corresponding ester hydrolysis. Alkaline hydrolysis of alkyl nitrites is much slower than that of the corresponding esters; during the reaction there is no concurrent oxygen exchange between the nitroso-oxygen of the alkyl nitrite and OH$^-$; the steric requirements of alkyl nitrites are less important than those of esters, but the polar effects of substituents on the leaving alkoxide group are greater than for esters.

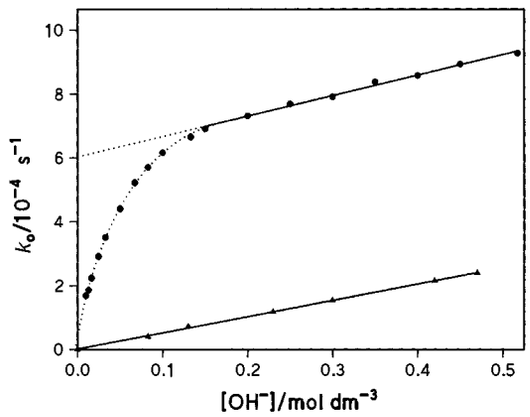


Fig. 5 Influence of [OH$^-$] on the basic hydrolysis of 1-phenylethyl nitrite (▲) in water and (●) in the presence of 5.6×10^{-3} mol dm^{-3} of β-cyclodextrin

These differences can be rationalized in terms of the greater electronegativity of the N-atom (the electrophilic center of an alkyl nitrite) with regard to the C-atom (the electrophilic center in esters), and of the presence of a lone pair on nitrogen but not on carbon; both features ensure that the alkyl nitrites are soft electrophiles and that the reaction is an 'orbital controlled' process.[24]

The basic hydrolysis of alkyl nitrites in water was catalysed by OH$^-$. Fig. 5 shows the variation of the pseudo-first-order rate constant as a function of [OH$^-$] obtained in the hydrolysis of 1-phenylethyl nitrite in the absence and presence of 5.6×10^{-3} mol dm^{-3} of β-CD. The reaction in water shows the normal behavior of a catalysed reaction resulting from the nucleophilic attack of OH$^-$, *i.e.*, of k_o increasing linearly with [OH$^-$]: $k_o = k_{OH}[OH^-]$, with $k_{OH} = (5.06 \pm 0.09) \times 10^{-4}$ mol^{-1} dm^3 s^{-1} being the slope of the corresponding straight line. The study of the influence of [OH$^-$] in the presence of 5.6×10^{-3} mol dm^{-3} of β-CD reveals strong catalysis of the reaction. The variation of k_o with the hydroxy ion concentration displays an ascending curve, which becomes a straight line up to a given [OH$^-$], corresponding to the total ionization of a secondary hydroxy CD-group. The catalysis can be qualitatively explained if the CD participates directly in the reaction: in other words, the complex CD·RONO is more reactive than the reaction of RONO not complexed.

In basic solution a secondary hydroxy group of β-CD with a wider rim is ionized; the pK_a of β-CD has been measured as 12.3.[1,25] If the ionized secondary group of a CD-host acts as a nucleophile towards the guest-alkyl nitrite, the NO transfer to the CD occurs in the reaction rate-limiting step, to yield the corresponding alcohol (ROH) and the cyclodextrin nitrite. Bearing in mind that the alkaline hydrolysis of alkyl nitrites is an 'orbital controlled reaction', meaning that the reaction center (N-atom) is a soft electrophile, we may aver that the reaction with the ionized CD-hydroxy group will be more efficient than the reaction with OH$^-$, which is the hardest nucleophile, as opposed to the soft nucleophile of the ionized CD-hydroxy group. Therefore, increasing [OH$^-$] will also increase the amount of ionized CD molecules, and, consequently, the percentage of the reaction that goes *via* the CD·RONO complex. In addition, the unique nucleophilicity argument is not enough to apply here; because, regarding the reactivity of the complex CD·RONO, it is not possible to separate the efficiency of an intramolecular reaction, which makes some contribution to transition-state stabilization, from the CD nucleophilicity.[26,6c]

We then studied the influence of [β-CD] at different [OH$^-$]. The results are shown in Fig. 6. Pseudo-first-order rate constants were obtained over a range of CD concentrations, and in every case CD gave rise to saturation kinetics. At the lowest [OH$^-$] investigated (0.025 and 0.050 mol dm^{-3}), part of the CD

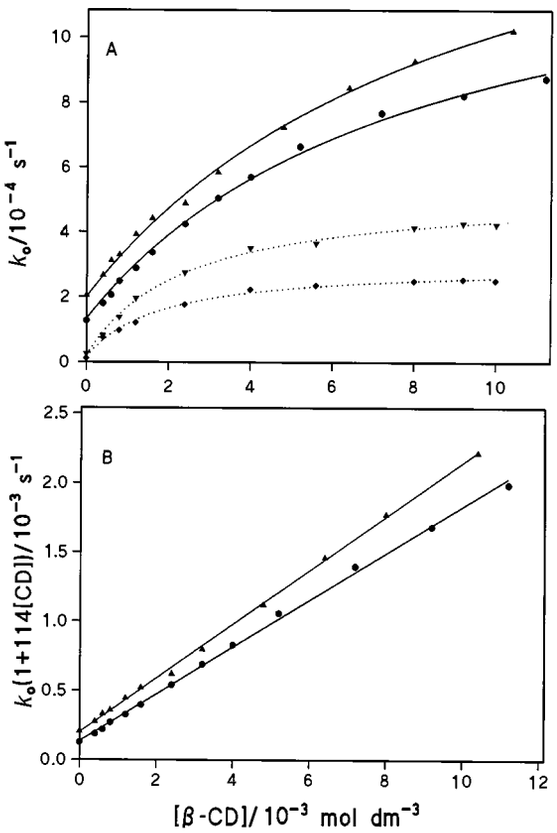
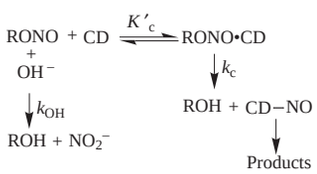


Fig. 6 A, Influence of [β-CD] on the basic hydrolysis of 1-phenylethyl nitrite at [OH^-] equal to (▲) 0.40, (●) 0.20, (▼) 0.050 and (◆) 0.025 mol dm^{-3}. Solid lines fit eqn. (3), for parameters see Table 3. B, Linearization of the data obtained at [OH^-] = 0.40 and 0.20 mol dm^{-3} according to eqn. (6).

was unionized and the complexation equilibrium constant may not have had a unique value; thus, alkyl nitrite binds to neutral and ionized CD; on the other hand, [OH^-] varies with an increase in the amount of ionized CD. Nevertheless, at high [OH^-] (0.20 or 0.40 mol dm^{-3}), the total β-CD concentration is practically in the ionized form (see Fig. 5), and K_c values obtained from the saturation kinetics refer basically to the binding of alkyl nitrite to ionized CD. As can be seen in Fig. 6, the value of k_o obtained at [β-CD] = 0 represents the hydrolysis reaction *via* OH^-, and, obviously, this value increases with the [OH^-]. Therefore, Scheme 5 can be proposed to explain the



Scheme 5

observed facts. According to this scheme, under the usual condition that [RONO•CD] < $[RONO]_t \ll [CD]$, the expression of the observed rate constant obtained is that of eqn. (6), where

$$k_o = \frac{k_{OH}[OH^-] + k_c K'_c[\beta\text{-CD}]}{1 + K'_c[\beta\text{-CD}]} \qquad (6)$$

$k_{OH}[OH^-]$ ($= k_o^w$) is the pseudo-first-order rate constant of the hydrolysis reaction of RONO by OH^- measured in the absence of β-CD.

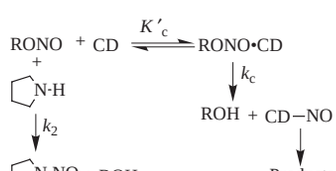
We fitted the experimental data to eqn. (6), introducing the values of k_o^w as a known parameter and determining the values of k_c, the rate constant for the hydrolysis reaction of the complex, and K'_c, the equilibrium constant for complex formation. The resulting values are reported in Table 3. As one can see, the K'_c values determined at high [OH^-], that is, under conditions in which all CD molecules have an ionized secondary hydroxy group, are lower than those determined for acid hydrolysis (see Table 2). In the latter case, K'_c is the equilibrium constant corresponding to the complex formation between alkyl nitrite and neutral cyclodextrin; conversely, in the former case, the complex is formed between the alkyl nitrite and the ionized cyclodextrin. In addition to the assumption made in the previous section of an intermolecular hydrogen-bonding interaction between the guest RONO in the cavity interior of the CD-host, two factors which operate in the same direction could explain the lower association of RONO to the ionized CD-host. These features unfavourably contribute to the free energy of the association process, mainly because of changes in the enthalpy complexation function. First, there is no possibility of H-bonding interaction between the N-atom of an alkyl nitrite and the ionized secondary hydroxy group of a CD-host; and second, the hydration of an ionized hydroxy group of CD is stronger than the hydration of an -OH group: the former situation generates strongly hydrogen-bonded water molecules that are displaced from the CD cavity and incorporated into the bulk solvent upon guest inclusion. Therefore, lower host–guest interaction and less favourable desolvation of the host provide for a poorer RONO•CD interaction; lower K'_c values are then observed, as compared with the results obtained for the acid medium. Equilibrium constants for the complex formation between the ionized β-CD and substrate smaller than those formed with neutral β-CD, have already been observed.[27]

Reaction with pyrrolidine. To obtain further information on the above point, we examined the aminolysis of alkyl nitrites by pyrrolidine in the presence of β-CD. Pyrrolidine is a very hydrophilic substrate and very reactive toward alkyl nitrites, producing the stable *N*-nitrosopyrrolidine and the alcohol corresponding to the alkyl nitrite.[28] Pyrrolidine has not been found to associate appreciably to micelles,[29] and the equilibrium constant of the inclusion complex formation with β-CD is approximated[30] to 6 mol^{-1} dm^3, *i.e.* much lower than those of alkyl nitrites. On the other hand, it is possible to study the aminolysis of an alkyl nitrite by pyrrolidine at pH conditions below and above the pK_a of β-CD, *i.e.* under conditions in which a secondary hydroxy group of β-CD may be unionized or ionized, respectively.

Fig. 7 displays the experimental data of the pseudo-first-order rate constant obtained in the nitrosation of pyrrolidine by 1-phenylethyl nitrite as a function of β-CD concentration, corresponding to three different experimental conditions: (1) [OH^-] = 0.10, $[PyR]_t = 6.4 \times 10^{-3}$; (2) [$OH^-$] = 0.05, $[PyR]_t = 4.0 \times 10^{-3}$ and (3) $[PyR]_t$ = 0.010, pyrrolidine-buffer of pH 11.35, with the concentrations given in mol dm^{-3}. In all cases an inhibition of the reaction is observed on increasing [β-CD].

Fig. 8 exhibits the results of the observed rate constant obtained in the nitrosation of PyR by cyclohexyl nitrite (at $[PyR]_t$ = 0.010 mol dm^{-3}, and [OH^-] = 0.10 mol dm^{-3}) and by 2-phenylethyl nitrite (at $[PyR]_t = 6.7 \times 10^{-3}$ mol dm^{-3} and [OH^-] = 0.10 mol dm^{-3}) as a function of [β-CD]; in the former case, k_o decreases with [β-CD], while the contrary is true of the latter case.

Experimental results were fitted to an eqn. of type (6), easily deducible from Scheme 6, with k_c being negligible or significant,



Scheme 6

Table 3 Experimental conditions used in the basic hydrolysis of alkyl nitrites, or in the nitrosation reaction of pyrrolidine in basic medium, performed in the presence of β-cyclodextrin; also the measured observed rate constant, k_o^w, in the absence of β-CD, and the determined values for the rate constant of the complex, k_c and the equilibrium constant for the complex formation, K_c'

Nucleophile (c/mol dm^{-3})	Effect	[OH$^-$]/mol dm^{-3}	$k_o^w/10^{-4}$ s^{-1}	$k_c/10^{-3}$ s^{-1}	K_c'/mol^{-1} dm^3	k_c/k_o^w	k_2^c/mol^{-1} dm^3 s^{-1}
1-Phenylethyl nitrite							
OH$^-$	Catalysis	0.20	1.33 ± 0.07	1.50 ± 0.05	118 ± 8	11.3	0.18
OH$^-$	Catalysis	0.40	2.06 ± 0.08	1.75 ± 0.02	110 ± 8	8.5	0.19
PyR (4.0×10^{-3})	Inhibition	0.05	55.8 ± 0.6	No reaction	112 ± 6	—	—
PyR (6.4×10^{-3})	Inhibition	0.10	97.4 ± 0.4	No reaction	117 ± 2	—	—
PyR (0.010)	Inhibition	Buffer PyR of pH 11.35	38.7 ± 0.08	No reaction	283 ± 16	—	—
Cyclohexyl nitrite							
OH$^-$	Catalysis	0.18	0.16 ± 0.03	0.23 ± 0.05	281 ± 37	14.4	0.065
OH$^-$	Catalysis	0.34	0.22 ± 0.03	0.35 ± 0.05	248 ± 16	15.9	0.087
PyR (0.01)	Catalysis	0.10	8.2 ± 0.1	0.35 ± 0.03	275 ± 36	0.43	0.096
tert-Butyl nitrite							
PyR (0.016)	Inhibition	0.20	5.2 ± 0.3	No reaction	53 ± 2	—	—
PyR (0.030)	Inhibition	Buffer PyR of pH 11.35	3.3 ± 0.1	No reaction	146 ± 5	—	—
2-Phenylethyl nitrite							
OH$^-$	Catalysis	0.40	1.34 ± 0.04	5.7 ± 0.3	85 ± 7	42.5	0.48
OH$^-$	Catalysis	0.20	0.75 ± 0.02	5.2 ± 0.2	106 ± 7	69.0	0.55
PyR (6.7×10^{-3})	Catalysis	0.10	56.5 ± 0.5	11.8 ± 0.6	92 ± 11	2.1	1.09

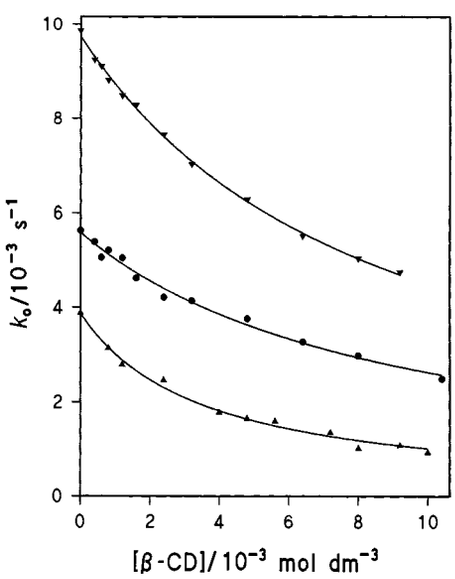


Fig. 7 Influence of β-CD concentration on the observed rate constant of the nitrosation reaction of pyrrolidine by 1-phenylethyl nitrite at (▼) [PyR] = 6.4×10^{-3}, [OH$^-$] = 0.10; (●) [PyR] = 4.0×10^{-3}, [OH$^-$] = 0.050; (▲) [PyR] = 0.010 (all concentrations in mol dm^{-3}) using a buffer of pyrrolidine–pyrrolidinium chloride of pH 11.35. Solid lines fit eqn. (6) with $k_c = 0$, for parameters see Table 3.

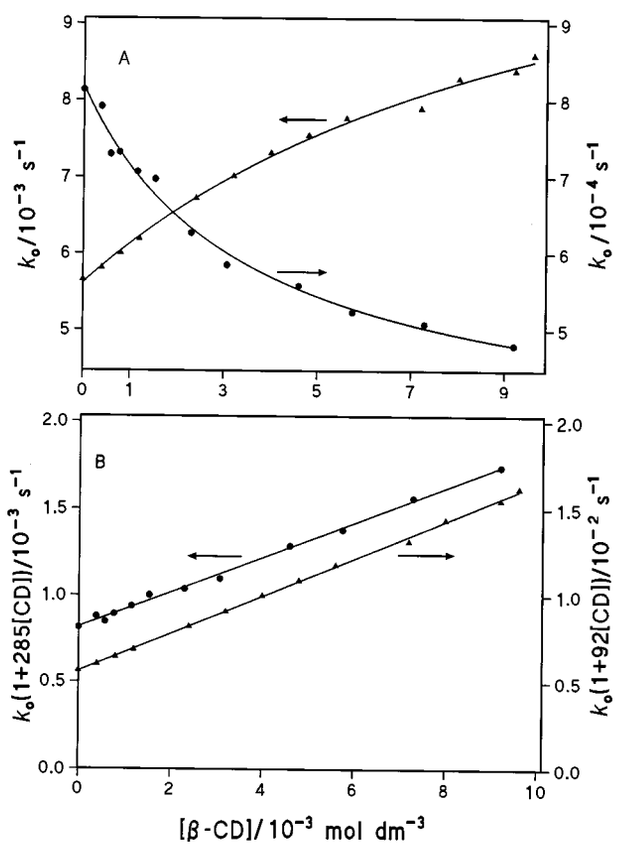


Fig. 8 A, Influence of β-CD concentration on the observed rate constant of the reaction of (●) cyclohexyl nitrite at [PyR] = 0.010 mol dm^{-3}, [OH$^-$] = 0.10 mol dm^{-3} and of (▲) 2-phenylethyl nitrite at [PyR] = 6.7×10^{-3} mol dm^{-3}, [OH$^-$] = 0.10 mol dm^{-3}; B, linearization of the data according to eqn. (6)

depending on the experimental conditions and on the nature of the alkyl nitrite. The measured values of k_o^w (= k_2[PyR], with PyR representing the unprotonated form), along with the determined values for the unknown parameters of k_c and K_c', are reported in Table 3.

We can now follow up on several situations, as elaborated below:

1-*Phenylethyl nitrite* (1-*PEN*).—The three sets of experimental results fit nicely into eqn. (6) if we allow that k_c is negligible. In the case of working with a buffer of pyrrolidine of pH 11.35, one may expect such conformity; thus, essentially no CD hydroxy group would be ionized; hence the inclusion complex formed between 1-PEN and neutral CD is unreactive. Furthermore, the value obtained for K_c' falls in line with this argument, permitting this parameter to compare quite well with that obtained for the acid medium (see Table 2). In the other two remaining situations, the pH of the reaction medium is higher than the pK_a of a secondary hydroxy group of β-CD. Therefore, the formation of a reactive inclusion complex is expected; but since the rate of the reaction with pyrrolidine is faster (>30 times) than the reaction of the complex (compare values of k_o^w and k_c in Table 3), aminolysis of 1-PEN is the only observed pathway. Nevertheless, the values determined for K_c'

reflect a situation of ionized β-CD; thus, they compare quite well with those obtained for the absence of pyrrolidine, being smaller than those obtained for acid hydrolysis.

Cyclohexyl nitrite (*CHN*).—Under the experimental conditions set, the reaction rate of the aminolysis pathway is approximately two times faster than the rate of the complex reaction, but the concentration of the complex is nearly three times that of the 1-PEN inclusion complex. Even though a greater percentage of the CHN decomposition goes through nitrosation with pyrrolidine, the increase of CD concentration causes a separation of the reagents, CHN and PyR, due to the formation of the less reactive inclusion complex. Therefore, the cyclohexyl nitrite included in the CD cavity reacts with the nucleophile CD–O^-, *i.e.* the ionized hydroxy group of the wider rim; whereas the CHN outside of CD reacts with pyrrolidine. Consequently, the k_c value agrees perfectly with that obtained in the absence of pyrrolidine.

tert-*Butyl nitrite* (*TBN*).—Measuring the basic hydrolysis of this alkyl nitrite is an extremely slow process, so only the reaction with pyrrolidine in basic medium was studied in the presence of β-CD. Independent from the use of a pyrrolidine-buffer of pH 11.35, or NaOH, to generate the basic medium, the observed rate constant always decreased when the [β-CD] increased. Nevertheless, the K_c' values obtained by fitting the experimental data to eqn. (6) with $k_c = 0$ depend on the acidity of the reaction medium, as expected.

2-*Phenylethyl nitrite* (2-*PEN*).—The inclusion complex of this alkyl nitrite proved to be more reactive than that of 1-PEN; in fact, under practically the same experimental conditions as 1-PEN ($[PyR] = 6.6 \times 10^{-3}$ mol dm^{-3} and $[OH^-] = 0.10$ mol dm^{-3}) the rate of the aminolysis pathway was only five times faster than the reaction of the inclusion complex. Therefore, the experimental results not only reflect the reaction of the complex, but an increase in the reaction rate through the increase of the host concentration (see Fig. 8B). But, contrary to what was observed in the case of CHN, the k_c value obtained in the presence of pyrrolidine was higher than the ones determined in its absence; meanwhile, the K_c' values are not only practically the same, but also very close to the values obtained for the acid medium. Both of these characteristics can be explained if one takes into account the degree of penetration in the cavity, which determines both the acceleration/retardation of the reaction rate and the reactivity of the guest. The value of K_c' reveals that this alkyl nitrite cannot be stabilized by hydrogen-bonding with the -OH groups of CD, due to the length of the molecule (see Scheme 4). On the basis of the bond length and the geometry of the molecule, one might calculate a value of 8.379 Å between the H-atom in the *para*-position of the phenyl ring and the N-atom of the nitroso group, *i.e.* slightly greater than the deepness of the CD cavity. Consequently, over an average of time, the −N=O group could be located quite outside the cavity, and then reaction of the complex with pyrrolidine is possible. The above explains the higher value of k_c obtained in the presence of pyrrolidine.

Rate acceleration (k_c/k_o^w).—This ratio measures the rate acceleration or retardation of the reaction at saturating levels of CD. Hydrolysis of RONO is accelerated by β-CD ($k_c > k_o^w$). The greatest acceleration is observed in the case of 2-PEN. However, in the presence of PyR, in which case a transnitrosation reaction occurs, a retardation of the reaction takes place, except in the case of 2-PEN, whose inclusion complex reacts also with pyrrolidine.

Substrate selectivity ($k_2^c = k_c K_s^N$).—k_2^c measures the reactivity of CD towards RONO. The values of k_2^c indicate, then, the ability of CD to select among different RONOs under non-saturating conditions, and variation of RONO structure provides clues to the mode of binding of RONO to the CD in the transition state of the nucleophilic reaction. Looking at the k_2^c values in Table 3, we might say that 2-PEN has the most favourable structure; by virtue of their small size, cyclohexyl and *tert*-butyl nitrites are located deep inside the CD cavity, and the methyl group of 1-PEN hinders the reaction, by comparison with 2-PEN. The hindrance is more severe in *tert*-butyl nitrite.

Conclusions

The acid hydrolysis of alkyl nitrites is inhibited by the presence of β-cyclodextrin due to the formation of 1:1 inclusion complexes that are unreactive or much less reactive than the RONO not complexed. The degree of inhibition increases with the greater association of the alkyl nitrite to CD: those with aromatic substituents interact more efficiently with the apolar CD cavity than do aliphatic alkyl nitrites. The basic hydrolysis of alkyl nitrites, at pH values higher than the pK_a of β-cyclodextrin, is powerfully catalyzed by the presence of β-cyclodextrin because the nucleophilic reaction of alkyl nitrite by an ionized secondary hydroxy group of CD is faster than the reaction with OH^-, *i.e.* the reaction rate of the complex is faster than that of the RONO not complexed. Finally, the influence of β-cyclodextrin on the reaction of alkyl nitrites in basic medium in the presence of pyrrolidine depends largely on the experimental conditions used and on the structure of the alkyl nitrite.

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