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Monitoring dediazoniation product formation by high-performance liquid chromatography after derivatization

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Abstract

A derivatization protocol that exploits the rapid reaction between arenediazonium ions and a suitable coupling agent followed by high-performance liquid chromatography analyses of the reaction mixture was employed to determine the product distribution, the rate constants for product formation and the association constant of 4-nitrobenzenediazonium, PNBD, ion with β-cyclodextrin, β-CD. The derivatization of PNBD with the coupling agent leads to the formation of a stable azo dye that prevents by-side reactions of PNBD with the solvents of the mobile phase, including water, or the metallic parts of the chromatographic system that would eventually lead to erroneous identification and quantification of dediazoniation products. The results show that in the presence of β-CD, nitrobenzene is formed at the expense of 4-nitrophenol, which is the major product in its absence. The observed rate constants for the interaction between PNBD and β-CD increase upon increasing [β-CD] showing a saturation profile indicative of the formation of an inclusion complex between PNBD and β-CD. By fitting the experimental data to a simplified Lineaweaver–Burk equation, the corresponding association constant and the maximum acceleration rate of β-CD towards PNBD were estimated. The protocol is applicable under a variety of experimental conditions provided that the rate of the coupling reaction is much faster than that of dediazoniation.

Keywords: Derivatization, LC; Dediazoniation; Rate constants; Cyclodextrins; 4-Nitrobenzenediazonium ion

1. Introduction

The complexation ability of cyclodextrins, CDs, has been exploited in the pharmaceutical industry, food technology and agriculture among other vital areas and a number of reviews on the topic are available [1–4]. Complexation by cyclodextrins can alter some of the physical and chemical properties of guest molecules, such as solubility, chemical reactivity and the spectroscopic and electrochemical properties, and has become a major research area for a number of reasons including their chiral discrimination ability, the solubilization of lipophilic substrates in aqueous media and stabilization of sensitive substances including electrogenerated radicals, modeling enzymatic reactions and drug delivery [5–9].

As expected, cyclodextrins also play an important role in all major areas of modern instrumental analysis and many of the effects mentioned above have been employed in a variety of analytical

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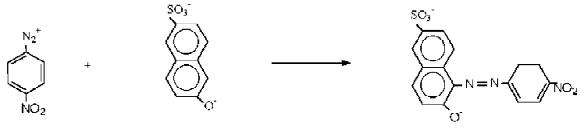
techniques [10–12]. During the past decade, much attention has been given to CDs and their derivatives in the field of chromatographic and non-chromatographic applications; [11–14] the wide interest arising from the fact that cyclodextrins can offer a high selective system for chromatographic analyses. Certainly, the partitioning and binding of many hydrophobic and hydrophilic organic molecules to the CD cavity can be much more selective than the partitioning and binding to a single solvent or to a single, traditional, stationary phase [15]. Particularly, in high-performance liquid chromatography, HPLC, the use of CDs has achieved spectacular success in two main fields; on one side through the development of chemically bonded cyclodextrin–silica stationary phases, leading to powerful tools for chiral separations into enantiomers. Alternatively, CDs have been employed dissolved in aqueous solution as mobile phase for isomer separations, offering significant advantages with respect to the use of mixed solvent mixtures [10,12].

Cyclodextrins form inclusion complexes with a number of substrates. This ability attracted attention from the biochemical point of view because CDs are widely employed as drug carriers or food additives and hence can be easily found in the human body both as free CDs and in the form of inclusion complexes. Particular attention has been given to those chemicals that lead to the formation of radicals. This is the case of arenediazonium ions, whose carcinogenic and mutagenic abilities are well known [16–20]. In this work we have exploited a derivatization protocol followed by HPLC analyses to investigate some features of the interaction between *p*-nitrobenzenediazonium, PNBD, ions and β-cyclodextrin, β-CD. The combined methodology allows simultaneous identification, quantification and monitoring the formation of all dediazoniation products with time, leading to estimations of the corresponding rate constants. Further quantitative analysis of the kinetic behavior makes possible the estimation of the corresponding association constant of PNBD with β-CD and to estimate the maximum acceleration rate.

The diversity of the reactions of aromatic diazonium salts together with their high reactivity and their extraordinary sensitivity to environmental changes [21–24] makes it inadvisable to directly inject ArN_2^+ reaction mixtures into the chromatographic system. A direct injection of reaction mixtures may lead readily to side reactions of the arenediazonium ions with any of the typical solvents employed in the mobile phase, including water [25], and hence leading to erroneous product identification and concentration values. Thus to monitor dediazoniations by HPLC it was necessary to employ a special protocol based on the derivatization of the arenediazonium ions with a suitable coupling agent to form a stable azo dye, Scheme 1. This derivatization reaction is well documented and has been, and still is, extensively employed in industrial processes to prepare dyes and pigments [23,26] and in analytical chemistry to determine a large variety of relevant compounds in different matrices [27–30].

PNBD was chosen because the presence of the electronwithdrawing $-NO_2$ group confers the molecule a completely different reactivity than that observed for arenediazonium ions with other substituents in the same position [24,31,32]. Since cyclodextrins may have an effect on the retention times and response factors of the expected dediazoniation products, which typically are the phenols, ArOH, halobenzenes, ArX, (when large amounts of X^- ions are present in solution) and the reductive benzene derivative, ArH, a study of the effects of β-CD on such chromatographic parameters was also performed.

The use of HPLC to monitor dediazoniations has some advantages with respect to more conventional techniques such as the commonly employed UV–Vis spectroscopy because with this technique typically only one single component can be monitored at a time and eventually it may become useless when the absorption bands of both the arenediazonium ions or



Scheme 1. Representative coupling reaction between PNBD and the sodium salt of 2-naphthol-6-sulfonic acid to yield the 6-sulfonate-2-naphthol-1-azo-*p*-nitrobenzene azo dye.

those of the products are masked by those of other compounds present in solution such as halocuprates (I and II), ascorbic acid, etc. [32,33]. On the contrary, when employing HPLC it is possible to identify, quantify and to obtain the rate constants for all dediazoniation products in one single experiment. This advantage becomes more feasible when using fully automated equipment routinely. Other advantages includes that products can be determined quantitatively at concentrations as low as 10^{-6} *M* in solutions containing catalysts or other products such as inert salts, micelles [28,34] or alcohols [35–37], in contrast with those typically achieved when employing older methods such as nitrogen evolution [38] or pressure changes [39].

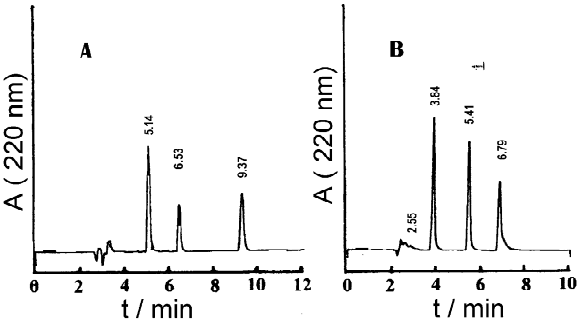


Fig. 1. Effect of solvent strength on the chromatograms of a standard solution prepared by dissolving β-CD ([β-CD]=9.5 m*M*) and the commercially available dediazoniation products 4-nitrophenol ([PNBOH]=$2.00\cdot10^{-4}$ *M*), nitrobenzene ([NBH]=$1.98\cdot10^{-4}$ *M*) and 4-chloro-nitrobenzene ([PNBCl]=$1.99\cdot10^{-4}$ *M*). (A) Mobile phase MeOH–water (75:25), (B) CH_3CN–water (75:25).

2. Experimental

2.1. Instrumentation

A Jasco high-performance liquid chromatographic system equipped with a Model PU-980 Intelligent pump, a Model 7725i Rheodyne injector, a Model UV-975 Intelligent detector, set at a wavelength of 220 nm, and a Waters Model 745B Data Module was used for product analyses. A sample loop of 100 μl was used. The HPLC separations were performed on a Prodigy-ODS Phenomenex (250×4.6 mm, 5 μm) column. The injection volume was 25 μl in all runs and the flow-rate was 0.8 ml min^{-1} at room temperature.

The composition of the mobile phase was selected from literature data as starting point [35–37]. Two different mobile phases were considered: MEOH–water (75:25), M/W, and acetonitrile (ACN)–water (75:25), A/W, mixtures. Typical chromatograms, in the presence of β-CD, are shown in Fig. 1A and B for M/W and A/W, respectively. Chromatographic parameters evaluated from chromatograms in Fig. 1 are shown in Table 1. Column efficiency is clearly higher for the A/W mixture than that for M/W. Peak separation is excellent for any one of the mobile phases given that a resolution, R_s, for two adjacent of R_s=1.5 corresponds to a peak overlap of about 1%. However, the sensitivity, given as the inverse of the detector response factor, D_{RF}, is excellent for the A/W mobile phase leading to a complete analyses in 8 min, meanwhile at least 10 min are needed when employing the M/W one. The combined data suggest, therefore, that a A/W (75:25) mobile phase is convenient for our purposes. However it must be noticed that lower concentration of salts such as NaX must be present in the system compared to those allowed when employing M/W to minimize salt precipitations. Changes in the percentages of A/W did not result in a significant improvement of the chromatographic separation (results not shown).

pH was measured by using previously calibrated Metrohm 713 pHmeter equipped with a temperature sensor. ^{1}H Nuclear magnetic resonance (NMR) spectra were obtained on a Varian VXR 200 spectrometer. Auxiliary spectrophotometric experiments, performed with a Beckman DU 640 UV–Vis spectrophotometer, indicated that an optimum wavelength to detect the potential dediazoniation products was 220 nm.

2.2. Reagents and materials

Reagents were of the maximum purity available and were used without further purification. 4-Nitrophenol, PNBOH, 4-nitrochlorobenzene, PNBCl, and nitrobenzene, PNBH, were purchased from Aldrich (USA) or Fluka (Switzerland). 2-Naphtol-6-sulfonic acid, sodium salt (2N6S) was purchased from Pflatz and Bauer (USA). Other materials employed were from Riedel-de Häen (Germany) or Panreac (Spain).

Table 1
Average values for some chromatographic parameters evaluated from the chromatograms in Fig. 1 and from other not shown

Analyte	MeOH–water (75:25), $t_M = 2.71$				ACN–water (75:25), $t_M = 2.55$			
	t_R	D_{RF}	N	R_s	t_R	D_{RF}	N	R_s
PNBOH	5.03	$1.52 \cdot 10^{-10}$	4448		3.84	$1.93 \cdot 10^{-10}$	5898	
PNBH	6.53	$6.17 \cdot 10^{-11}$	7581	5.0	5.41	$2.22 \cdot 10^{-10}$	8130	6.3
PNBCl	9.41	$3.90 \cdot 10^{-10}$	7855	8.2	6.79	$2.36 \cdot 10^{-10}$	8172	3.9

Both the dead time t_M and the retention time t_R are given in min.

All solutions were prepared by using Milli-Q grade water system (Millipore, USA).

PNBD, tetrafluoroborate was purchased from Aldrich, 97%, and was purified by recrystallization from acetonitrile–cold ether mixtures and stored in the dark at low temperature to minimize its decomposition. The UV–Vis spectrum of $1.0 \cdot 10^{-4}$ *M* PNBD in $3.0 \cdot 10^{-3}$ *M* HCl solution shows two broad bands, the main one centered at $\lambda = 258$ nm and a shoulder at $\lambda = 310$ nm consistent with literature results [40]. The Beer's law plot up to $9.3 \cdot 10^{-4}$ *M* PNBD in $3.36 \cdot 10^{-4}$ *M* HCl is linear (correlation coefficient = 0.999) yielding $\varepsilon_{258} = 16\,400\ M^{-1}\ cm^{-1}$ in agreement with the literature value [40]. The ^1H NMR spectra of PNBD in CD_3CN at 25 °C is a pair of doublets of equal area centered at $\delta = 8.72$ ppm ($J = 5$ Hz) and $\delta = 8.86$ ppm ($J = 5$ Hz).

The HCl solutions were prepared from dilution from concentrated commercial HCl. The pH was determined potentiometrically from convenient diluted solutions. The universal Britton-Robinson, BR, buffer was prepared by mixing sufficient amounts of H_3BO_3, CH_3COOH, and H_3PO_4 with a concentrated NaOH solution to obtain the desired pH. The final concentration of each electrolyte was 0.04 *M*.

2.3. Derivatization protocol

Chromatographic kinetic data were obtained by quenching the dediazoniation reaction at convenient time intervals with an aliquot of a stock quenching solution. This quenching solution, that leads to the formation of a stable azo dye, Scheme 1, was prepared by dissolving the sodium salt of 2N6S in a BR buffer solution to yield final concentrations of 0.003 *M* 2N6S. This coupling agent was chosen because their coupling reactions with a variety of arenediazonium ions may be very fast under appropriate experimental conditions and because both 2N6S and the derivatized azo dye bear a sulfonic group in their molecules making them to elute with other salts in the front peak and hence no interferences from these analytes are expected in the chromatograms.

A complete, representative, experimental protocol is as follows. Typically, 15–20 volumetric flasks containing all reagents except PNBD were prepared under identical experimental conditions and thermostated at $T = 35$ °C. Dediazoniation was initiated by rapidly adding an aliquot of the freshly prepared stock solution of PNBD to each volumetric flask so that final volume was 3 ml. At progressively longer intervals of time, 1 ml of the quenching 2N6S solution was added to the reaction mixture so that after addition the final 2N6S concentration was in about 10-fold excess over that of the arenediazonium salt and the final pH was ca. 8.0.

Coupling rates change dramatically with pH because naphthoxide ions are much more reactive than their parent naphthols [22–24], but as pH increases, the reaction of arenediazonium ions with OH^- to form diazotates [41] becomes significant. Control experiments showed that pH 8.0 is an optimal pH to quench efficiently the dediazoniation reaction because control experiments showed that at pH 8.0 the rate of the coupling reaction, measured by monitoring azo dye formation spectrophotometrically at $\lambda = 480$ nm, is over one order of magnitude faster than the fastest dediazoniation reaction.

After dediazoniation was complete, the solutions were cooled to room temperature, carefully transferred to 5-ml volumetric flasks and diluted with ACN up to the mark to ensure that the ArOH and

particularly ArH, which has a limited solubility in water, were completely dissolved. Aliquots of these solutions were transferred to HPLC vials and analyzed in triplicate. The relative standard deviation of the peak areas was less than 2%.

In each set of experiments one sample was quenched immediately (i.e., $t=0$) and a second one was allowed to go to completion without adding the 2N6S quenching solution. The unquenched sample was used to estimate product concentrations at infinite time. The sample at $t=0$ was used to check for possible decomposition or impurities of the starting PNBD material and to check that the coupling reaction was much faster than the dediazoniation one. Chromatograms of the immediately quenched sample were free of extraneous peaks confirming the purity of the substrate employed and that the dediazoniation reaction is quenched effectively by the 2N6S quenching solution employed.

2.4. Kinetic methods

The observed rate constants for the formation of dediazoniation products were obtained by fitting the percentage of formation of a particular product, PF, and time data to the integrated first order Eq. (1) using a commercial non linear least squares method:

$$\ln\frac{(PF_\infty - PF_t)}{(PF_\infty - PF_0)} = -k_{obs}t \quad (1)$$

where k_{obs} stands for the observed rate constant and PF_t, PF_0 and PF_∞ represent the percentages of formation of a particular dediazoniation product at any time, at zero time and at infinite time, respectively. PF values were obtained from the initial PNBD concentration, estimated by mass, and the dediazoniation product concentration, [Analyte], which was estimated from the corresponding HPLC peak areas by employing the corresponding detector response factor (see later), Eq. (2). All experiments were carried out at $T=35\pm0.1$ °C with PNBD under pseudo-first order conditions, i.e., [PNBD]<<<[β-CD]. The good agreement between the experimental and the optimized PF_∞ values confirmed that the reactions were first order with respect to β-CD.

$$PF = 100\frac{[Analyte]}{[PNBD]} \quad (2)$$

3. Results and discussion

3.1. Effects of β-CD on t_R and on D_{RF}

The possibility of formation of inclusion complexes between the potential dediazoniation products and β-CD prompted us to study the effect of [β-CD] on representative chromatographic parameters of PNBOH, PNBH and PNBCl. Tabulated data are given as supplementary material. For a given pH 2 either in unbuffered (HCl) or buffered (BR) solutions, both the retention times and the response factors values are not affected by the concentration of β-CD up to 10 m*M*, being the average values for PNBOH $t_R=3.4$ min, $D_{RF}=(1.90\pm0.06)\cdot10^{-10}$, for PNBH $t_R=5.42$ min, $D_{RF}=(2.28\pm0.05)\cdot10^{-10}$, and for PNBCl, $t_R=6.80$ min, $D_{RF}=(2.37\pm0.11)\cdot10^{-10}$. Thus, under the chosen experimental conditions, β-CD shows no effect on t_R and on D_{RF} and hence it is possible to carry out the separation of the expected products for the interaction between PNBD and β-CD under optimal conditions.

3.2. Effects of pH on t_R and on D_{RF}

Given that ionizable phenolic compounds may be formed during the dediazoniation course, it was considered of interest to investigate the effects of pH on the mentioned chromatographic parameters for typical dediazoniation products in the presence of β-CD. Tabulated data are given as supplementary material. Either t_R and D_{RF} for any of the investigated dediazoniation products remain essentially constant within the pH range investigated (2–8) except for the more hydrophilic PNBOH, for which t_R, and especially D_{RF} decrease significantly at pH> 5. The average values for PNBH are $t_R=5.41$ min, $D_{RF}=(2.33\pm0.07)\cdot10^{-10}$ and for PNBCl, $t_R=6.78$, $D_{RF}=(2.28\pm0.05)\cdot10^{-10}$. The observed decrease in t_R (3.84 min at pH 2, 3.01 min at pH 8) and D_{RF} ($1.91\cdot10^{-10}$ at pH 2, $0.96\cdot10^{-10}$ at pH 8) can be interpreted in terms of the ionization of PNBOH, whose pK_a value has been reported as $pK_a=7.14$ in

the absence of β-CD and p$K_a \approx 6.1$ in the presence of β-CD due to its inclusion into the CD cavity [42].

3.3. Determination of the rate constants for product formation

Fig. 2 shows a typical kinetic plot in the absence of β-CD for the variation in the percentage of formation, PF, of the major dediazoniation product, PNBOH, with time. By fitting the PF vs. time data to the integrated first order Eq. (1), the corresponding observed rate constant was obtained, yielding a value of $k_{obs} = 0.125\ h^{-1}$, which is in excellent agreement with reported values obtained employing different techniques [24,43].

In aqueous acid solution, in the dark, and in the absence of catalysts, the major PNBD dediazoniation product is PNBOH and only traces of the reduction product PNBH are detected [31,32]. However when β-CD is present in the system, a completely different product distribution from that in its absence is obtained, as illustrated in Fig. 3. The percentage of formation of the heterolytic PNBOH product decreases upon increasing β-CD with a concomitant increase the percentage of formation of the reduction product PNBH, and quantitative conversion to products is obtained when [β-CD]/[PNBD]>20. Formation of high amounts of PNBH at the expense of PNBOH is consistent with a radical mechanism, thus the change in the product distribution is suggestive of a β-CD-induced change in the reaction mechanism [24].

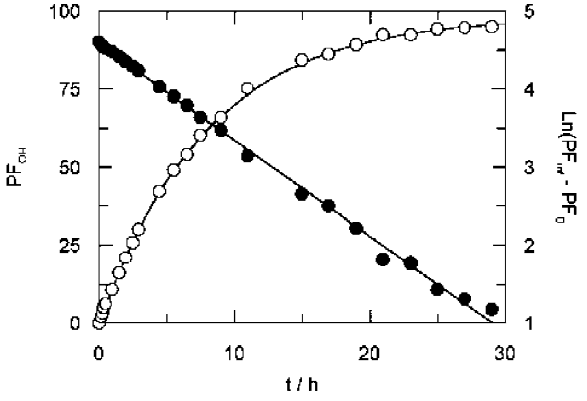


Fig. 2. Variation in the percentage of formation of PNBOH with time (○) and first-order plot (●) according to Eq. (1).

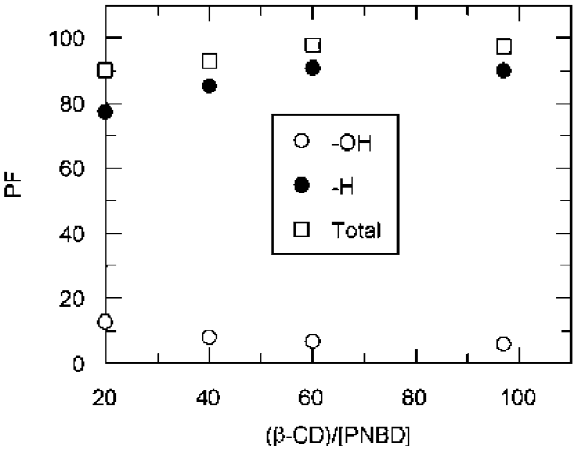


Fig. 3. Effect of β-CD on PNBD dediazoniation product distribution.

Fig. 4 shows the effects of [β-CD] on k_{obs}, which was obtained by monitoring the formation of the major dediazoniation product PNBH. Similar k_{obs} values were obtained when monitoring PNBOH formation but larger errors were obtained because its yield is much lower than that of PNBH, as indicated in Fig. 3. Fig. 4 shows that at low [β-CD] k_{obs} increase linearly upon increasing [β-CD] becoming independent of [β-CD] at higher concentrations. This saturation kinetic profile, similar to those obtained in some enzymatic reactions, is typical of reaction mechanisms in which the rate-determining step is preceded by the formation of reaction intermediates in one or more rapid pre-equilibrium steps, i.e., it is suggestive of the rapid formation of an inclusion complex [1,42].

3.4. Determination of the association constant of PNBD with β-CD

Inclusion complex formation in solution is a dynamic equilibrium process [1,10,42] that can be illustrated by Eq. (3), where CD is the cyclodextrin, G is the guest molecule and CD-G stands for the inclusion complex:

$$CD + G \leftrightarrows CD\text{-}G \quad (3)$$

The stability of the inclusion complex can be

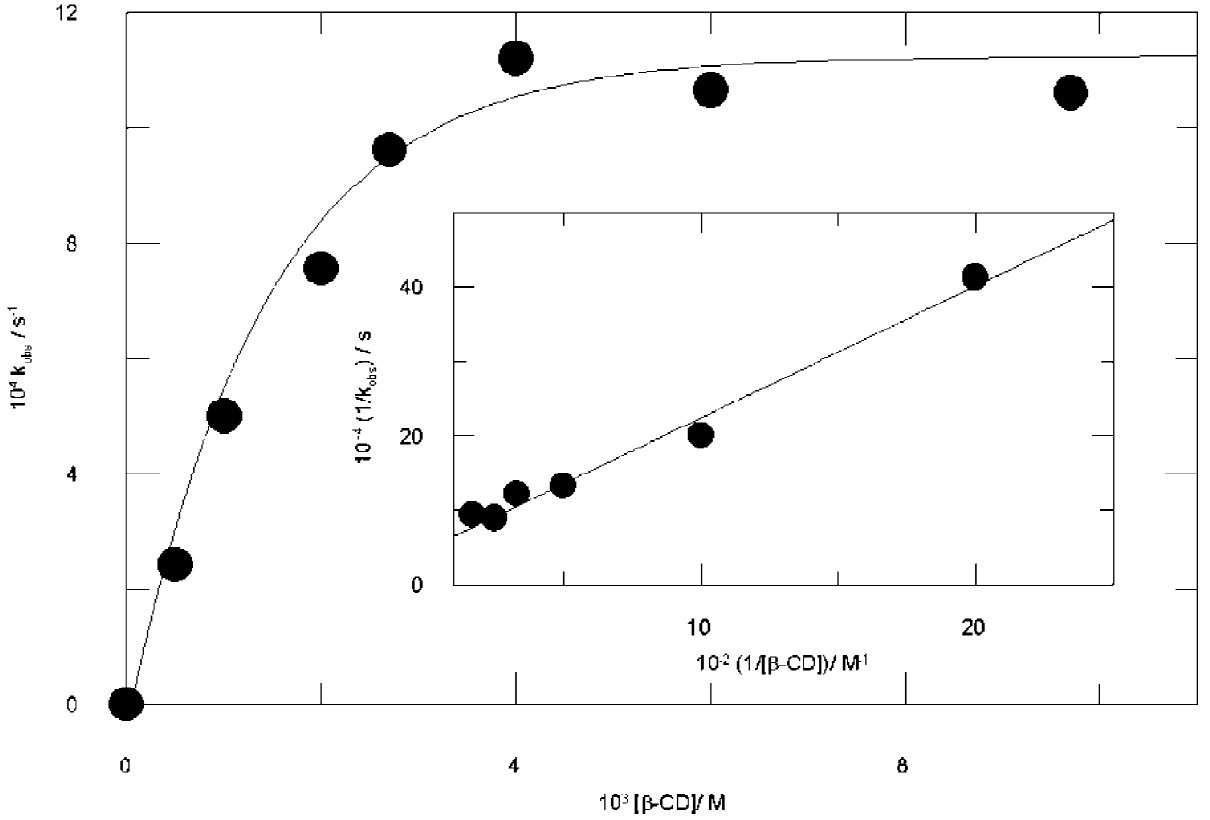


Fig. 4. Effect of β-CD on the observed rate constant as determined by HPLC. The inset figure illustrates the linear plot according to Eq. (6).

described in terms of a formation constant, K_f, which is given by Eq. (4):

$$K_f = [\text{CD-G}]/[\text{CD}][\text{G}] \quad (4)$$

and hence the observed rate constant is given by Eq. (5) [3,8,44]:

$$k_{obs} = \frac{k_{nc} + k_c K_f[\beta\text{-CD}]}{1 + K_f[\beta\text{-CD}]} \quad (5)$$

where k_{nc} is the rate constant for the disappearance of the non-complexed substrate, k_c is that for the complexed substrate and K_f the formation constant of the inclusion complex and [β-CD] the total cyclodextrin concentration. Note the similarity of Eq. (5) and that of Michaelis–Menten for the enzymatic reactions [8,42]. Eq. (5) can be linearized according to the Lineweaver–Burk method, which in turn can be simplified to Eq. (6) by assuming $k_{nc} <<< k_c K_f[\beta\text{-CD}]$:

$$\frac{1}{k_{obs}} = \frac{1}{k_c} + \frac{1}{k_c K_f} \cdot \frac{1}{[\beta\text{-CD}]} \quad (6)$$

Eq. (6) predicts that the double reciprocal plot of k_{obs} vs. [β-CD], i.e., $1/k_{obs}$ vs. $1/[\beta\text{-CD}]$ should be linear, inset in Fig. 4, with an intercept $i = 1/k_c$ and a slope $s = 1/k_c K_f = i/K_f$. Hence values of $k_c = (2.1 \pm 0.8) \cdot 10^3\ s^{-1}$ and $K_f = 2600\ M^{-1}$ can be estimated from such a plot. The maximum acceleration rate, estimated as $k_c/k_{nc} = 2.4 \cdot 10^4$ indicates the tremendous catalytic effect that β-CD presents for this reaction.

4. Conclusions

Our results show that our methodology allows

simultaneous identification, quantification and estimations of the rate constant for product formation, providing valuable kinetic information on the system. Dediazoniation of PNBD in the presence of β-CD proceeds through a homolytic pathway because of the practical absence of products associated with the ionic pathway, i.e., ArOH, as a result of the formation of an inclusion complex.

The key of the method is to quench rapidly the dediazoniation reaction prior to HPLC analyses. This condition can be easily fulfilled because rates for coupling reactions are, under selected conditions, very fast and a large number of coupling agents are available. The methodology can be useful to identify, quantify and to monitor dediazoniations carried out in a variety of experimental conditions including alcohol–water mixtures, nonaqueous systems, micellar and macromolecular systems. This information cannot be obtained solely by the classical UV–Vis spectroscopy, which is basic to explore the interactions of aromatic diazonium ions.

5. Supplementary material

Tabulated data of t_R and D_{RF} values (two pages) under different experimental conditions are available from the authors.

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