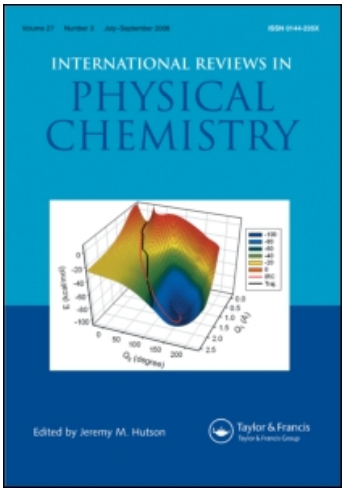

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Mechanisms of hydrolysis and nitrosation reactions of alkyl nitrites in various media

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We review some of the work that we have been doing in the field of chemical kinetics on the reactivity of alkyl nitrites in microorganized media. For comparative purposes, the reactivity of alkyl nitrites in water, organic solvents, aqueous β-cyclodextrin solutions and aqueous micellar solutions is reviewed. After a brief description of common properties of alkyl nitrites and of microorganized media, we report kinetic studies on the reactivity of alkyl nitrites. The emphasis is on three important reactions undergone by these reagents in solution, namely acid-catalysed hydrolysis, base-catalysed hydrolysis and NO-transfer reactions, mainly to amines to produce nitroso compounds. The principal features observed through the experimental study of these reactions allow reaction mechanisms in each reaction medium to be prepared; these give information on the constitution of the *transition state* and its energy characteristics, the presence of possible *intermediates*, the effects of structural variation on rate and the role of the solvent.

Contents

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1. Introduction

Nitrosation reactions have been much used synthetically and many aspects have been investigated from the mechanistic viewpoint. The chemistry of the nitroso compounds has also attracted considerable research effort owing to the proven toxic, carcinogenic, mutagenic and teratogenic effects of these substances (Montesano and Bartsch 1976, Pegg 1977, Yarosh 1985, Lijinsky 1992) on many animal species (Magee *et al*. 1976). In particular, since the discovery that nitrosamines are powerful carcinogens in all animal species that have been tested, the nitrosation of secondary amines has been widely studied, mainly from the viewpoint of the possible *in vivo* formation of nitrosamines from naturally occurring secondary amines and sources of nitrosating agents in foods and in water supplies.

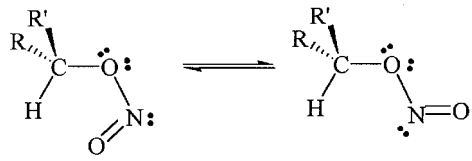
Alkyl nitrites are among the very few nitrosating agents that are effective at physiological pH or in basic media. The chemistry of the alkyl nitrites has been much studied in aqueous or organic solvents (Challis and Shuker 1979, Williams 1983, 1985, 1988, Crookes and Williams 1988, 1989, Patel and Williams 1989, 1990). In the past few years we have extended these investigations to microorganized or microcompartmentalized media, such as aqueous solutions of cyclodextrins (CDs), micelles or microemulsions (García-Río *et al*., 1993b).

In recent decades, novel chemistry of practical utility has been developed, based on mimicking membrane-mediated processes in relatively simple systems. Advantage can be taken of micelles, host–guest systems and polyions, together with microemulsions referred to collectively as membrane mimetic agents, to organize substrates and to alter microenvironments and reactivities, as well as to act as carriers. Membrane mimetic agents have been utilized in reactivity control, photochemical reactions and providing unique environments for substrates and enzymes. Surfactant monolayers and bilayers, as well as phospholipid vesicles, have been used the most extensively as membrane models. Biological membranes provide compartments of defined sizes, shapes and microenvironments (Fendler 1982). They organize living matter in the cell and allow for the controlled transport of solutes. Much of our chemical understanding of membrane structures has been obtained through the investigation of models.

2. Physicochemical characteristics of alkyl nitrites

2.1. *Physical properties of alkyl nitrites*

Alkyl nitrites (R-ONO) are *O*-nitroso compounds, which are very volatile yellow liquids (except methyl and ethyl nitrites which are gases at room temperature), and slightly soluble in water, but unstable. However, they are very soluble in organic solvents, such as dioxane or acetonitrile, and stable in dried solvents. Their ultraviolet (UV) spectra seem to consist essentially of two absorption bands: diffuse bands between 300 and 400 nm with approximately the same frequency interval of 1100 cm^{-1} and another absorption band, more intense, centred at approximately 220 nm. The relative intensities of the two bands vary strongly from one class of nitrite to another (primary, secondary or tertiary) but remain roughly constant within a given class. In the infrared (IR), the O-N=O group is characterized by very strong absorption in the three regions 600, 800 and 1650 cm^{-1}, corresponding to O-N=O bending, N-O stretching and N=O stretching frequencies respectively. Alkyl nitrites are *O*-nitroso compounds which can exist as a mixture of *cis* and *trans* isomers, see scheme 1.



Scheme 1. *Cis-trans* isomerism of alkyl nitrites.

From gas-phase IR and UV spectra it has been suggested (Tarte 1952) that the *cis* conformation should be more stable in the case of Me-ONO, while, for higher *n*-alkyl nitrites, the *trans* conformer has been proposed to be the most stable form. However, nuclear magnetic resonance experiments seem to indicate the opposite relative stabilities for *n*-alkyl nitrites (Piette *et al.* 1957). Quantum mechanical calculations of ethyl nitrite (Suter and Nonella 1997) indicate the existence of only three conformers of the four geometrically possible isomers with *cis* and *trans* configurations with respect to the C-O and O-N bonds.

2.2. *Synthesis of alkyl nitrites*

The most important methods used in the preparation of alkyl nitrites are derived from the action of cold dilute sodium nitrite ($NaNO_2$) on an aqueous solution of very pure alcohol and H_2SO_4 (Noyes 1943). The crude product must be desiccated and purified by repeated low-temperature distillation in vacuum, except for low-molecular-weight nitrites, which must be distilled at atmospheric pressure. However, some alkyl nitrites, such as *t*-butyl nitrite, are now commercial products. Since this alkyl nitrite undergoes rapid nitrosyl exchange with alcohols, that is,

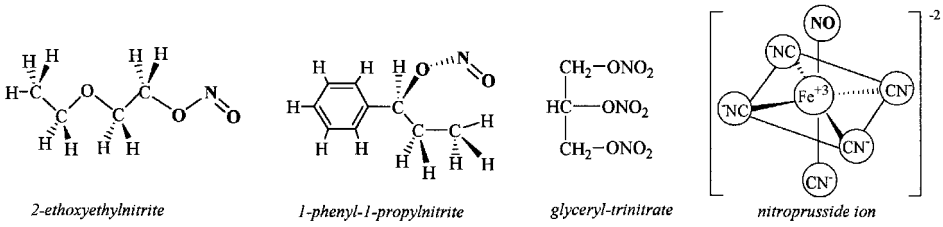
$$t\text{-Bu-ONO} + \text{R-OH} \rightleftharpoons t\text{-BuOH} + \text{R-ONO}, K, \quad (1)$$

and the equilibrium constant K of reaction for some alcohols (e.g. methanol, ethanol, *n*-propanol) is higher than 10 at room temperature either in inert organic solvents or even in the corresponding alcoholic solution (Doyle *et al.* 1983, Casado *et al.* 1984), the alkyl nitrites that are gases at room temperature or other structurally

more complex alkyl nitrites, derived for example from steroidal alcohols, may be prepared by this method.

2.3. *Biological properties of alkyl nitrites*

Alkyl nitrites undergo rapid nitrosyl transfer (NO transfer) to several nucleophiles. Biologically, NO was first characterized as an endothelial-derived relaxing factor, being formed by endothelial cells in blood vessels and diffusing to the adjacent smooth muscle to cause vasodilation. Blood pressure regulation, inhibition of platelet aggregation and neurotransmission are among the important physiological functions of NO (Moncada *et al.* 1991, Butler and Williams 1993, Averill 1996). When present at sufficient concentrations, however, NO and its nitrogen oxide derivatives have cytotoxic and mutagenic effects (Stamler *et al.* 1994, Tannenbaum 1995, Tannenbaum *et al.* 1995) owing to nitrosation of various secondary amine groups to form *N*-nitrosamines that may indirectly damage DNA, because nitrosamines can be metabolized to form strong alkylating electrophiles that react with DNA. A number of NO-donating compounds (alkyl nitrites, sodium nitroprusside, glyceryl trinitrate; see scheme 2) are recognized as vasodilators and used in the treatment of diseased conditions where increased blood flow is required. There has been considerable speculation that the oxidation of haemoproteins such as haemoglobin was due to the nitrite ion formed by the hydrolysis of alkyl nitrites (DiCarlo and Melgar 1970). The discovery in the late 1980s of NO biosynthesis in mammalian cells and numerous physiological roles of NO led to a virtual explosion of NO-related research, because NO not only represents the pharmacologically active species of nitrovasodilator drugs such as nitroglycerin but also is produced by vascular endothelial cells to regulate blood flow and thrombosis (Ignarro 1990, Snyder 1994, Fukuto and Ignarro 1997). With the aim of modelling biological NO-transfer processes in water, the reactivity of many systems, including that of the alkyl nitrites, has been investigated in organized structures such as aqueous solutions of CDs or of micellar aggregates.



Scheme 2. Molecular structures of some NO-generating compounds.

3. Physicochemical characteristics of microorganized media

3.1. *Cyclodextrins*

The cyclo-oligosaccharides composed of six, seven and eight D-glucopyranose units so as to give different structural forms are called α-, β- and γ-CDs respectively; see figure 1. The number of D-(+)-glucopyranose units defines the width of the central cavity and the flexibility of the compound. As a consequence of the $^4C_1$ conformation of the glucopyranose units, all secondary hydroxy groups are situated on one of the two edges of the ring, whereas all the primary ones are placed on the

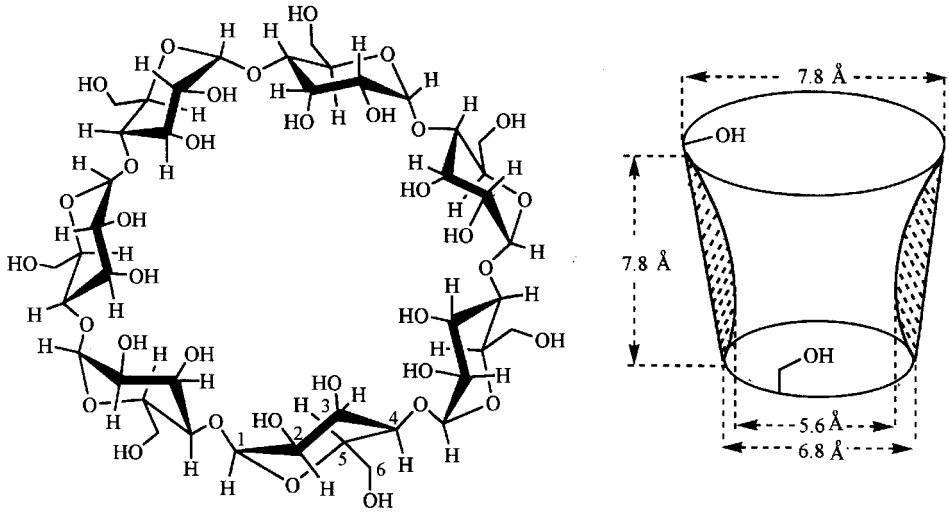


Figure 1. Molecular structure and dimensions of a β-CD molecule.

other edge. The ring in reality is a conical cylinder, which is frequently characterized as a doughnut- or wreath-shaped truncated cone. The cavity is lined by the H atoms and the glycosidic oxygen bridges (-O-). The non-bonding electron pairs of the glycosidic oxygen atoms are directed towards the inside of the cavity, producing there a high electron density and lending to it some Lewis base character. The C-2 OH groups of one glucopyranose unit can form a H bond with the C-3 OH group of the adjacent glucopyranose unit. In the β-CD molecule a complete secondary belt is formed by these H bonds, so that β-CD is a rather rigid structure. This probably explains the observation that β-CD has the lowest solubility of all CDs, since in the α-CD molecule the H bond belt is incomplete and the γ-CD molecule has a non-coplanar, more flexible structure. These three major CDs are crystalline, homogeneous, non-hygroscopic substances (Szejtli 1988, 1996a).

The most important feature of CDs is their cavity. Because of this, CDs are able to interact with a variety of ionic and molecular species to form non-covalent inclusion complexes (Connors 1996, Szejtli 1996b). Geometrical factors, such as size and shape, rather than chemical factors are decisive in determining the kind of guest molecule that can penetrate into the CD cavity. 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 physicochemical properties, as well as reactivities, result from such host–guest interactions (see, for example, Woncho *et al.* (1994), Tee *et al.* (1996), Iglesias and Fernández (1998) and Davies and Deary (1999)). The ability of CDs to form inclusion complexes means that these compounds can act as regulators of chemical and photochemical reactivity. In fact, CDs have proved to be the most enduringly popular enzyme mimics, catalysing or inhibiting various reactions (Tee 1994, Breslow and Dong 1998). 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 because CDs are weak acids. In basic media, a secondary OH group is ionized, giving thus a strong nucleophile host which may react with included electrophiles. The pK_a values of α-, β- and γ-CDs have been measured by potentiometry as 12.3, 12.2 and 12.0 respectively (Gelb *et al.* 1982).

3.2. *Micelles*

Surfactants or detergents are amphiphilic materials which contain both apolar hydrophobic, and polar hydrophilic, groups. Amphiphiles spontaneously organize themselves in water to create dynamic aggregates, called micelles, that impart unique properties to the solution. Micelles can be regarded as microreactors that influence reaction rates and equilibria by taking up reactants and providing a medium different from that of the bulk water solvent (Fendler and Fendler 1975, Romsted 1977, 1984, Bunton and Savelli 1986, Bunton 1991, Bunton *et al.* 1991). The observations of micellar effects on chemical reactivity and equilibria lead to the generalization that aqueous micelles could be regarded as submicroscopic reaction media or solubilization media. Micelles are small, relative to the wavelength of light. The dilute solutions of micellized single-chain surfactants are optical transparent, but they scatter light, and this property provided evidence for the formation of discrete micelles.

Micellization depends on a balance between hydrophobic and van der Waals interactions which bring monomers together and repulsions between the polar or ionic head groups. Nevertheless, a minimum length of the hydrophobic alkyl group is required for the formation of micelles in water, which is eight to ten methylene groups. The critical micelle concentration (CMC) decreases with increasing hydrophobicity of the apolar groups and for ionic amphiphiles also depends on the nature and concentration of counterions in solution. The CMC is a key property, because it is related to the free energy difference between monomers and micelles. The onset of micellization is detected by marked changes in such properties as surface tension, refractive index, solubilization of hydrophobic solutes, conductivity (for ionic micelles) and chemical reactivity.

Micelles are dynamic aggregates with an interfacial region separating the polar bulk aqueous phase from an apolar hydrocarbon-like region, which is formed by the hydrophobic tails. The interfacial region or Stern layer, having a width about the size of the surfactant head group, contains the ionic head groups of the amphiphile, a fraction of the counterions (60–90% of the surfactant monomers forming the micelle) and water (the micelle head groups and associated counterions are fully hydrated). The Stern layer is an extremely anisotropic region with properties intermediate between those of water and hydrocarbon (alcohol-like is the common description of its polarity); see figure 2.

4. Reactions of alkyl nitrites

Alkyl nitrites undergo both acid-catalysed and base-catalysed hydrolysis and can be used as electrophilic nitrosating agents quite generally, reacting with the same range of substrates as do other nitrosating agents. So R–ONO may transfer the NO group to amines, thiols, carbanions and other nucleophiles. In addition, alkyl nitrites are among the few nitrosating agents for basic media.

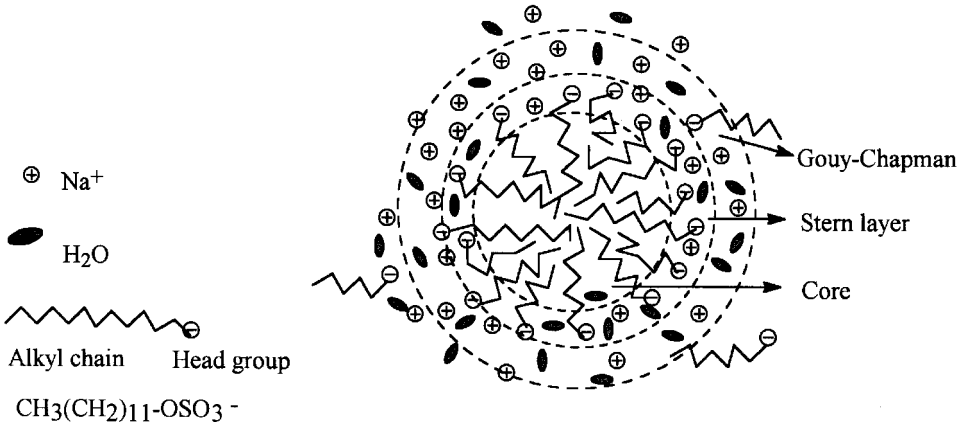


Figure 2. A two-dimensional schematic representation of an SDS micelle.

4.1. *Acid-catalysed hydrolysis*

4.1.1. *Acid hydrolysis reaction in water*

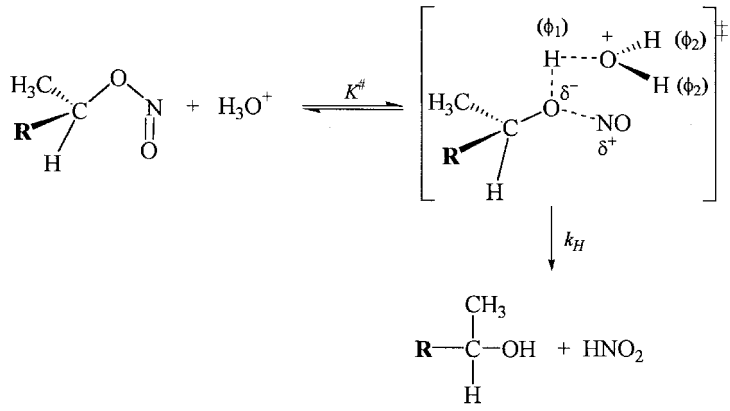
The hydrolysis of alkyl nitrites to the parent alcohol and nitrous acid in aqueous acid media is a very fast process (Iglesias *et al.* 1992). The reaction is not catalysed by nucleophiles such as Cl^- or Br^-. Reaction rates increase with the ionic strength of the medium and decrease with the dielectric constant of the reaction medium; for example, with the increasing percentage of dioxane according to data in table 1. The reaction is also subject to general acid catalysis:

$$\text{rate} = (k_H[H^+] + k_{HA}[\text{acid}])[\text{RONO}]. \quad (2)$$

The rate constants k_H for the H^+, along with the rate constants k_{HA} for the acetic acid, monochloroacetic acid and phosphate monoanion reactions, lead to a linear Brönsted plot with $\alpha = 0.62$. This result suggests that protonation is involved in the rate-controlling step. In addition, the ratio of the rate constants measured in water (k_H) and in D_2O (k_D) when the hydrolysis is promoted by H_3O^+ gives a solvent isotope effect of $k_H/k_D = 0.7$. This low value can be understood in terms of the fractionation factor theory (Melander and Saunders 1980). Given that L_3O^+

Table 1. Values of the pseudo-first-order rate constant, k_0, obtained in the acid-catalysed hydrolysis of iso-propyl nitrite at 25°C measured as a function of the acidity (controlled with HCl), ionic strength (controlled with $NaClO_4$) and the dioxane percentage.

Variable ionic strength		[HCl] = 0.022 M		[HCl] = 0.022 M	
k_0 (s^{-1})	$[H^+]$ (M)	k_0 (s^{-1})	I (M)	k_0 (s^{-1})	% dioxane (vol%)
1.99	0.005	13.7	0.06	9.95	5.5
4.91	0.010	15.5	0.18	8.26	10.5
7.79	0.015	16.9	0.30	5.17	20.5
16.7	0.030	18.0	0.42	2.72	30.5
22.5	0.040	19.9	0.54	1.38	40.5
28.9	0.050	22.1	0.78	0.29	60.5
32.5	0.067	—	—	0.12	80.5



Scheme 3. Mechanism of the acid-catalysed hydrolysis of alkyl nitrites.

($L^+ = H^+$ or D^+) is the proton donor, then $k_H/k_D = l^3/(\phi_1\phi_2^2)$ (see scheme 3), where l ($= 0.69$) is the fractionation factor of the three sites in the reactant L_3O^+; ϕ_1 corresponds to the hydrogen being transferred in the transition state and ϕ_2 is the fractionation factor of the other two hydrogens, which are in an intermediate state between that of L_3O^+ and that of water ($\phi_2 = 1$). The fractionation factor of RONO is assumed to be unity, as is usual for uncharged substrates (Isaacs 1987). Assuming that the fractional extent of hydrogen transfer in the transition state measures the same properties of the transition state as the Brönsted exponent, then $\phi_2 = l^{1-\alpha}$, and a value of $\phi_2 \approx 0.92$ could be determined. This value conforms with a transition state of the reaction formed in a concerted process ($0.4 < \phi_1 < 0.7$) with an imbalanced transition state ($\alpha > 0.5$) (Bernasconi 1992a,b) in which a significant negative charge has been developed on the O atom prior to proton transfer. The situation can be appropriately represented by reaction-coordinate diagrams of the kind described by More O'Ferrall (1970) and Jencks (1972) displayed in figure 3 in which the horizontal axis represents the protonation process and the vertical axis the O-N bond-breaking process. The broken straight line represents the route followed by the transition state in a balanced concerted mechanism, that is when both precesses are perfectly synchronized, whereas the full curve represents the approximate position of the transition state suggested by the kinetic results obtained in the acid hydrolysis of RONO; according to them and possibly because of the high electronegativity of the O atom, the N-O bond breaking somewhat leads protonation.

Table 2 shows values of k_H and k_{HA} (for the case of acetic acid catalysis). When comparing the reactivities of the different alkyl nitrites, one observes the following. First, the H^+-catalysed pathway occurs more than 5×10^3 times faster than the general acid-catalysed pathway; second, tertiary alkyl nitrites hydrolyse somewhat faster than secondary ones and primary ones; third, the most striking feature is the much higher reactivities of alkyl nitrites with the electron-withdrawing substituents: the more electronegative the alkyl nitrite's O substituents, the faster its hydrolysis.

The acid hydrolysis of alkyl nitrites is inhibited by the addition of non-electrolytes, such as ureas (Iglesias and Montenegro 1995) and amides (Iglesias and Montenegro 1996). The inhibition is due to protonation of the non-electrolytes. Both ureas and amides are weak bases; thus their protonation in strong mineral acid

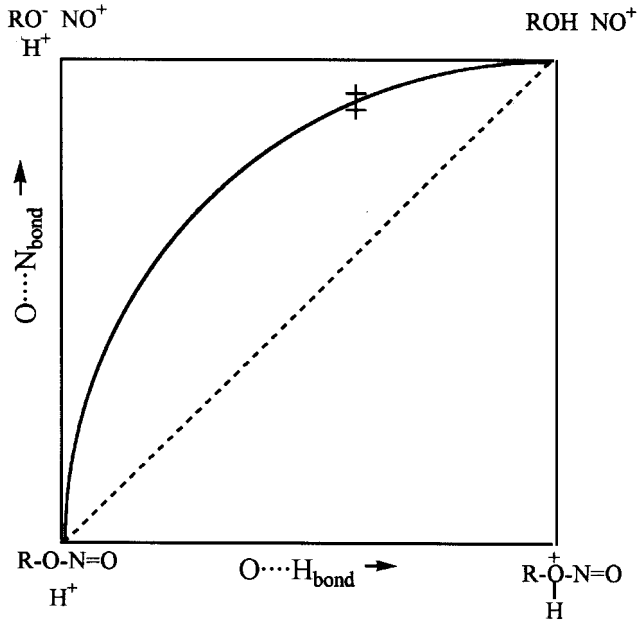


Figure 3. Qualitative reaction coordinate energy diagram postulated for the acid hydrolysis of alkyl nitrites.

Table 2. Values of k_H and k_{HA} (for acetic acid) obtained at 25°C for the acid hydrolysis of alkyl nitrites as a function of the O substituent: R– in R–ONO.

R– (in R–ONO)	k_H ($mol^{-1}\,dm^3\,s^{-1}$)	k_{HA} ($mol^{-1}\,dm^3\,s^{-1}$)
CH_3–	378	0.040
CH_3–CH_2–	541	0.036
$(CH_3)_2CH$–	584	0.042
$(CH_3)_3C$–	953	–
$C_2H_5O(CH_2)_2$–	860	0.0679
$ClCH_2CH_2$–	1869	–
$BrCH_2CH_2$–	1314	–
Ph-CH_2CH_2–	756	–
Ph-$(CH_3)CH$–	695	–
C_6H_{11}–	693	–
Ph-$(CH_2)_3$–	469	0.078
Ph-$C(CH_3)_2$–	1163	0.243

decreases the effective $[H^+]$ in the aqueous medium (scheme 4). A detailed kinetic study made it possible to determine the acid ionization constants of both ureas (K_{UH}) and amides (K_{AH}). Some of the results obtained are reported in table 3.

$$UH^+ \overset{K_{UH}}{\rightleftharpoons} U + H^+$$

$$RONO + H_3O^+ \xrightarrow{k_H} ROH + HNO_2 + H^+$$

Scheme 4. Kinetic scheme of the inhibition by ureas or amides of the acid hydrolysis of alkyl nitrites.

Table 3. Acidity constants of some ureas and amides determined from the kinetic study of the influence of both kinds of compound on the acid-catalysed hydrolysis of 1-phenylethyl nitrite and literature values in parentheses (Perrin *et al.* 1981, Stewart 1985, Wada and Takenaka 1971).

Urea	K_{UH} (M)	Amide	K_{AH} (M)
Urea	0.75 (0.79, 0.63)	Formamide	1.23 (0.76, 1.78)
Methylurea	1.30	Methylformamide	2.40 (0.71, 1.10)
Ethylurea	0.64	Dimethylformamide	1.71 (1.02, 1.55)
Dimethylurea	0.60	Methylacetamide	1.11 (1.29, 2.60)
Tetramethylurea	0.63	Dimethylacetamide	0.65 (0.56, 1.90)

4.1.2. *Acid hydrolysis reaction in aqueous β-CD solutions*

The influence of β-CD on the acid-catalysed hydrolysis of RONO has been analysed in both strong mineral acid (HCl) and aqueous buffered solutions of acetic acid–acetate (Iglesias 1998, Iglesias and Fernández 1998). The study of the influence of $[H^+]$ at fixed β-CD concentrations revealed no changes in the reaction mechanism due to the presence of β-CD. In this sense, k_0 versus $[H^+]$ describes good straight lines with negligible intercept at the origin, which means that the uncatalysed reaction is not significant. The plot of k_0 versus [buffer] at fixed pH results also in a straight line but with significant intercept at the origin owing to the reaction pathway via H^+. In both experimental situations the slope of the line, as well as the intercept at the origin in the latter case, obtained in the presence of fixed amounts of β-CD is lower than the values obtained in water. These findings are consistent with the formation of unreactive or less reactive inclusion complexes between RONO and β-CD. In fact, addition of β-CD strongly inhibits the acid hydrolysis of RONO promoted in either strong mineral acid or aqueous buffered solutions of acetic acid–acetate; see figure 4.

The structure of the alkyl nitrite is of key importance in predicting the observed effect. For example, 2-ethoxyethyl nitrite (EEN) is supposed to form inclusion complexes with β-CD (*vide infra*). However, the rate of its acid-catalysed hydrolysis is unaffected by β-CD addition. This experimental observation could be understood by looking at the possible structure of the complex EEN·β-CD: if the ether O atom forms H bonds with secondary -OH groups of the wide rim of β-CD, then this geometry of the complex will leave the O-N=O group quite outside the β-CD cavity; thus, the nucleophilic centre toward H^+ is immersed in the aqueous medium, and, therefore, no changes in the reactivity could be expected. For the other RONO investigated, the acid-catalysed hydrolysis is strongly inhibited by the presence of β-CD owing to the formation of inclusion complexes of stoichiometry 1:1 which are unreactive or much less reactive than uncomplexed RONO. Experimental kinetic results can be explained by means of scheme 5. Some values of rate and equilibrium constants appearing in this scheme are collected in table 4.

4.1.3. *Acid hydrolysis reaction in aqueous micellar solutions*

The acid-catalysed hydrolysis of several alkyl nitrites has been studied in aqueous micellar solutions of cationic and anionic surfactants (Iglesias *et al.* 1993) as well as in non-ionic micelles or in mixed micelles of anionic and non-ionic surfactants (Freire *et al.* 1994, Iglesias and Montenegro 1999).

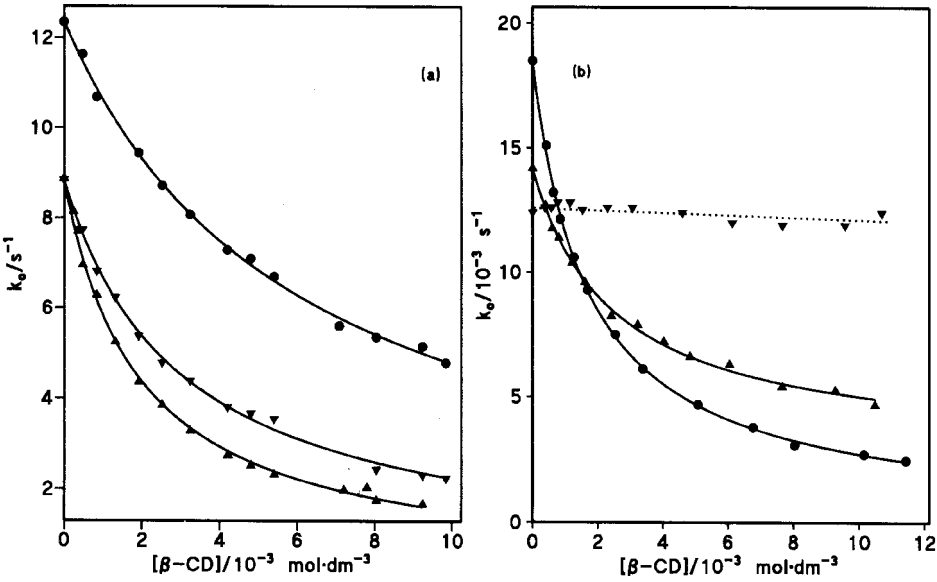
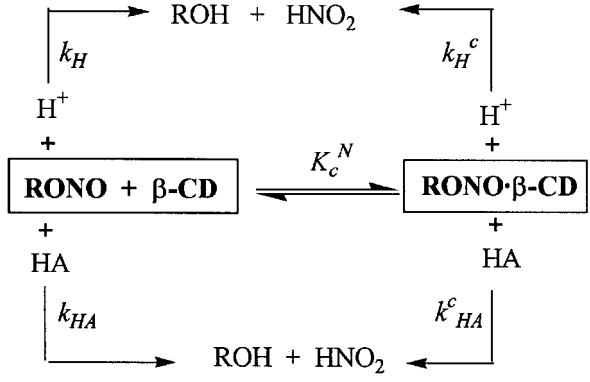


Figure 4. Variation of k_0 (25°C) as a function of [β-CD] for the acid hydrolysis of alkyl nitrites performed in (*a*) aqueous hydrochloric acid (0.014 M; ●, *t*-butylnitrite; ▼, 1-phenylethyl nitrite; ▲, cyclohexyl nitrite) and (*b*) a buffer of 0.020 M of acetic acid–acetate of pH 4.89 (●, 2-phenyl-2-propyl nitrite; ▲, 3-phenyl-1-propyl nitrite; ▼, 2-ethoxyethyl nitrite).



Scheme 5. Mechanism for the acid hydrolysis of alkyl nitrites in the presence of β-CD.

Both cationic and non-ionic micelles inhibit the reaction (figure 5), and rate–surfactant concentration profiles can be analysed quantitatively with regard to the distribution of alkyl nitrites between micellar and aqueous phases which, according to the simple pseudophase model, are treated as separate reaction media (scheme 6). On the basis of this model, the overall reaction rate constant k_0 is be the sum of the contributions of rate constants k_w in water and the rate constants k_m in micelles and therefore depends on the distribution of reactants between each pseudophase and the appropriate rate constants in each pseudophase. The inhibition arises because with cationic micelles the H^+ is excluded from the cationic surface owing to electrostatic repulsions; in the case of non-ionic micelles the uncharged micellar surface cannot

Table 4. Rate constants and stability constants (K_c^N) of the complex RONO·CD obtained in the kinetic study of the influence of β-CD concentration on the acid hydrolysis of alkyl nitrites studied in hydrochloric acid and in acetic acid–acetate buffer.

R–ONO	k_H ($M^{-1}\,s^{-1}$)	k_H^c ($M^{-1}\,s^{-1}$)	k_{HA} ($M^{-1}\,s^{-1}$)	k_{HA}^c ($M^{-1}\,s^{-1}$)	K_c^N ($mol^{-1}\,dm^3$)
$CH_3(CH_2)_3$–	522	~0	–	–	50
$CH_3(CH_2)_5$–	479	~0	–	–	141
$(CH_3)_3C$–	914	74	0.165	0.016	158
EtO–$(CH_2)_2$–	860	—	—	—	Unknown
cyclo–C_6H_{11}–	667	~35	0.030	~0.0016	538
Ph–CH–CH_3	673	66	0.135	0.013	320
Ph–$(CH_2)_3$–	469	53	0.078	0.019	355
Ph–CH–CH_2CH_3–	545	~0	0.061	~0	530
Ph–$C(CH_3)_2$–	1163	~0	0.243	~0	589

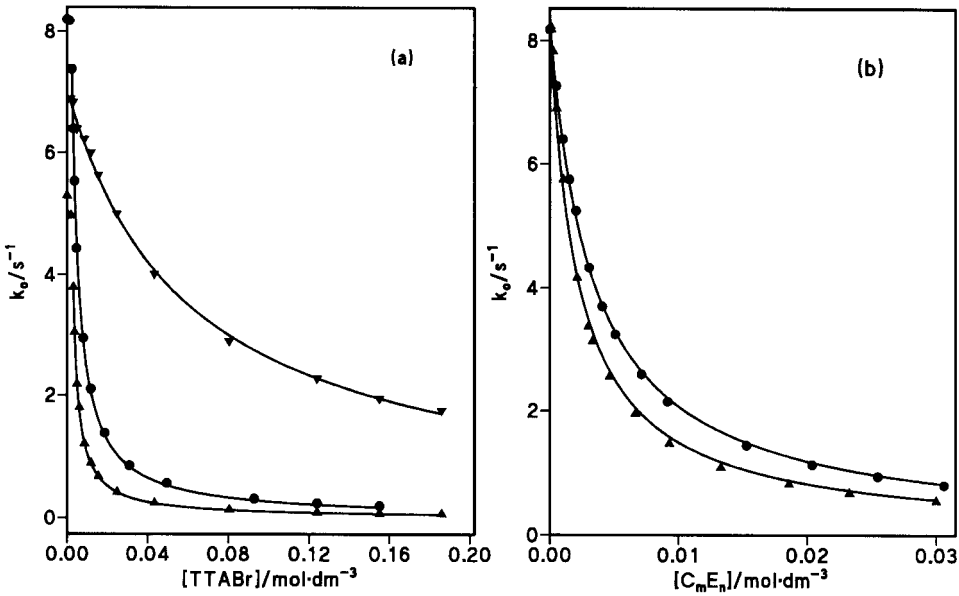
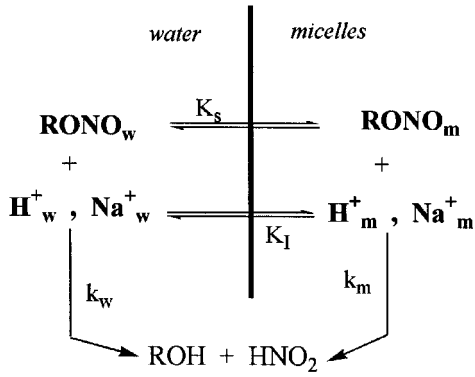


Figure 5. Variation of the overall rate constant for the acid hydrolysis of alkyl nitrites performed in aqueous micellar solutions of (*a*) TTABr (▼, *n*-propyl nitrite; ●, 1-phenylethyl nitrite; ▲, *n*-hexyl nitrite) and (*b*) $C_{12}E_9$, poly(ethylene oxide)-9-dodecyl-ether (●) and $C_{16}E_{20}$, poly(ethylene oxide)-20-cetyl-ether (▲) for the acid hydrolysis of 1-phenylethyl nitrite, measured at 25°C in 0.013 M of HCl.

interact with H^+ ions either coulombically or specifically because of the high hydrophilic character of H^+. As a consequence there can be no increase in the concentration of the reactive ions in the micellar interface; $[H^+]$ at the micellar interface will be much smaller than that of the bulk water pseudophase, and then the reaction at the micellar phase can be negligible and the following equation applies, where $k_w = k_H[H^+]$, K_s^N is the binding constant of the alkyl nitrite to the corresponding micelles and [Dn] represents the micellized surfactant concentration,



Scheme 6. Acid hydrolysis of alkyl nitrites in SDS micelles.

that is the total concentration of the surfactant less the concentration of the monomeric surfactant given by the CMC:

$$k_0 = \frac{k_H[H^+]}{1 + K_s^N[Dn]}. \quad (3)$$

Some values of k_H are reported in table 2, and those of K_s^N obtained for different alkyl nitrites are given in table 5.

Anionic micelles of SDS catalyse the acid hydrolysis of RONO at low surfactant concentration; the overall reaction rate goes through maxima and decreases at still higher [SDS] (figure 6). The appearance of maxima reflects the opposing effects of [SDS] increments: on the one hand the acceleration of the reaction, due to the micelles concentrating the reagents in the small volume of the micellar pseudophase, and, on the other, deceleration due to both dilution of H^+ within micelles with increasing [SDS] and exclusion of H^+ from the micellar interface by competition

Table 5. Binding constants (K_s^N in $mol^{-1}\,dm^3$) of alkyl nitrites (R–ONO) to TTABr micelles, to $C_{16}E_{20}$ micelles and to SDS micelles and the bimolecular rate constants, k_2^m, for the acid hydrolysis of alkyl nitrites in the SDS micellar interface (k_2^m values correspond to $V = 0.14\,dm^3\,mol^{-1}$).

Number	R–	K_s^N (TTABr)	K_s^N ($C_{16}E_{20}$)	K_s^N (SDS)	k_2^m ($mol^{-1}\,dm^3\,s^{-1}$)	k_2^w/k_2^m
1	CH_3–	1.6	5.5	–	–	–
2	CH_3CH_2–	4.9	12.8	3.3	51	10.5
3	$CH_3(CH_2)_2$–	17	31.5	10.6	29	18.5
4	$CH_3(CH_2)_3$–	49	81.4	24	27	18.7
5	$CH_3(CH_2)_4$–	168	305	52	24	20
6	$CH_3(CH_2)_5$–	584	1090	140	19	24.3
7	$CH_3O(CH_2)_2$–	1.6	4.3	2.3	134	7.05
8	$BrCH_2CH_2$–	15.5	28	5	188	8.2
9	$(CH_3)_3C$–	32	62	9	78	11.4
10	C_6H_5–$(CH_2)_2$–	230	393	46	56	13.5
11	C_6H_5–$(CH_3)CH$–	309	510	79	45	14.7

TTABr, tetradecyltrimethylammonium bromide; $C_{16}E_{20}$, poly(ethylene oxide)-20-cetyl-ether (CH_3–$(CH_2)_{15}$–$(O$–$CH_2CH_2)_{20}$–OH); SDS, sodium dodecylsulphate.

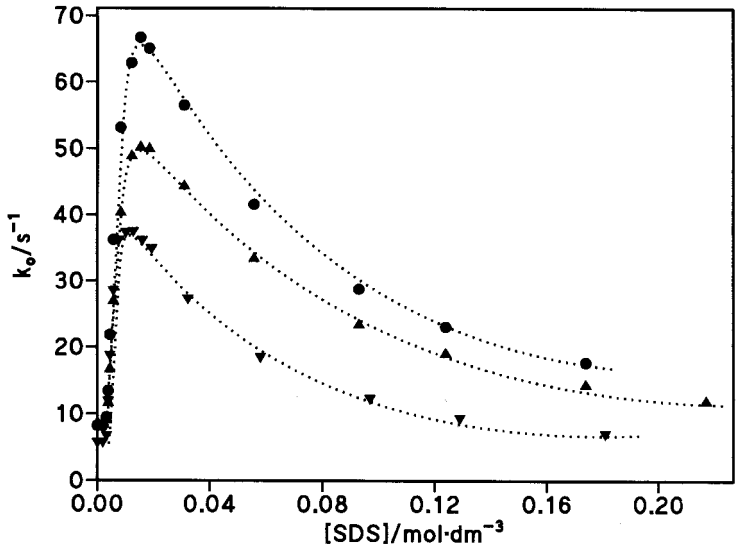


Figure 6. Effect of [SDS] on the overall rate constant measured for the acid hydrolysis of 1-phenylethyl nitrite (●), cyclohexyl nitrite (▲) and *n*-hexyl nitrite (▼) carried out at 25°C and 0.013 M of HCl.

from increasing Na^+ concentrations in accordance with the equilibrium $Na_w^+ + H_m^+ \rightleftharpoons Na_m^+ + H_w^+, K_I$, where subscripts w and m refer to the aqueous and micellar phases respectively, and K_I is the corresponding equilibrium ion-exchange constant which takes values between 0.6 and 1 (Bunton and Wolfe 1973). The relative contributions of these competing factors result in the experimental maximum. Therefore, the shapes of k_0–[SDS] profiles are typical of an ionic exchange process. The concentration of H^+ at the micellar surface of SDS depends on competition with inert surfactant counterions of Na^+, and this competition can be treated quantitatively by the pseudophase ion-exchange model developed by Romsted (1985).

The quantitative treatment of the observed behaviour can be made through

$$k_0 = \frac{k_2^w[H^+]_t + (k_m K_s^N - k_2^w) m_H [Dn]}{1 + K_s^N[Dn]}, \tag{4}$$

where m_H ($= [H^+]_m/[Dn]$) may be calculated according to the following equation, easily derived from the mass balance equations and the equilibrium condition given by K_I by assuming a constant value of $\beta = ([H^+]_m + [Na^+]_m)/[Dn]$, the degree of micelle neutralization:

$$m_H^2 + m_H \left\{ \frac{[H^+]_t + K_I[Na^+]_t}{(K_I - 1)[Dn]} - \beta \right\} - \frac{\beta[H^+]_t}{(K_I - 1)[Dn]} = 0. \tag{5}$$

Typical values of k_m reported in table 5, along with values of K_s^N, indicate that the reactivity in water is 4–25 times higher (compare with data in table 2) than that in the micellar pseudophase, owing to the lower polarity of the micellar interface with respect to that of the water phase. A comparison between the relative reactivities found in both pseudophases, i.e. the values of k_2^w/k_2^m, where $k_2^m = k_m/V$, with V being the volume of the micellar pseudophase where the reaction takes place and

assumed to be 0.14 $dm^3\,mol^{-1}$ (Bunton *et al.* 1978), leads to the result that, within a homologous series of alkyl nitrites (methyl, ethyl, *n*-propyl, *n*-butyl, *n*-pentyl and *n*-hexyl nitrites), the ratio k_2^w/k_2^m increases slightly along the series, that is with the hydrophobic character of the substrate. This result reveals the anisotropic properties of the micellar interface, in particular the degree of hydration decreases with deeper penetration in the micelle. On the other hand, the relative degree of catalysis, that is k_0^{max}/k_w with k_0^{max} being the maximum value of the overall rate constant obtained in aqueous SDS micellar solutions, increases with the hydrophobicity of the alkyl nitrite, which means that the percentage of the reaction which goes in the micellar phase increases with the degree of association of the substrate to the micelle.

Concerning the association constants of alkyl nitrites and a given kind of micelle, the driving forces for the partition between both phases depend intimately on the molecular structure of the substrate. For a series of linear alkyl nitrites, the values of K_s^N increase with the van der Waals interactions between the micellar core and the alkyl chains of alkyl nitrites; these interactions increase with the exposed molecular surface, that is with the alkyl chain length. In this sense, the plot of $\ln K_s^N$ against N^0 (the number of C atoms in the alkyl chain of R-ONO) is linear; moreover, the K_s^N values of those alkyl nitrites with branched alkyl chains have been found to be lower than those of the corresponding compounds with straight chains, and thus branching in the chain results in less surface area than for the corresponding straight chain, and, finally, the alkyl nitrites bearing a halogen atom have higher association constants, which indicates that a halogen atom is simply equivalent to a hydrocarbon residue of the same size in its direct effect of permeability through interfaces (Iglesias *et al.* 1993). On the other hand, the presence of an aromatic ring decreases the value of the binding constant. Hydrogen bonds between aromatic π-electrons and hydroxyl groups of the water molecules at the interface cause molecules containing aryl moieties to reside on the average in a more aqueous region of the micelle than that occupied by compounds with aliphatic alkyl chains. However, the existence of charge-transfer complexes between aromatic π-electrons and head groups of cationic surfactants will favour micellar incorporation of aromatic compounds compared with their association with anionic micelles.

Finally, the value of the binding constants K_s^N increases with the hydrophobicity of the micelle, that is with the number of C atoms in the alkyl chain of the surfactant; the linear relationship found between K_s^N and the number of C atoms in the alkyl chain of the surfactant indubitably indicates that the distribution of alkyl nitrites between the aqueous and micellar interfaces is mainly due to hydrophobic interactions (Freire *et al.* 1994).

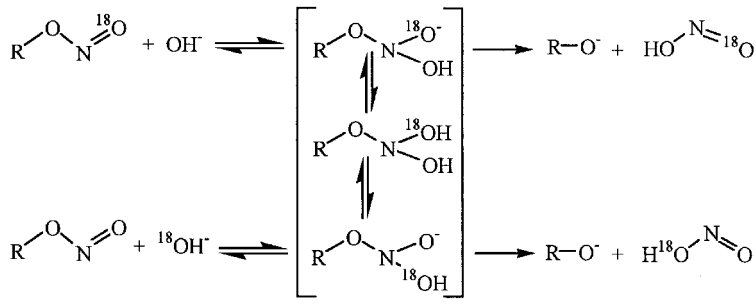
4.2. *Base-catalysed hydrolysis*

4.2.1. *Basic hydrolysis reaction in water*

Compared with structurally equivalent carboxylic esters, alkaline hydrolysis of alkyl nitrites is much slower while acid hydrolysis of alkyl nitrites is markedly faster than that of the corresponding ester.

Pioneering work on the hydrolysis of alkyl nitrites was carried out by Allen (1954) who determined the kinetics of hydrolysis of *n*-propyl and *t*-butyl nitrite and confirmed O-N bond fission. Later, Kobayashi (1972) reported oxygen exchange between iso-amyl nitrite and solvent water in an addition–elimination mechanism. Oae *et al.* (1978a) have found that accurate results about the hydrolysis mechanism could only be obtained when the original organic compound is labelled with ^{18}O but

not when ^{18}O-enriched aqueous media are used as the only ^{18}O-labelled compound. Therefore, the authors carried out the alkaline hydrolysis of ^{18}O-labelled *n*-hexyl nitrite and the results demonstrated that no O exchange took place between *n*-hexyl nitrite and OH^- during alkaline hydrolysis, even up to 80% completion of the reaction at both 45.0 and 55.1°C, thus revealing that OH^- attacks nitrogen exclusively, as is displayed in scheme 7.



Scheme 7. Isotopic exchange for the base-catalysed hydrolysis of alkyl nitrites.

The kinetic study, carried out by Oae *et al.*, of the alkaline hydrolysis of several alkyl nitrites conducted in 61% dioxane–water indicates the following. First, there is no possibility that NO_2^-, generated by the reaction, competes with OH^- as the nucleophile during the reaction because true second-order rate constants, k_{OH}, are obtained; second, the effects of substituents on the departing alkoxide group are characterized by a ρ^* value of $+2.54$ for the alkaline hydrolysis of alkyl nitrites (or $+1.46$ for substituted benzyl nitrites) and a Taft δ value of 1.03 (whereas the Taft δ values for alkyl benzoates and alkyl acetates are 1.52 and 1.50 respectively), signifying a larger polar effect and a smaller steric influence on alkyl nitrites in comparison with the ester hydrolysis.

More recently, Doyle *et al.* (1983) reported the results of the hydrolysis of several alkyl nitrites in 55% acetonitrile–water under neutral conditions of phosphate-buffered aqueous media. The results indicate that alkyl nitrites undergo relatively slow hydrolysis with small but significant dependence on structure. Primary alkyl nitrites are relatively insensitive to steric influence, but increasing alkyl substitution at the β-position of alkyl nitrites facilitates hydrolysis; however, the effect is small.

Very recently, the basic hydrolysis of alkyl nitrites in water was considered (Fernández *et al.* 1995, Iglesias 1998). The reaction is catalysed by OH^-, that is the observed rate constant increases in proportion to $[OH^-]$ ($k_0 = k_{OH}[OH^-]$), and also by the trifluorethoxide (TFE) anion, in which case a linear relationship between the overall rate constant and the concentration of TFE anion was found:

$$k_0 = k_{OH}[OH^-] + k_{TFE}[TFE]. \tag{6}$$

Figure 7 shows the variation of k_0 as a function of both [TFE] and $[OH^-]$ for the case of 2-ethoxyethyl nitrite and 2-bromoethyl nitrite respectively. OH^- is the hardest nucleophile, whereas the TFE anion is a softer nucleophile than OH^-; then, in accordance with Pearson's principle of hard and soft acids and bases (HSAB), the reaction between TFE anion and alkyl nitrites should be faster than with OH^-. Data in figure 7 corroborate this statement. Some bimolecular rate constants obtained in

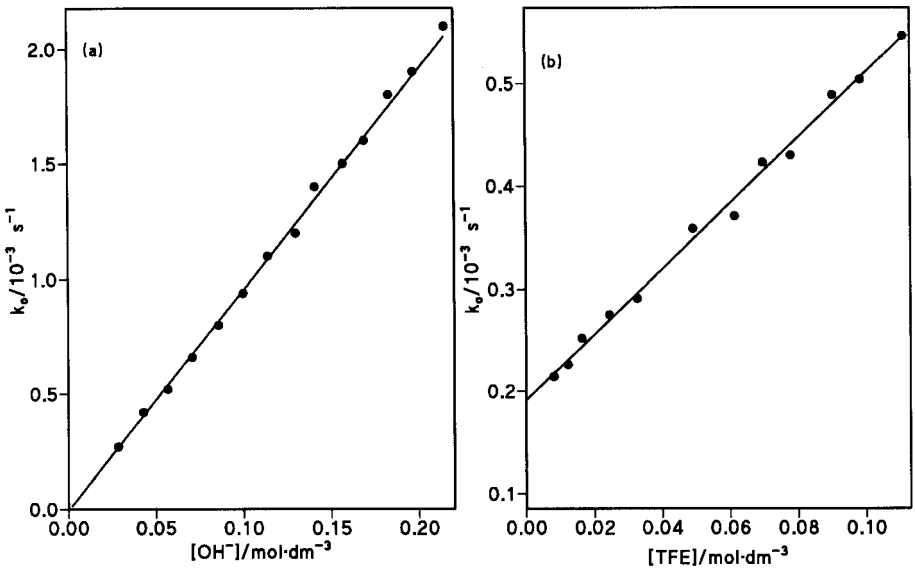


Figure 7. (*a*) Alkaline hydrolysis of 2-bromoethyl nitrite catalysed by OH^- and (*b*) catalysis by the TFE anion of the alkaline hydrolysis of 2-ethoxyethyl nitrite measured in 0.20 M of NaOH at 25°C.

the alkaline hydrolysis of different alkyl nitrites are collected in table 6, along with some for carboxylic esters for comparative purposes.

The previous characteristic features can be rationalized as follows. The N atom in alkyl nitrites retains a pair of unshared electrons, unlike the C atom in the carboxylic esters. On the other hand the electronegativity of N is greater than that of C (Pauling electronegativities are 3.5 for O, 3.1 for N and 2.5 for C). Such properties may

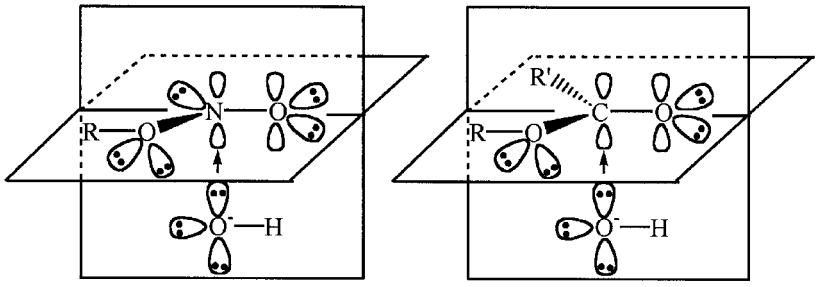
Table 6. Bimolecular rate constants obtained in the basic hydrolysis by OH^- or by anion TFE of nitroso compounds and esters at 25°C.

Substrate	k_{OH} ($mol^{-1}\,dm^3\,s^{-1}$)	k_{TFE} ($mol^{-1}\,dm^3\,s^{-1}$)	Medium
MNTS	0.127	–	23 vol% ethanol–water
2-Bromoethyl nitrite	0.010	–	Water
n-Pentyl nitrite	1.0×10^{-4}	2.6×10^{-4}	Water
2-Ethoxyethyl nitrite	9.5×10^{-4}	3.2×10^{-3}	Water
3-Phenyl-1-propyl nitrite	2.2×10^{-4}	5.3×10^{-4}	Water
1-Phenyl-1-propyl nitrite	4.7×10^{-4}	8.1×10^{-4}	Water
n-Butyl nitrite	7.5×10^{-5}	2.3×10^{-4}	Water
1-Phenylethyl nitrite	5.2×10^{-4}	–	Water
1-Phenylethyl nitrite	1.2×10^{-4}	–	61 vol% dioxane–water, 35°C
Cyclopentyl nitrite	2.6×10^{-5}	–	Water
Cyclopentylbenzoate	1.2×10^{-3}	–	61 vol% dioxane–water, 35°C
1-Phenylethylbenzoate	2.1×10^{-3}	–	61 vol% dioxane–water, 35°C
2-Phenylethylbenzoate	7.8×10^{-3}	–	61 vol% dioxane–water, 35°C
Benzylbenzoate	6.8×10^{-3}	–	61 vol% dioxane–water, 25°C
n-Propyl-formate	41.2	–	Water

MNTS, *N*-methyl-*N*-nitrosotoluene-*p*-sulphonamide.

account for the differences observed between the behaviour of both family compounds, alkyl nitrites and carboxylic esters, in the following way. A lone pair is considered to be less bulky than any alkyl group; then steric hindrance in the transition state of the reaction of the alkyl nitrite must be smaller than that of the corresponding carboxylic ester. However, when the rate of the reaction of the alkyl nitrite is compared with that of an ester derived from formic acid which is sterically similar, the reaction of the formate ester is about 10^5 faster than the corresponding nitrite. This difference in rates might be explained as follows.

The interaction between nucleophiles and electrophiles is expressed by two terms, an electrostatic and an orbital interaction term. When the reaction is charge controlled, the electrostatic term dominates over the other; in this case a large energy gap separates the highest occupied molecular orbital (HOMO) of a nucleophile from the lowest unoccupied molecular orbital (LUMO) of an electrophile. The contrary situation corresponds to an orbital-controlled reaction, that is when the HOMO of a nucleophile and the LUMO of the electrophile are near in energy. The OH^- is a typical hard nucleophile which favours the charge-controlled reactions. Since the electronegativity difference between C and O is large, an ester is a hard enough electrophile to give charge-controlled reactions and reacts with OH^- at fast rates. By contrast, the electronegativity difference between N and O is small, i.e. the nitroso group (-N=O) is less polarized than the carbonyl group (>C=O), and thus the nitroso group is considered to be a soft electrophile which reacts faster with soft nucleophiles than with hard nucleophiles. Therefore, the rate of OH^- attack on an alkyl nitrite is slower than on a carboxylic ester. On the other hand, by considering the stability of the transition state of the reactions of both substrates with OH^- illustrated in scheme 8, it is not difficult to understand that the transition state generated with carboxylic esters is more stable than that of alkyl nitrites owing to the repulsions between the lone pair of nitrogen and that of OH^-, while this type of lone pair–lone pair interaction is absent in the reaction between OH^- and carboxylic esters.



Scheme 8. Frontier-orbital approach in the transition state of the basic hydrolysis of alkyl nitrites and carboxylic esters.

4.2.2. *Basic hydrolysis reaction in aqueous β-CD solutions*

The basic hydrolysis of several alkyl nitrites has been studied in aqueous β-CD solutions (Iglesias and Fernández 1998, Iglesias 1998, 2000). CDs behave as weak acids in water; the acid dissociation of α-, β- and γ-CDs was studied potentiometrically as a function of temperature (Gelb *et al.* 1980, 1982). Acid dissociation involves both C_2 and C_3 secondary hydroxyl groups. The pK_a values depend

strongly on the temperature. At 25 °C the pK_a value of β-CD has been measured as 12.30. This means that in aqueous β-CD solutions of [OH^-] higher than 0.10 M, approximately, the entire amount of β-CD molecules has ionized the C_2 or C_3 -OH group, and then the possible formation of inclusion complexes must consider an anionic host.

The influence of β-CD on the alkaline hydrolysis of several alkyl nitrites has been studied at [OH^-] of both 0.10 and 0.20 M. Except for those alkyl nitrites whose alkaline hydrolysis reaction in water is relatively fast, such as for EEN, with the other alkyl nitrites there is no noticeable difference between the kinetic results obtained at whatever OH^- concentration. The effect of increasing [β-CD] is a strong catalysis of the reaction giving rise to saturation kinetics at high [β-CD] (figure 8). However, among the studied alkyl nitrites, an exception was found with 2-phenyl-2-propyl nitrite (2P2P), whose alkaline hydrolysis was not affected by β-CD at all.

The observed behaviour might be generally interpreted by the consideration of the formation of 1:1 inclusion complexes between RONO and β-CD. The overall hydrolysis rate is the sum of two reaction pathways: the reaction between uncomplexed RONO and OH^- plus the reaction of the complex β-CD·RONO. The observed catalysis is qualitatively understood if the complex reacts at faster rates than the bimolecular reaction does: RONO + OH^-. Scheme 9 can be proposed to account for the observed facts, from which the following equation of Michaelis–Menten type is easily deduced to relate k_0 and [β-CD]:

$$k_0 = \frac{k_0^{w} + k_c K_c[\beta\text{-CD}]}{1 + K_c[\beta\text{-CD}]}. \tag{7}$$

Typical values of the rate constant k_c and equilibrium constant K_c, are reported in table 7, together with values of k_0^{w} (= $k_{OH}[OH^-]$). A comparison between the

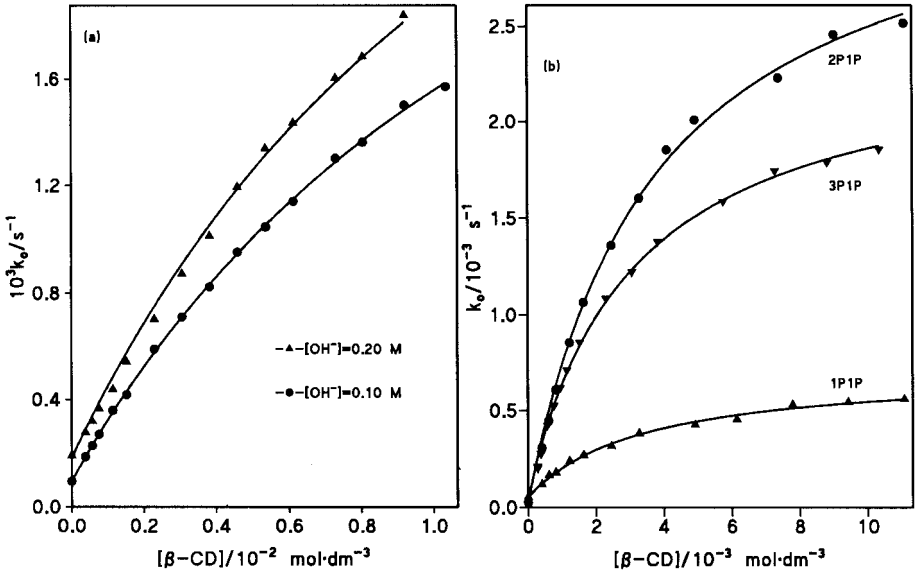
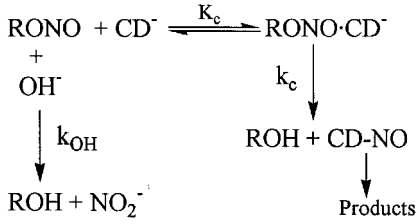


Figure 8. Catalytic effect of β-CD observed in the alkaline hydrolysis of (*a*) 2-ethoxyethyl nitrite and (*b*) 1-phenyl-1-propyl (1P1P), 2-phenyl-1-propyl (2P1P) and 3-phenyl-1-propyl (3P1P) nitrites studied at 25°C.



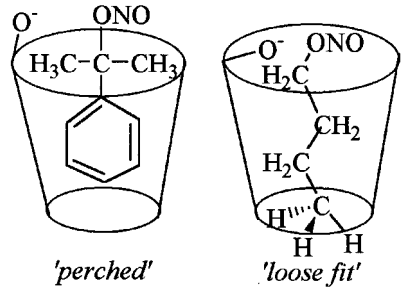
Scheme 9. Reaction mechanism for the basic hydrolysis of alkyl nitrites mediated by β-CD.

Table 7. Experimental conditions and parameters (scheme 9) obtained in the study of the influence of β-CD concentration on the basic hydrolysis of alkyl nitrites ($k_0^w = k_{OH}\,[OH^-]$).

RONO	t (°C)	$[OH^-]$ (M)	[DTABr] (M)	k_0^w ($10^{-4}\,s^{-1}$)	k_c ($10^{-3}\,s^{-1}$)	K_c (M^{-1})
EEN	25.0	0.10	–	9.5	3.8 ± 0.1	64.5 ± 2.4
EEN	25.0	0.20	–	18	4.52 ± 0.04	65.4 ± 0.7
n-Bu nitrite	25.0	0.20	–	~0.20	2.0 ± 0.2	51.5 ± 6.7
n-Pe nitrite	25.0	0.20	–	~0.15	2.1 ± 0.2	50.5 ± 8.0
2P2P nitrite	25.0	0.20	–	Reaction too slow; no good first-order reactions		
3P1P nitrite	25.0	0.10	–	0.20	2.34 ± 0.02	360 ± 10
3P1P nitrite	25.0	0.20	–	0.35	2.53 ± 0.07	301 ± 19
3P1P nitrite	10.4	0.20	–	~0	0.76 ± 0.02	336 ± 22
3P1P nitrite	15.0	0.20	–	~0	1.13 ± 0.03	324 ± 23
3P1P nitrite	20.1	0.20	–	~0.05	1.79 ± 0.05	278 ± 18
3P1P nitrite	31.0	0.20	–	0.52	4.5 ± 0.1	287 ± 21
1P1P nitrite	25.0	0.10	–	0.38	0.56 ± 0.01	279 ± 13
1P1P nitrite	25.0	0.20	0.0	0.75	0.71 ± 0.02	253 ± 20
1P1P nitrite	25.0	0.20	3.4×10^{-3}	0.75	1.37 ± 0.04	295 ± 25
1P1P nitrite	25.0	0.20	5.1×10^{-3}	0.75	1.69 ± 0.04	246 ± 13
1P1P nitrite	25.0	0.20	6.8×10^{-3}	0.75	2.17 ± 0.06	179 ± 11
1P1P nitrite	25.0	0.20	10.2×10^{-3}	0.75	2.78 ± 0.08	137 ± 7

DTABr, docecyltrimethylammonium bromide; *n*-Bu, *n*-butyl; *n*-Pe, *n*-pentyl; 2P2P, 2-phenyl-2-propyl; 3P1P, 3-phenyl-1-propyl; 1P1P, 1-phenyl-1-propyl.

reactivities found for the bimolecular (k_{OH}) and unimolecular (k_c) processes indicates that rates of inclusion complexes are more than 30 times faster than the bimolecular process, which in some cases is too slow to measure; this is easy to understand if one takes into account that, in the unimolecular process, the inclusion complex β-CD·RONO is the activated complex of the reaction. In this sense, the analysis of the influence of temperature on the hydrolysis of 3P1P nitrite gives the activation energy for the bimolecular process as $E^{\#} = 84$ kJ mol^{-1}, while the activation energy associated with k_c has been determined as 63 kJ mol^{-1}, that is there is significant stabilization of the transition state of the reaction through the complexed 3P1P with respect to the reaction via OH^-. However, the catalytic efficiency depends on the structure of RONO, which, obviously, determines the mode of inclusion in the β-CD cavity. The simplest systems, such as EEN, or *n*-Bu or *n*-Pe nitrites, bind loosely to CD because of their linear structure, and their molecules can adjust their depth in the β-CD cavity in order to approach the reacting groups closely. By contrast, the branched 2P2P nitrite binds perched to β-CD (scheme 10), and consequently the



Scheme 10. Possible conformation of the inclusion complexes 2P2P·CD$^-$ and *n*-BuN·CD$^-$.

nitroso group cannot come near the ionized -O$^-$ group of β-CD, making impossible the reaction between them and no catalysis has been detected. In a middle position would be the case of 3P1P nitrite which binds tightly to β-CD. In this sense, making use of the approach developed by Kurz (1963, 1972) (see also Tee (1989) and Kirby (1996), for its application) for estimating the stabilization of the transition state by a catalyst, the definition of the apparent stability constant of formation of the transition state of the CD-mediated reaction, symbolized by TS·CD, from the transition state of the normal reaction (TS) and the CD, as $K_{TS} = [TS \cdot CD]/[TS][CD] = k_c K_c / k_0^w$, leads to values of 1642, 2395, 5200, 7000 and 21 758 mol^{-1} dm^3 corresponding to EEN, 1P1P, *n*-Bu, *n*-Pe and 3P1P nitrites respectively. This variation of K_{TS} with the alkyl nitrite structure reveals the importance of the way the guest molecule adapts to the CD cavity.

The alkaline hydrolysis of RONO mediated by β-CD shows also allosteric activation effects typical of the enzyme action. In this sense, the addition of potential inhibitors, such as monomers of DTABr enhances even more the catalytic effect of β-CD on the hydrolysis of 1P1P: the effect is greater if one increases either the host or the DTABr monomer concentrations. The equilibrium constant formation of the complex RONO·β-CD decreases slightly on increasing the concentration of DTABr monomers, whereas the reaction of the complex (k_c values) increases strongly with [DTABr], k_c being 4 times the value corresponding to the unmodified reaction (no added DTABr) at 0.010 M of DTABr monomers (table 7). The DTABr monomers modify the catalytic efficiency of β-CD, possibly by inducing conformational changes or a more proper disposition of the guest, thus altering the reactivity of the complex. Alternatively, if the -O$^-$ group of β-CD is surrounded by DTABr monomers, there could be a decrease in the hydration number of the -O$^-$ group and an increase in its nucleophilicity.

4.3. *Nitrosation reactions by alkyl nitrites*

As already mentioned, the N atom of an alkyl nitrite (R-O-N=O) is a soft electrophile. Then, according to Pearson's principle of HSAB, RONO would transfer the -NO group to soft nucleophiles such as amines, ketones (Crookes *et al.* 1989), carbanions (Iglesias 1995), thiols (Patel and Williams 1989, 1990) or other nucleophiles (Bhattacharjee 1981) to give the corresponding nitroso compounds which in the case of secondary amines are stable. The reaction requires basic conditions in order to avoid the fast acid hydrolysis of alkyl nitrites. The most widely studied nitrosation reactions involve the reaction with amines.

4.3.1. *Nitrosation of amines in water*

The kinetic features of the nitrosation reaction of amines by alkyl nitrites in basic media have a first-order dependence with respect to both the amine and the alkyl nitrite concentrations:

$$\text{rate} = k_2[\text{amine}][\text{RONO}]. \tag{8}$$

The second-order rate constant, k_2, is unaffected by ionic strength, as appropriate for reactions between neutral species, and the reciprocal values of k_2 increase linearly with $[H^+]$ (for $[H^+]$ in the range of basic pHs). These characteristics are typical of a reaction mechanism in which the slow step is the reaction between the alkyl nitrite and the neutral form of the amine (Oae *et al.* 1978b, Challis and Shuker 1979, Casado *et al.* 1986).

For a given amine, the nitrosation reaction goes faster with alkyl nitrites bearing electron-withdrawing substituents, such as CF_3CH_2ONO, $ClCH_2CH_2ONO$, $BrCH_2CH_2ONO$, $EtOCH_2CH_2ONO$. The results can be rationalized in terms of the stability of the leaving alkoxide (RO^-): the higher its stability, the less important is the proton transfer during the rate-controlling step and the more the mechanism resembles an S_N1 process, that is the asynchronous character of bond breaking and bond formation is greater (Casado *et al.* 1987). For a given alkyl nitrite, the nitrosation reaction increases with the basicity of the amine, and bimolecular rate constants correlate well with the amine pK_a for the series of the cyclic amines displayed in figure 9, but the correlation fails if aliphatic amines are also included.

Another important characteristic of the nitrosation reaction is its large negative activation entropy values, which suggest that the reaction takes place *via* a highly ordered cyclic transition state, see scheme 11, of a four-centre nature (scheme 11(*a*))

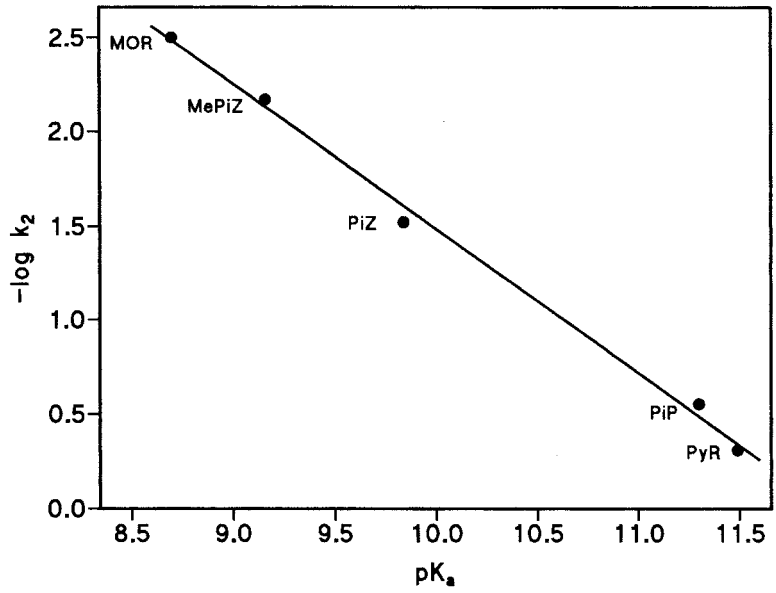
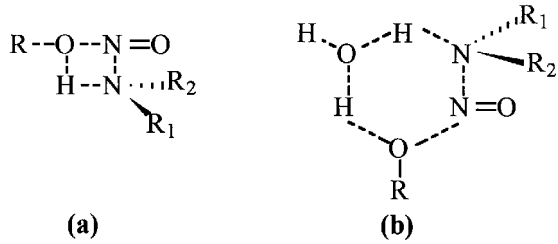


Figure 9. Linear correlation observed between the bimolecular rate constant, k_2, for the nitrosation by 2-hydroxyethyl nitrite of morpholine (MOR), *N*-methyl-piperazine (MePiZ), piperazine (PiZ), piperidine (PiP) and pyrrolidine (PyR) in aqueous medium at 25°C and the pK_a of the amine.



Scheme 11. Possible transition states in the NO transfer from RONO to amines in water.

in which the amine aids removal of the -OR group by partial protonation, although the possibility of a six-membered ring, with the participation of a water molecule (scheme 11(*b*)), was also considered (Calle *et al.* 1992).

A detailed study of the nitrosation of piperidine by propyl, iso-propyl, butyl, iso-butyl, *sec*-butyl and *tert*-butyl nitrites in 0.1 M NaOH suggested an orbital-controlled reaction in that, the less the alkyl group 'contaminates' the neighbourhood of the nitrite LUMO with negative charge, the easier it is for the latter to receive charge from the amine HOMO (García-Santos *et al.* 1996). This would explain the fact that the nitrosation of amines by RONO is favoured by the presence of electron-withdrawing groups in the latter. In addition, when studying nitrosation reactions of cyclic secondary amines, such as 2-methylaziridine, acetidine, pyrrolidine, piperidine and homopiperidine, by propyl and butyl nitrites, a tendency for the reactivity to increase on decreasing the vertical ionization potential was found. No reaction was observed when nitrosation of 2-methylaziridine was attempted. This finding was rationalized in terms of the hypothesis of an orbital-controlled reaction in the following way: in cycloalkanes the s character of the C-H bond increases with decreasing ring size in such a way that the value of the nuclear-spin coupling constant $J(^{13}C–^{1}H)$ in cyclopropane (161 Hz) is very similar to that of benzene (159 Hz). Thus, an explanation is readily found in the overall hybridization of the N atom of the amine ring; that is, a change of the lone pair from an sp^2 hybrid orbital in methylaziridine to sp^3 in larger rings would occur (Calle *et al.* 1992).

A comparison of the reactivities of 43 nucleophilic nitrogen compounds (including primary, secondary and tertiary amines as well as other nitrogen nucleophiles such as azide, ammonia, hydrazine and semicarbazide), towards the nitroso group of MNTS and of alkyl nitrites (RONO) reveals that reactivities do not correlate well with either the basicity or the vertical ionization potential of the nucleophile, despite results covering eight powers of 10 in pK_a and almost five in $\log k_2$ (García-Río *et al.* 1993a). Nevertheless, the empirical reactivity parameter of Ritchie's N_+ index (Ritchie 1986, 1972), which has been determined for a wide variety of nucleophiles on the basis of data for nucleophile–carbocation recombination and other chemical processes, allows prediction of reactivity from

$$\log k = \log k_0 + N_+ \tag{9}$$

where $\log k_0$ depends solely on the electrophile and N_+ on the nucleophile and the solvent. The plot of $\log k_2$ against N_+ reveals remarkably good correlation, showing that the validity of N_+ values extends to prediction of reactivity with the N=O group (García-Río *et al.* 1993a). It appears that the reactivities of nucleophiles in a wide range of chemical processes, including reaction at different atoms and with

nitroso compounds, are governed by some unknown intrinsic characteristic of the nucleophiles themselves.

From the previous mechanistic considerations, nitrosation by alkyl nitrites involves the leaving group being assisted by strong solvation. Then stabilization of the leaving alkoxide by a polar and protic solvent plays a major role in determining the reactivity. Therefore, the more basic leaving alkoxide will be expected to be strongly hydrogen bonded to the solvent. This feature explains the higher reactivity of those alkyl nitrites with electron-withdrawing substituents, for example trifluoro-, chloro- or bromoethyl nitrites show greater reactivity than the parent ethyl nitrite. Regarding the characteristics of the nucleophiles, the reactivity towards alkyl nitrites depends not only on their basic character but also on other factors, such as the influence of dipole–dipole interactions in the formation of the encounter pair and the polarizability of the lone pair of the N atom undergoing nitrosation. Some of the characteristics of the nitrosation reaction of amines by alkyl nitrites are illustrated through the data reported in table 8.

4.3.2. *Nitrosation of amines in organic solvents*

The nitrosation of several strongly basic secondary amines, such as PyR, PiP or dimethylamine (DMA), by the reactive alkyl nitrites 2-bromoethyl nitrite, 2,2-dichloroethyl nitrite or 2,2,2-trichloroethyl nitrite was studied in several organic inert solvents including cyclohexane, isooctane, dichloromethane, 1,4-dioxane, tetrahydrofuran, chloroform, acetonitrile, and dimethylsulphoxide (García-Rio *et al.* 1997a,b). In every case, quantitative *N*-nitrosamine formation was determined and absorbance–time profiles were fitted by the first-order integrated rate equation perfectly when working with [RONO] ≪ [amine]:

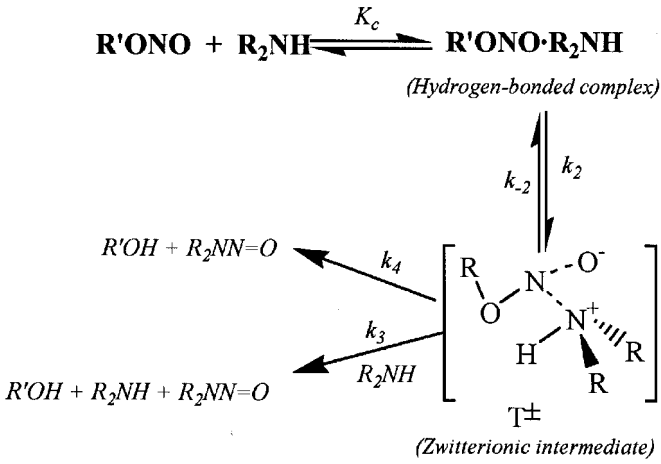
$$\text{rate} = k_0[\text{RONO}]. \tag{10}$$

Nevertheless, the dependence of the overall rate constant, k_0, on [amine] is not as simple as that found in water. The k_0 versus [amine] profiles were sigmoid curves at low [amine] and tended to level off at high [amine], but the resulting profile depends

Table 8. Bimolecular rate constants for the reaction of dimethylamine with various alkyl nitrites and of 2-bromoethyl and 1-phenylethyl nitrites with several amines at 25°C.

Dimethylamine		2-Bromoethyl nitrite		1-Phenylethyl nitrite	
R–ONO	k_2 ($mol^{-1}\,dm^3\,s^{-1}$)	Amine	k_2 ($mol^{-1}\,dm^3\,s^{-1}$)	Amine	k_2 ($mol^{-1}\,dm^3\,s^{-1}$)
CH_3–	0.094	MEA	2.40	MEA	0.22
CH_3CH_2–	0.064	DEA	1.01	DEA	0.074
$OHCH_2CH_2$–	0.503	MIP	1.02	MIP	0.093
$EtO(CH_2)_2$–	0.66	MBA	2.90	MBA	0.302
$ClCH_2CH_2$–	3.42	DBA	1.20	DBA	0.108
CF_3CH_2–	718	MCH	1.56	MCH	0.140
$CH_3CH_2CH_2$–	0.066	PiP	2.70	PiP	0.227
$(CH_3)_2CH$–	0.022	2MPiP	0.44	2MPiP	0.043
$(CH_3)_3C$–	0.0087	PyR	14.1	PyR	1.60

MEA, methylethylamine; DEA, diethylamine; MIP, methyl-isopropylamine; MBA, methyl-butylamine; DBA, dibutylamine; MCH, methylcyclohexylamine; PiP, piperidine; 2MPiP, 2-methylpiperidine; PyR, pyrrolidine.



Scheme 12. Reaction mechanism for the nitrosation of amines by RONO in organic solvents.

on the solvent, the alkyl nitrite or the amine. A generalized explanation of the results can be provided by means of a reaction mechanism involving the formation of zwitterionic tetrahedral intermediates, $T^{\pm}$ (see scheme 12), whose evolution to reaction products can be catalysed by a second amine molecule.

The existence of these intermediates was recently detected by García-Rio *et al.* (1999) in an elegant study in which the authors worked with weakly basic amines, such as *N*-methylaniline ($pK_a = 4.85$) or *N*-methylmethoxyamine ($pK_a = 4.75$), and highly reactive alkyl nitrites, such as 2,2,2-trichloroethyl nitrite, in cyclohexane. The previous experimental conditions favour the accumulation of intermediates and absorbance–time profiles are typical of a consecutive reaction scheme.

4.3.3. *Nitrosation of amines in aqueous β-CD solutions*

The nitrosation reaction of PyR, PiP and *N*-methylcyclohexylamine (MCH) by alkyl nitrites to give *N*-nitrosamines in quantitative yield has been studied in the presence of β-CD (Iglesias 1998, 2000). The kinetic analysis has been done for both alkaline medium and buffered aqueous solutions of the amines (e.g. in buffer solutions of pyrrolidine–pyrrolidinium ion or piperidine–piperidinium ion). In all cases the concentration of the alkyl nitrite was much smaller than either [amine] or [β-CD].

The neutral form of PyR, PiP or MCH produces inclusion complexes with β-CD. The stability constants of complex formation were estimated (Iglesias and Fernández 1998) or measured (Barra *et al.* 1987) as 6, 50 and 550 $mol^{-1}\,dm^3$ for PyR, PiP and MCH respectively. The protonated forms of the amines do not appear to bind in the β-CD cavity.

As already mentioned, β-CD is a weak acid whose pK_a has been measured as 12.30. On the other hand, β-CD is slightly soluble in water: the maximum attained solubility is around 10^{-2} M. As a consequence, working under alkaline conditions of $[OH^-] = 0.10$ or 0.20 M, all β-CD molecules are ionized, that is one has to consider an anionic host; by contrast, working under buffer solutions of for example

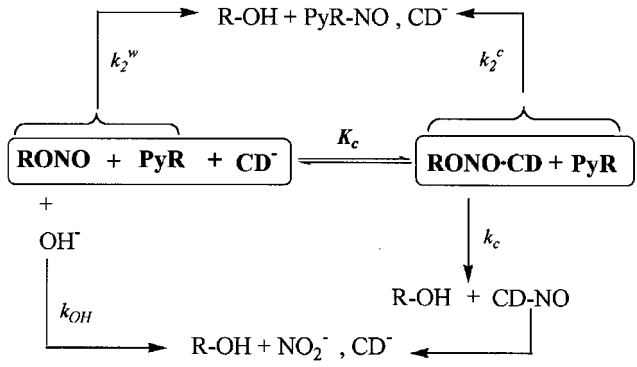
pyrrolidine–pyrrolidinium ion of pH 11.15, most of the β-CD molecules are not ionized and one has to consider a neutral host.

The kinetic features observed in the nitrosation of amines by alkyl nitrites in the presence of β-CD depend on the structures of both the amine and the alkyl nitrite, as well as on whether the β-CD is neutral or ionized. Table 9 summarizes some of the observed behaviours.

All the alkyl nitrites investigated form inclusion complexes with β-CD. In the study of the acid-catalysed hydrolysis of RONO, the kinetic treatment of the experimental data allows the determination of the stability constants of complex formation, K_c^N, between neutral β-CD and the corresponding RONO; see table 4. In the same way, the kinetic results obtained in the study of the influence of β-CD on the alkaline hydrolysis of RONO yield the stability constants of complex formation, K_c, between ionized β-CD and the corresponding RONO; see table 7. One can note that the same alkyl nitrite binds more strongly to neutral than to ionized β-CD, which could be attributed to the formation of H bonds in the former case but it is not possible in the latter.

So to explain the gamut of behaviours reported in table 9 it is necessary to consider the nature of the amine as well as the possible conformation of the RONO·β-CD complex. In relation to the nature of the amine, two different patterns of behaviour are observed.

(1) *Pyrrolidine*. Remembering that the equilibrium inclusion constant between neutral PyR and β-CD has been estimated as $K_c^A = 6\,M^{-1}$, working at $[PyR] < 10^{-2}\,M$, the amount of amine forming inclusion complexes will be insignificant. On the other hand, RONO binds to either neutral or ionized β-CD. Then, in aqueous buffered solutions of pyrrolidine–pyrrolidinium ion, only the reaction between RONO free (k_2^w) or complexed (k_2^c) and pyrrolidine has to be considered. In alkaline medium, where the host β-CD is ionized, it is necessary also to take into account the reaction of the included RONO, k_c, to give the *O*-nitroso-β-CD; in addition, if $[OH^-]$ is high, the alkaline hydrolysis of uncomplexed RONO, k_{OH}, is not negligible, especially with the most reactive alkyl nitrites, such as EEN. Therefore, scheme 13 might be proposed and values of rate and equilibrium constants for some representative cases are depicted in table 10.



Scheme 13. Reaction scheme of RONO and pyrrolidine in aqueous alkaline solution of β-CD.

Table 9. Observed effect on the influence of β-CD in the nitrosation of amines by alkyl nitrites.

	Pyrrolidine (PyR)			Piperidine (PiP)		
	R-ONO	Medium	Effect	R-ONO	Medium	Effect
1.	Ethoxyethyl-	Buffer (pH 11.15)	No effect	Ethoxyethyl-	Alkaline (0.10 M)	Catalysis
2.	Ethoxyethyl-	Alkaline (0.10 M)	Catalysis	–	–	–
3.	Cyclohexyl-	Alkaline (0.10 M)	Catalysis	–	–	–
4.	1-Phenylethyl-	Buffer (pH 11.35)	Inhibition	–	–	–
5.	1-Phenylethyl-	Alkaline (0.10 M)	Inhibition	2-Phenyl,1-propyl-	Buffer (pH 11.02)	Catalysis[a]
6.	2-Phenylethyl-	Alkaline (0.10 M)	Catalysis	2-Phenyl,1-propyl-	Alkaline (0.20 M)	Catalysis
7.	1-Phenyl,1-propyl-	Buffer (pH 11.15)	Inhibition	1-Phenyl,1-propyl-	Buffer (pH 11.02)	Inhibition
8.	1-Phenyl,1-propyl-	Alkaline (0.20 M)	Inhibition	1-Phenyl,1-propyl-	Alkaline (0.20 M)	Catalysis
9.	3-Phenyl,1-propyl-	Buffer (pH 11.15)	No effect	3-Phenyl,1-propyl-	Alkaline (0.20 M)	Catalysis
10.	3-Phenyl,1-propyl-	Alkaline (0.20 M)	Catalysis	–	–	–

[a] Catalysis at low [β-CD], but inhibition at high [β-CD].

Table 10. Reaction rates between the amines PyR, PiP and MCH and alkyl nitrites (RONO) obtained in aqueous buffered solutions of the amine and in alkaline medium in the absence and presence of β-CD (see schemes 13 and 14 for the meaning of the parameters).

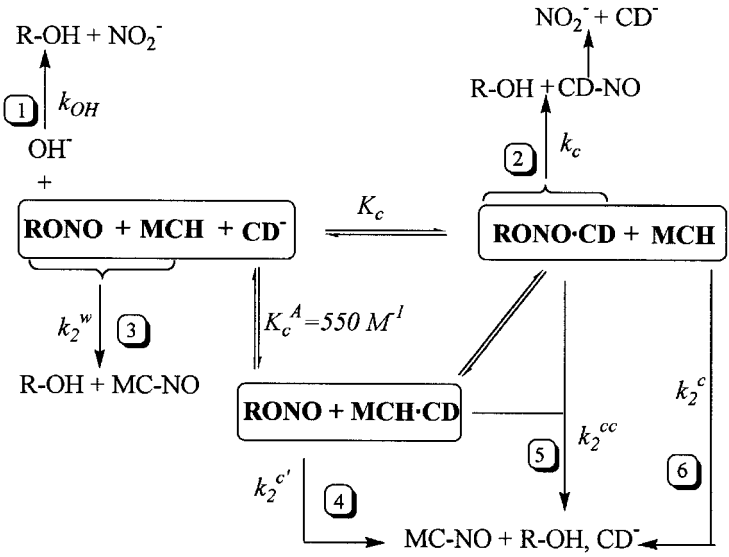
	Amine–buffer medium (neutral β-CD)			Alkaline medium (ionized β-CD)		
RONO	k_2^w ($M^{-1}s^{-1}$)	K_c^N (M^{-1})	k_2^c ($M^{-1}s^{-1}$)	K_c (M^{-1})	k_2^c ($M^{-1}s^{-1}$)	k_2^{cc} ($M^{-1}s^{-1}$)
			PyR, $K_c^A = 6\,M^{-1}$			
EEN	1.36, 1.46	–	–	65	1.60	–
1P1P	1.07	528	0.050	269	0.339	–
2P1P	0.69	?	?	280	0.665	–
3P1P	0.30	355	0.240	310	0.339	–
			PiP, $K_c^A = 50\,M^{-1}$			
EEN	0.33	–	–	65	0.40[a]	2.0
1P1P	0.80	590	0.030[a]	260	0.04[a]	0.20
2P1P	0.80	430	0.21[a]	280	0.279[a]	0.922
3P1P	0.50	354	?	310	0.153[a]	0.884
			MCH, $K_c^A = 550\,M^{-1}$			
EEN	0.170	—	—	65	0.46[a]	0.50
1P1P	0.092	550	?	264	0.163[a]	0.093
2P1P	0.055	580	?	273	0.53[a]	0.30
3P1P	0.0283	354	?	310	0.36[a]	0.26

[a] Values of k_2^c or $k_2^{c'}$ because they are kinetically indistinguishable.
MCH, *N*-methylcyclohexylamine.

The lack of influence of β-CD found, for example, in the systems PyR + 3P1P or PyR + EEN, both in buffered solutions of the amine, could be due to the similar values of the rate constants k_2^w and k_2^c, which can be understood if one looks at the structure and dimensions of 3P1P or EEN molecules in comparison with the size of the β-CD cavity. While the NO group in both 3P1P and EEN must lie completely outside the β-CD cavity, which results in no difference in its reactivity, the same group in the case of for example 1P1P lies completely inside the β-CD cavity and a strong inhibition is observed.

(2) *Piperidine and* N-*methylcyclohexylamine*. The nitrosation of both PiP and MCH by the alkyl nitrites listed in table 10 is catalysed by the presence of β-CD; the k_0 versus [β-CD] profiles describe an ascending curve which levels off at high [β-CD]. These amines are less reactive but more hydrophobic than PyR. The stability constants of the inclusion complexes formed between β-CD and PiP or MCH are 50 and 550 $mol^{-1}\,dm^3$ respectively, that is much higher than those of PyR. Therefore, with PiP and MCH the amount of complexed amine is not negligible.

In alkaline medium the reaction scheme may be represented as in scheme 14, where, besides the basic hydrolysis reaction via either OH^- (reaction 1) or ionized β-CD (reaction 2), the possibility of nitrosation reactions of free RONO with free amine (reaction 3), the complexed amine (amine·β-CD) with free RONO (reaction 4), or its kinetically equivalent reaction of the free amine with the complexed RONO (reaction 5), and the complexed RONO



Scheme 14. Reaction scheme of RONO and MCH (or PiP) in aqueous alkaline solution of β-CD.

and complexed amine (reaction 6) are represented. The overall reaction rate is the sum of the six reaction pathways, even though, with reactive amines, such as PiP or MCH, reaction 1 may be ignored because it is much slower than the others.

The resulting expression for the observed rate constant, k_0, is

$$k_0 = \frac{k_0^{\mathrm{w}} + \gamma[\beta\text{-CD}]_{\mathrm{f}} + \delta[\beta\text{-CD}]_{\mathrm{f}}^2}{(1 + K_{\mathrm{c}}[\beta\text{-CD}]_{\mathrm{f}})(1 + K_{\mathrm{c}}^{\mathrm{A}}[\beta\text{-CD}]_{\mathrm{f}})}, \tag{11}$$

which was used to obtain good correlation between the experimental data. In this equation, $\gamma = k_{\mathrm{c}}K_{\mathrm{c}} + (k_2^{\mathrm{c}}K_{\mathrm{c}} + k_2^{\mathrm{c}'}K_{\mathrm{c}}^{\mathrm{A}})[\mathrm{amine}]_{\mathrm{t}}$, $\delta = k_{\mathrm{c}}K_{\mathrm{c}}K_{\mathrm{c}}^{\mathrm{A}} + k_2^{\mathrm{cc}}K_{\mathrm{c}}K_{\mathrm{c}}^{\mathrm{A}}[\mathrm{amine}]_{\mathrm{t}}$, and the term $[\beta\text{-CD}]_{\mathrm{f}}$ is the free β-CD concentration, which can be determined by means of

$$[\beta\text{-CD}]_{\mathrm{f}}^2 + [\beta\text{-CD}]_{\mathrm{f}}\left([\mathrm{amine}]_{\mathrm{n}} + \frac{1}{K_{\mathrm{c}}^{\mathrm{A}}} - [\beta\text{-CD}]_{\mathrm{t}}\right) - \frac{[\beta\text{-CD}]_{\mathrm{t}}}{K_{\mathrm{c}}^{\mathrm{A}}} = 0. \tag{12}$$

As the alkyl nitrite concentration is always much smaller than the β-CD concentration, in a good approximation one can neglect the [β-CD] complexing to the alkyl nitrite but not the [β-CD] complexing the amine.

As the binding constants of both RONO and amine to β-CD are known, a modified graphical representation of the form $k_0(1 + K_{\mathrm{c}}[\beta\text{-CD}]_{\mathrm{f}})(1 + K_{\mathrm{c}}^{\mathrm{A}}[\beta\text{-CD}]_{\mathrm{f}})$ (henceforth k_0^{mod}) versus $[\beta\text{-CD}]_{\mathrm{f}}$ can be drawn, resulting in an ascending curve through the [β-CD] range, that is the typical plot of a second-order dependence on [β-CD] (figure 10).

In conditions of neutral β-CD, namely buffered aqueous solutions of for example piperidine–piperidinium ion, reactions 1 and 2 of scheme 14 cannot take place; in addition, the plot of k_0^{mod} against $[\beta\text{-CD}]_{\mathrm{f}}$ describes perfect straight lines (figure 11), which means that reaction 5 in scheme 14 does not take place either.

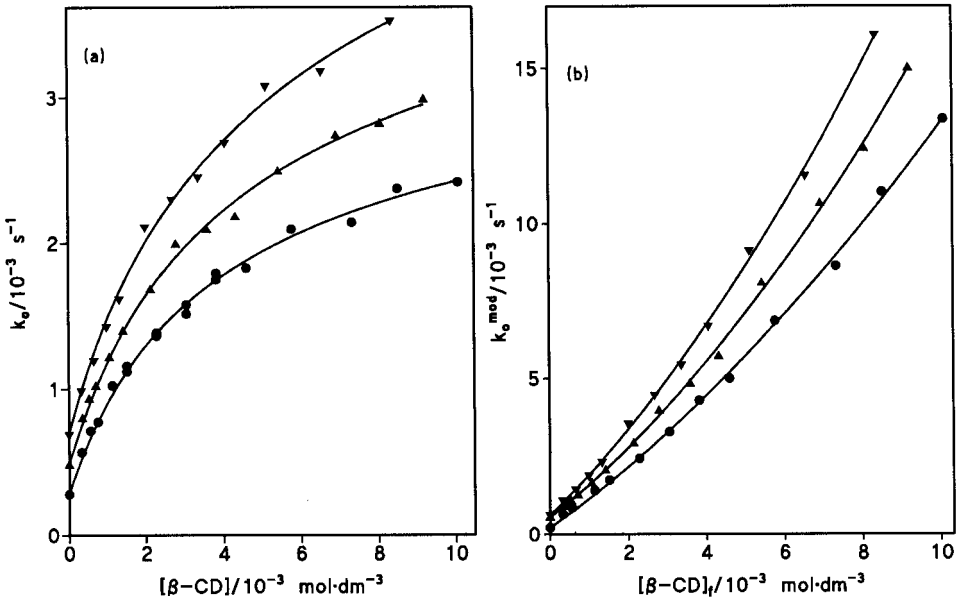


Figure 10. (*a*) Variation of k_0 as a function of free β-CD concentration obtained in the nitrosation in aqueous alkaline medium ($[OH^-] = 0.20$ M) of PiP by 2P1P at [PiP] = 1.67 (●), 3.3 (▲) and 5.0 (▼) mM; (*b*) plot of k_0^{mod} ($= k_0(1 + K_c[\beta\text{-CD}]_f)(1 + K_c^A[\beta\text{-CD}]_f)$) with $K_c = 265\,mol^{-1}\,dm^3$ and $K_c^A = 50\,mol^{-1}\,dm^3$ against free [β-CD].

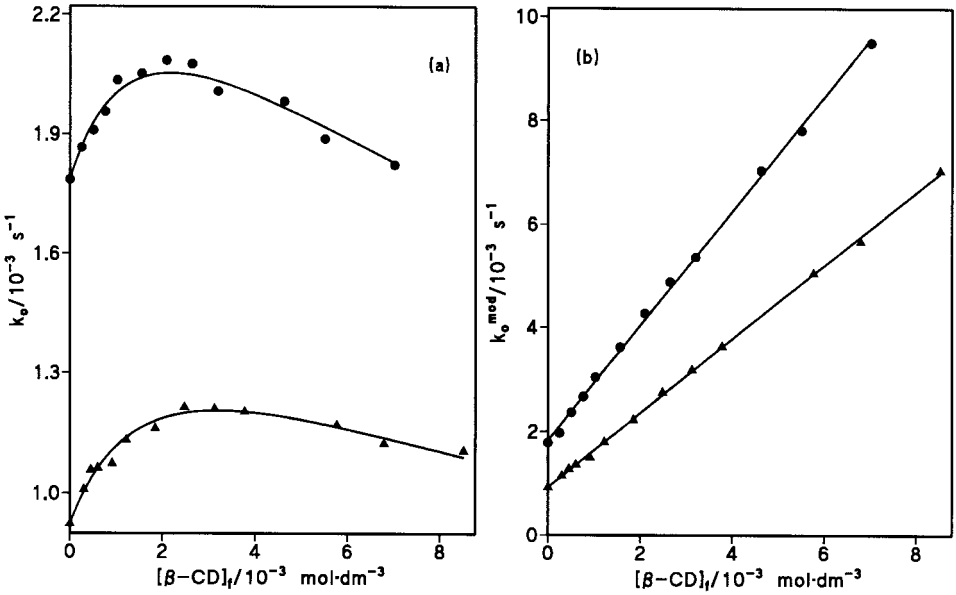
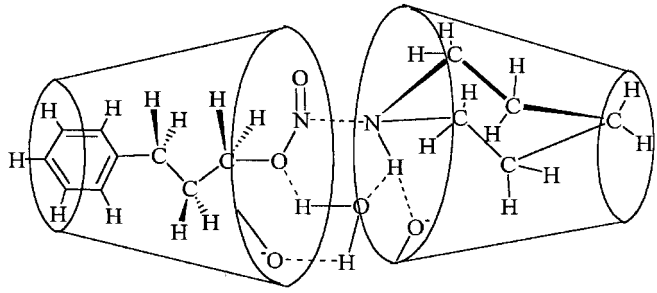


Figure 11. Variation of (*a*) k_0, the pseudo-first-order rate constant and (*b*) k_0^{mod} ($= k_0(1 + K_c^N[\beta\text{-CD}])(1 + K_c^A[\beta\text{-CD}])$) obtained in the nitrosation of PiP by 2P1P in a buffer of piperidine–piperidinium chloride of pH 11.02 and $[PiP]_t = 0.020$ (▲) or 0.033 M (●) as a function of free [β-CD].

The observed experimental facts can be rationalized because the reaction between both complexed reactants (the rate constant represented by k_2^{cc}) is higher than, or at least of the same order as, either k_2^w or k_2^c (or $k_2^{c'}$). The results obtained, listed in table 10, account for this statement. In other words, this fact means that, when the reaction goes through both complexed substrates, the activation energy of the rate-determining step must decrease significantly. To understand this, a particular way of fixing both reactants to ionized β-CD in the transition state of the reaction should occur. We postulate the formation of channel-like structures that, besides serving to fix the reacting species in close proximity, might intervene in the formation of the transition state. The ionized $-O^-$ group of a β-CD molecule will form H bonds with either water molecules or with the amine included in the β-CD cavity. This special arrangement of the reactants in the activated complex, shown in scheme 15, with a water molecule participating in the fixation of the reagents to the ionized host, should result in a strong decrease in the activation energy, even though the gain in entropy will not be negligible. The proposed structure for the transition state also explains the absence of the reaction through both complexed reactants when the reaction is studied in a buffer of the amine, that is to say in conditions of non-ionized β-CD, in which case the possibility of H bond formation between the $-OH$ groups of β-CD and the amine, or a water molecule, is much more constrained.



Scheme 15. Possible conformation of the transition state of the nitrosation reaction between the inclusion complexes 3P1P·CD^- and PiP·CD^- in alkaline medium (CD^-, ionized β-CD).

4.3.4. *Nitrosation reactions in micelles*

4.3.4.1. *Cationic micelles.* The nitrosation reactions of several amines by the alkyl nitrites 2-bromoethylnitrite (BEN) and 1-phenylethylnitrite (PEN) have been studied in the presence of cationic micelles of TTABr (Iglesias *et al.* 1994, Fernández *et al.* 1995).

Addition to the reaction medium of TTABr at a surfactant concentration higher than the CMC causes an inhibition of the reaction. The degree of inhibition is greater when the transnitrosation reaction is promoted by PEN than by BEN, the latter being more reactive but less hydrophobic than the former. Therefore, the different micellar effects between both alkyl nitrites can be understood by considering the greater association of PEN with micellar aggregates as well as the lower reactivity in the micellar phase with respect to the aqueous medium. The degree of inhibition also increases with the hydrophobicity of the amine.

These experimental facts were explained by applying the pseudophase model. According to it, the distribution of the neutral form of the amine between aqueous and micellar pseudophases is considered, K_s^A being the corresponding equilibrium

constant, and the reaction may occur in both pseudophases with different reactivities. In the case of the more hydrophilic amines, such as PyR, PiP or MOR, and when the nitrosation is promoted by BEN, the reaction in the micellar phase was negligible. The reactivity in the micellar phase is lower than that in water owing to the lower polarity of the micellar interface. When a particular amine is considered, PEN reacts at lower rate than BEN, a fact which can be attributed to the different sites of average location of both substrates in the micellar interface. The more hydrophilic BEN will be located near the micellar surface, in a highly hydrated zone, while PEN will reside in a deeper zone of the Stern layer, whose properties are quite anisotropic, in a less polar environment possible near the plane core head group with the aryl ring inside the hydrocarbon core.

Results obtained for the association constants of the amine to the TTABr micelles, K_s^A, as well as for the rate constants in the micellar phase, k_2^m, are reported in table 11.

4.3.4.2. *Anionic micelles.* The study of the transnitrosation reaction between alkyl nitrites and amines in basic medium in the presence of anionic micelles of SDS needs to consider two aspects: the micellar effects (1) on the acid–base equilibrium of amines and (2) on reaction rate (Iglesias *et al.* 1994, Fernández *et al.* 1995).

(1) *Micellar effects on equilibria.* The protonated form of amines interacts with negatively charged SDS micelles giving rise to an increase in their protonation degree. The process is favoured by two factors, first, the exclusion from the micellar surface of the OH^- ions being formed and, second, the attraction for the micellar surface of the alkylammonium ions that are formed. The latter process provokes a change in the basic ionization equilibrium constant of the amine, K_b, on addition of SDS. This change is due to specific and electrostatic interactions between $RR'NH_2^+$ cations and the sulphate head groups of the SDS micelles.

This interaction may be quantified by direct measurements of the absorbance of the aqueous amine solutions at a wavelength in the range 200–220 nm, where only the neutral form of the amine absorbs, and in the presence of varying SDS concentrations.

The apparent basic ionization constant $K_b^{(ap)}$ of a weak base, such as a secondary amine of general structure RR′NH, in the presence of SDS micellar aggregates, can be defined by the following expression, where $[OH^-]_w$ represents the intermicellar concentration of hydroxide ions, $RR'NH_2^+$ and RR′NH are the protonated and unprotonated forms of the amine and the subscripts w, m and t represent the aqueous, micelle and total analytical concentrations of each amine species:

$$K_b^{(ap)} = [OH^-]_w \frac{[RR'NH_2^+]_w + [RR'NH_2^+]_m}{[RR'NH]_w + [RR'NH]_m} = [OH^-]_w \frac{[RR'NH_2^+]_t}{[RR'NH]_t}. \quad (13)$$

The total concentration of the neutral form of the amine can be determined from absorbance measurements. Therefore, at a given pH, the variation of the $pK_b^{(ap)}$ with the SDS concentration can be determined from the absorbance readings according to

$$pK_b^{(ap)} = pOH + \log \frac{A}{A_0 - A}, \quad (14)$$

where A and A_0 represent the absorbance measurements in the presence of a given [SDS] and in the absence of the surfactant respectively.

Table 11. Reactivities of several amines in water and in aqueous micellar solutions of TTABr and SDS at 25°C towards 2-bromoethyl nitrite and 1-phenylethyl nitrite.

	Nitrosation in TTABr micelles			Nitrosation in SDS micelles			
				2-Bromoethyl nitrite		1-Phenylethyl nitrite	
Amine	K_s^A (M^{-1})	2-Bromoethyl nitrite: k_2^m ($M^{-1}s^{-1}$)	1-Phenylethyl nitrite: k_2^m ($M^{-1}s^{-1}$)	k_2^m ($M^{-1}s^{-1}$)	k_2^w/k_2^m	k_2^m ($M^{-1}s^{-1}$)	k_2^w/k_2^m
PiP	0.3	–	5×10^{-3}	0.16	18	6.1×10^{-3}	37
MEA	2.5	0.030	0.82×10^{-3}	0.017	14	9.8×10^{-3}	22
DEA	4.1	0.011	0.27×10^{-3}	0.027	37	1.23×10^{-3}	60
MBA	10	0.032	1.05×10^{-3}	0.032	91	4.5×10^{-3}	67
DPA	19	0.0094	0.24×10^{-3}	0.019	56	6.3×10^{-3}	157
DBA	86–79	0.0082	0.23×10^{-3}	0.015	81	0.62×10^{-3}	174
DPEA	220–265	0.013	0.28×10^{-3}	0.016	85	0.67×10^{-3}	190
MCH	30	0.014	0.40×10^{-3}	0.023	68	1.24×10^{-3}	113

Experimental conditions: [amine] $\sim 3 \times 10^{-3}$ mol dm^{-3} and [OH^-] $\sim 2 \times 10^{-2}$ mol dm^{-3}.

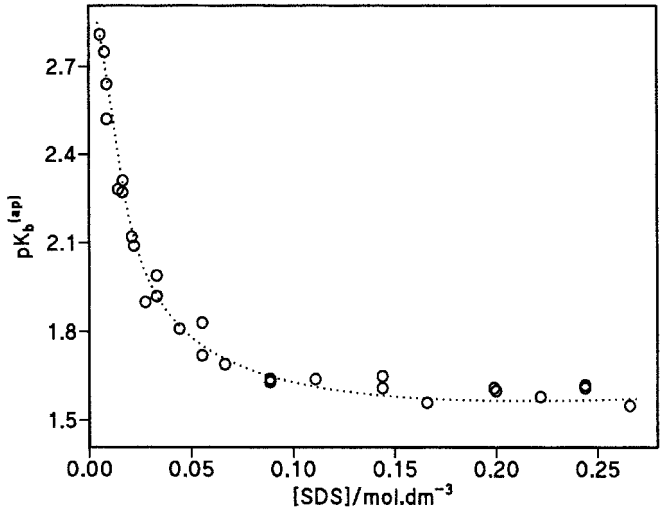
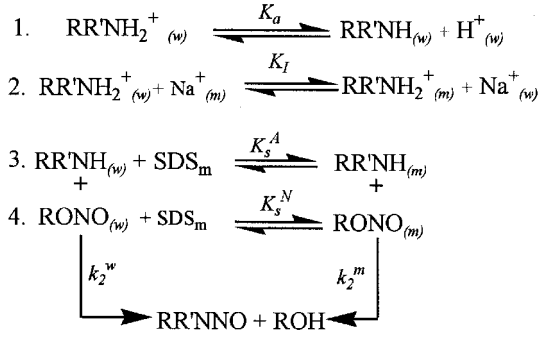


Figure 12. Variation of $pK_a^{(ap)}$ of piperidine as a function of [SDS] measured at [NaOH] = 0.054, 0.027 and 0.013 M and 25°C.

On increasing [SDS], the amount of the unprotonated form of the amine decreases and also A, which, in view of equation (14), results in a reduction of $pK_b^{(ap)}$ values, i.e. the presence of SDS micelles increases the basic character of amines owing to electrostatic attractions between alkylammonium cations and the negatively charged micellar surface. In general, at [SDS] = 0.1 mol dm^{-3} the saturation level is reached when [amine] is of the order of 3×10^{-3} mol dm^{-3} and $pK_b^{(ap)}$ has been reduced in one pK_b unit, see figure 12.

As for other ions, the association of alkylammonium cations with SDS micelles implies a competition between those cations and the Na^+ counterions of the surfactant, equilibrium 2 in scheme 16, governed by the ion-exchange constant K_I. This equilibrium constant decreases with the hydrophobic character of the alkylammonium ions and displays the highest value in the case of cyclic amines, such as PiP and its derivatives or MCH; see table 12.

In addition, the neutral form of the amine binds also to SDS micelles by hydrophobicity, for which the equilibrium constant is denoted by K_s^A. A comparison of K_s^A values obtained with SDS and TTABr micelles indicates that, even though less



Scheme 16. Reaction mechanism of the nitrosation of amines by RONO in SDS micelles.

Table 12. Experimental conditions and thermodynamic parameters obtained from the measurements of absorbance of the solutions of amines and from kinetic experiments varying [SDS].

Amine (c (mol dm^{-3}))	[OH$^-$] (mol dm^{-3})	K_I	Δ (pK_b)	K_S^A (mol^{-1} dm^3)
4MPiP (3.5×10^{-3})	0.035	60	1.83	6.8
2MPiP (3.5×10^{-3})	0.035	32	1.60	5.4
PiP (3.0×10^{-3})	0.054	14.5	1.28	4.6
PiP (3.0×10^{-3})	0.035	13.2	1.25	3.7
PiP (3.0×10^{-3})	0.027	12.8	1.24	3.2
MCH (3.0×10^{-3})	0.020	34	0.95	63
DPA (3.5×10^{-3})	0.033	20	0.93	36
HMI (6.5×10^{-3})	0.010	22	0.77	65
MBA (3.4×10^{-3})	0.033	9	0.75	22
MIP (3.0×10^{-3})	0.033	7.4	1.11	1.5
DEA (3.3×10^{-3})	0.020	4.5	0.85	3.4

4MPiP, 4-methylpiperidine; 2MPiP, 2-methylpiperidine; DPA, dipropylamine; HMI, hexamethylenimine; MBA, methylbutylamine; MIP, methyl-isopropylamine.

hydrophobic than the micelles of TTABr, SDS micelles provide for a greater association of amines. A possible cause may be that, in the interaction of neutral amines with SDS micelles, formation of H bonds between the sulphate head groups of surfactant and the >NH groups of amines may account for the total energy of interaction.

(2) *Micellar rate effects*. The SDS micellar effects on the transnitrosation reaction of amines by alkyl nitrites can be quantitatively explained on the basis of scheme 16.

To adapt the experimental kinetic data quantitatively to the theoretical equation resulting from scheme 16, we must take into account that, (1) the distribution constants of RONO between water and micellar pseudophases have been determined from the acid hydrolysis of alkyl nitrites, (2) the distribution constants of unprotonated amines to SDS micelles have been determined either from absorbance measurements at constant pH, controlled with a fixed and high [OH$^-$], or from kinetic experiments performed in the presence of high [OH$^-$] in order to avoid the protonation of amines, (3) the ion-exchange constants between the alkylammonium ions and Na^+ counterions have also been determined from absorbance measurements and (4) the reactivity in water was determined by studying the reaction in the absence of surfactant. Therefore, the reactivity in micelles is the sole parameter being determined in fitting the kinetic experimental data to the equation resulting from scheme 15. Some of these results are reported in table 11.

In accordance with the lower polarity of the micellar interface than that of the bulk aqueous phase, the reactivity in the micellar medium is lower than that in water. Nevertheless, the fact that the ratio k_2^w/k_2^m does not depend very much on which alkyl nitrite promotes the nitrosation reaction indicates that the reaction site in the micelle is independent of the varying hydrophobic character of the alkyl nitrite. This observation supports the previous assumption of H bond formation in the association of the neutral form of the amine with SDS micelles, a fact that makes the amine reside in a very hydrated zone of the micelle.

5. Concluding remarks

In this review we have discussed the reactivity of alkyl nitrites in water, aqueous solutions of β-CD or of surfactants forming micelles and in organic solvents. We have focused on three reactive processes undergone by alkyl nitrites in solution, namely the acid- and base-catalysed hydrolysis and the nitrosation reaction of secondary amines. In some cases the results were compared with those for carboxylic esters, which are structurally equivalent compounds, but behave quite differently. In all cases, kinetic features were explained on the basis of the reaction mechanism proposed for each experimental situation. Special attention was given to a detailed description of transition states with the aim of obtaining evidence for the principal features of the reaction. The results could have a direct projection to the possible occurrence *in vivo* of the reactive processes analysed here, inasmuch as alkyl nitrites are NO-generating compounds, or precursors of them, whose vasodilator properties are nowadays well known.

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