Inhibition of Acid-Induced Decomposition of Diphenyltriazenes by Complexation with Cyclodextrins

TINGTING XU, ATEFEH VAEZ-ZADEH ASADI, MÓNICA BARRA

Department of Chemistry, University of Waterloo, Waterloo, Ontario, Canada N2L 3G1

Received 23 October 2009; revised 3 February 2010; accepted 3 February 2010

DOI 10.1002/kin.20503
Published online 25 June 2010 in Wiley InterScience (www.interscience.wiley.com).

ABSTRACT: Acid-promoted N—N bond cleavage in 1,3-diphenyltriazenes (X-Ph-N=N-NH-Ph-X; X = H, 4-OCH_3), leading to formation of diazonium ions and anilines, is strongly inhibited in aqueous solutions in the presence of cyclodextrins (CDs). The inhibition is ascribed to the formation of inclusion complexes that render the guest diphenyltriazene significantly less basic as a result of the less polar nature of the CD cavity (a microsolvent effect). Association equilibrium constants for 1:1 host–guest complexes increase in the order α-CD <β-CD ∼ permethyl-β-CD < hydroxypropyl-β-CD, with values for X = 4-OCH_3 being larger than those for X = H. In the case of α-CD, formation of 2:1 host–guest complexes is also involved. © 2010 Wiley Periodicals, Inc. Int J Chem Kinet 42: 567–574, 2010

INTRODUCTION

Triazenes (compounds characterized by having a diazoamino group, —N1=N2—N3<) are commonly used in organic synthesis to protect or generate amines [1] and are known as well for their mutagenic and carcinogenic properties [2]. Both the utility of triazenes as protecting groups/source of amines and their capacity to modify (alkylate) DNA result from the ability of triazenes to generate diazonium ions via heterolytic N2—N3 bond cleavage triggered by protonation of N3. The likelihood of triazenes to undergo (significant) decomposition under typical human gastric pH conditions, however, limits the capability of aryltriazenes known for their antiviral [3] and trypanocidal [4] activity, for instance, to be administered orally. Such a limitation could in principle be overcome by developing coated formulations based, for example, on the use of host molecules such as cyclodextrins, as drug carriers.

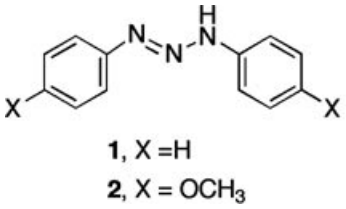
Cyclodextrins (CDs) are doughnut-shaped cyclic oligosaccharides of six to eight α-D-glucose units and represent one of the most commonly employed (water-soluble) host systems [5]. Since water is the solvent where most biological processes take place, the

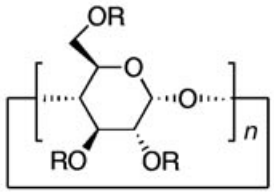
Correspondence to: Mónica Barra; e-mail: mbarra@uwaterloo.ca.

Contract grant sponsor: Department of Chemistry of the University of Waterloo, Waterloo, Canada.

Contract grant sponsor: Natural Sciences and Engineering Research Council (NSERC) of Canada.

Experimentally observed rate constants are available as Supporting Information in the online issue at www.interscience.wiley.com.





Host	n	R
ACD	6	H
BCD	7	H
HPBCD	7	$CH_2CHOHCH_3$
PMBCD	7	CH_3

Figure 1 Target substrates and hosts.

characterization of inclusion compounds (complexes) derived from water-soluble CDs continues to be a subject of significant interest for applications, among others, in drug transport and delivery, catalysis, and the binding and detection of biomolecules [6].

The present article reports on the effects of cyclodextrin complexation on the acid-catalyzed decomposition of 1,3-diphenyltriazene (**1**) and 1,3-bis-(4-methoxyphenyl)triazene (**2**), two diaryltriazenes of known biological activity [3,7]. Rate constants for acid-promoted N2—N3 bond cleavage were measured in the presence of α-, β-, 2-hydroxypropyl-β-, and permethyl-β-cyclodextrin (Fig. 1), to assess the influence of host (cavity) size and rim substitution on triazene degradation.

EXPERIMENTAL

Reagents

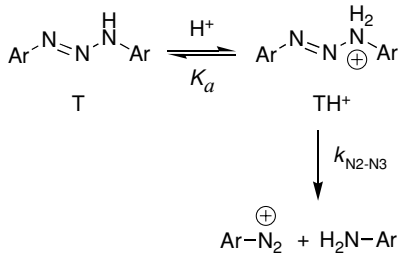
1,3-Diphenyltriazene and 1,3-bis-(4-methoxyphenyl)-triazene employed were existing samples from a previous study [8]. Methanol and acetonitrile (OmniSolv grade; EM Science, Gibbstown, NJ), 2-hydroxypropyl-β-cyclodextrin (FW = 2,354), α-cyclodextrin, and β-cyclodextrin (Aldrich, St. Louis, MO), permethyl-β-cyclodextrin (TCI, Portland, OR), soluble starch (Baker, Phillipsburg, NJ), and D-glucose (EM Science) were used as received. Buffer solutions were prepared using analytical grade salts (EM Science) and water purified in a Millipore apparatus.

Instrumentation and Procedures

Decomposition of target diphenyltriazenes was monitored photometrically using a Varian Cary 1 Bio spectrophotometer with a thermostated cell compartment connected to a circulating water bath. Reactions were initiated by adding 41 μL of an appropriate stock triazene solution in methanol (unless noted otherwise) to 2 mL of an aqueous buffer solution containing all the other constituents; resulting aqueous solutions thus contained 2% (v/v) MeOH and substrate concentrations ranging in the order of (3–4) × 10^{-5} M. The buffer concentration employed was 0.05 M, and the ionic strength of the solutions was kept constant at 0.5 M using NaCl as compensating electrolyte. Kinetic traces were obtained at (21.0 ± 0.1)°C by monitoring the disappearance of target diphenyltriazenes at 352 nm (**1**) or 367 nm (**2**). All reactions were followed until at least 80–90% conversion of the starting material was observed. Values for observed rate constants, as well as for rate coefficients and association equilibrium constants, were obtained by fitting to appropriate functions using the general curve-fitting procedure of KaleidaGraph (version 3.6.4) from Synergy Software. Fittings based on Eqs. (2)–(6) were carried out setting [CD] = $[CD]_0$, where $[CD]_0$ refers to the total cyclodextrin concentration. Proton concentrations were calculated from the observed pH by using a value of 0.732 for the proton activity coefficient [9]. Induced circular dichroism spectra were recorded on a JASCO J-715 spectropolarimeter (0.2-nm resolution, 10 accumulations, 1-cm cell) at (24 ± 1)°C.

RESULTS AND DISCUSSION

Acid-promoted decomposition of aryltriazenes dissolved in aqueous media typically involves general acid catalysis (A-S_E2) [10] or specific acid catalysis (A1) [8,11]. Decomposition of **1**, under experimental conditions analogous to those of this study, has been found to follow an A1 mechanism (Scheme 1), as rates increase with decreasing pH and are independent of the buffer concentration [12]. The expression



Scheme 1

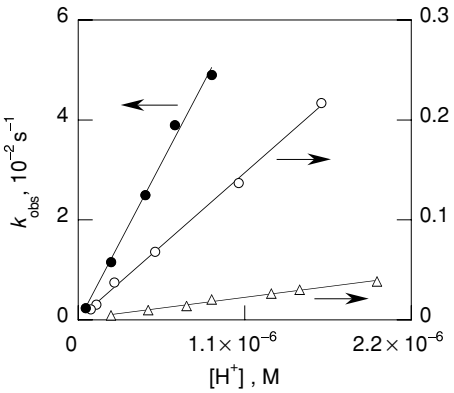


Figure 2 Proton dependence of the observed rate constant for acid-promoted decomposition of **1** (○, aqueous solution; △, 11 mM BCD aqueous solution) and **2** (●, aqueous solution).

for the observed rate constant (k_{obs}) corresponding to Scheme 1 is given by Eq. (1), where K_a and k_{N2-N3} represent, respectively, the acid dissociation equilibrium constant (expressed in terms of concentration) for the N3-protonated intermediate (TH^+) and the first-order rate constant for heterolytic cleavage of the N2—N3 bond.

$$k_{obs} = \frac{k_{N2-N3}[H^+]}{K_a + [H^+]} \quad (1)$$

For both substrates **1** and **2**, decay traces were collected using a series of solutions at different pH, and in all cases traces follow first-order kinetics.* Resulting k_{obs} vs. [H^+] plots are linear (Fig. 2, circles), indicating that, under the experimental conditions of this study, $K_a \gg [H^+]$ in the denominator of Eq. (1). Instability of triazenes in acidic media precludes measurement of their basicity; however, theoretical calculations have systematically shown that protonation of N3, in spite of being thermodynamically less favorable, is able to compete with that of the (more basic) N1 position [13]. That the pK_a of TH^+ (for **1** and **2**) is much lower than the lowest pH used in this study (i.e., p$K_a \ll 6$) is fully consistent with the pK_a value of 4.95 reported for acid-promoted decomposition of triazene ($HNNNH_2$) [14], since resonance effects are expected to decrease the electron density, and hence basicity, of the triazeno moiety in diphenyltriazenes relative to that of triazene. It is also in agreement with the assumption that the electron-withdrawing character of the N=NAr moiety (e.g., $\sigma_m = 0.32$ and $\sigma_p = 0.39$ for N=NPh [15]) would render the N3-protonated forms of **1** and **2** more acidic than the conjugate forms of aniline ($pK_a^{BH^+} = 4.63$ [16a]) and *p*-anisidine ($pK_a^{BH^+} = 5.34$ [16b]), respectively.

The linear plots shown in Fig. 2 (circles) yield k_{N2-N3}/K_a values of $(1.33 \pm 0.03) \times 10^3$ M^{-1} s^{-1} and $(5.3 \pm 0.1) \times 10^4$ M^{-1} s^{-1} for **1** and **2**, respectively. The second-order rate coefficient k_{N2-N3}/K_a clearly increases with increasing electron-donating (ED) ability of the phenyl ring, in agreement with previous reports on substituent effects on acid-catalyzed decomposition of aryltriazenes [8,11a,17]. The trend is attributed to an increase in N3 basicity and in stabilization of the developing aryldiazonium ion with increasingly stronger ED groups. Figure 2 also displays observed rate constant values (triangles) for decomposition of **1** in solutions containing 11 mM BCD. The corresponding slope, namely (196 ± 8) M^{-1} s^{-1}, is significantly smaller than that determined for **1** in the absence of CD, indicating a clear retardation effect on the rate of acid-promoted N2—N3 heterolytic bond cleavage.

To assess the dependence of this inhibitory effect on CD (cavity) size and rim substitution, for both substrates and for each of the CDs employed in this study, kinetic traces were recorded using a series of solutions at constant pH but varying host concentration. In all cases, corresponding k_{obs}^{CD} values (i.e., observed rate constants in the presence of CDs) are found to decrease nonlinearly with the CD concentration (Figs. 3–5). The lack of any effect in the presence of glucose (10 mM) and of only a slight retardation (if at all significant) upon addition of soluble starch (in an amount equivalent to 2 mM BCD) of the rate of decomposition of **1** in aqueous phosphate buffer solutions (pH 6.16)

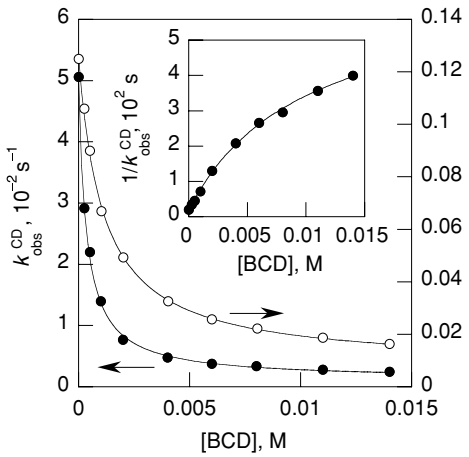


Figure 3 Influence of β-cyclodextrin concentration on the observed rate constant for acid-catalyzed decomposition of **1** (○) and **2** (●) in 2% MeOH aqueous phosphate buffer (pH 6.16). Inset: reciprocal plot of data for **2**.

*Experimentally observed rate constants are available as Supporting Information.

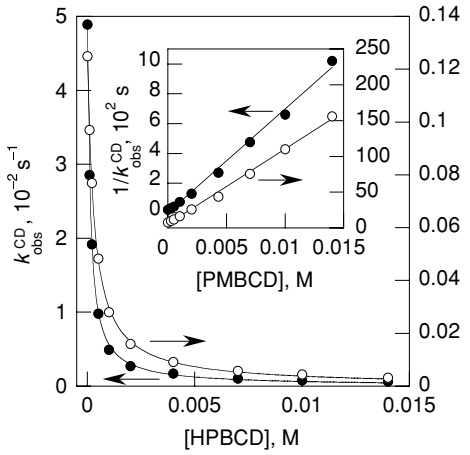


Figure 4 Influence of 2-hydroxypropyl-β-cyclodextrin and permethyl-β-cyclodextrin (inset) concentration on the observed rate constant for acid-catalyzed decomposition of **1** (○) and **2** (●) in 2% MeOH aqueous phosphate buffer (pH 6.16).

clearly indicates that the kinetic effects observed in the presence of CDs are due to the formation of inclusion complexes and not just to unspecific interactions; thus, and assuming the conventional 1:1 host–guest stoichiometry, acid-catalyzed decomposition of target triazenes in the presence of CDs can be represented as shown in Scheme 2. Bearing in mind that under the experimental conditions of this study, target substrates are essentially in their neutral form (i.e., molar fraction of neutral substrate ≈1, as inferred from the linear plots shown in Fig. 2), the expression for

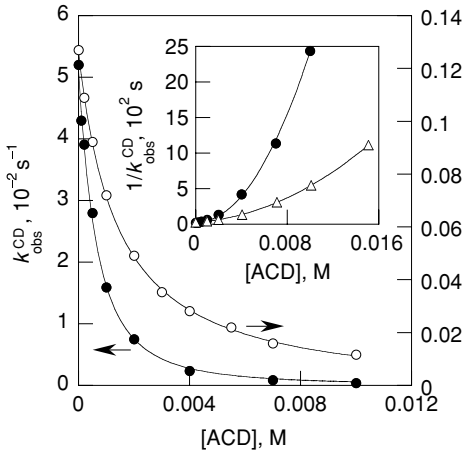
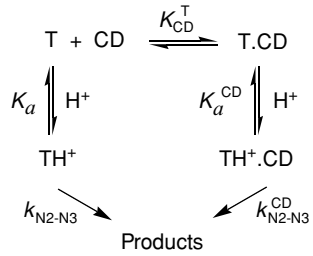


Figure 5 Influence of α-cyclodextrin concentration on the observed rate constant for acid-catalyzed decomposition of **1** (○) and **2** (●) in 2% MeOH aqueous phosphate buffer (pH 6.16). Inset: reciprocal plot of data for decomposition of **2** in phosphate buffer (pH 6.16) with different organic cosolvents (●, 2% MeOH; △, 2% MeCN).



Scheme 2

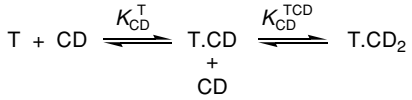
the observed rate constant corresponding to Scheme 2 would be given by Eq. (2), where K_{CD}^{T} represents the association equilibrium constant (concentrations quotient) for cyclodextrin–neutral substrate complex (T.CD), whereas K_a^{CD} and k_{N2-N3}^{CD} represent, respectively, the acid dissociation equilibrium constant and the first-order rate constant for heterolytic cleavage of the complexed N3-protonated intermediate (TH^+.CD).

$$k_{obs}^{CD} = \frac{\left\{(k_{N2-N3}/K_a) + \left(k_{N2-N3}^{CD}/K_a^{CD}\right) K_{CD}^{T}[CD]\right\}[H^+]}{1 + K_{CD}^{T}[CD]} \quad (2)$$

For BCD as host, nonlinear curve fittings according to Eq. (2) render the first-order rate coefficients and association equilibrium constant values listed in Table I. For HPBCD and PMBCD as hosts, however, fittings according to Eq. (2) reveal that the term $(k_{N2-N3}^{CD}/K_a^{CD})K_{CD}^{T}[CD]$ is actually negligible in comparison to k_{N2-N3}/K_a, in agreement with linear $1/k_{obs}^{CD}$ vs. [CD] plots (e.g., Fig. 4 inset). Thus, nonlinear curve fittings according to Eq. (3) ultimately render association equilibrium constant values for HPBCD and PMBCD (Table I).

$$k_{obs}^{CD} = \frac{(k_{N2-N3}/K_a)[H^+]}{1 + K_{CD}^{T}[CD]} \quad (3)$$

For ACD as host, data cannot be explained on the basis of the mechanism proposed in Scheme 2 and Eq. (2). As illustrated in Fig. 5 (inset), plots of $1/k_{obs}^{CD}$ vs. [CD] curve upward, particularly in the case of data for decomposition of **2**. This nonlinear dependence is consistent with a mechanism involving formation of host–guest complexes with 2:1 stoichiometry (Scheme 3), a common observation when using



Scheme 3

Table I First-Order Rate Coefficients and Association Equilibrium Constants Obtained for Decomposition of **1** and **2** in the Presence of CDs[a]

	1			**2**		
CD	$k_{N2-N3}[H^+]/K_a$ (10^{-3} s^{-1})	K_{CD}^{T} (10^2 M^{-1})	$K_{CD}^{T}K_{CD}^{TCD}$ (10^5 M^{-2})	$k_{N2-N3}[H^+]/K_a$ (10^{-3} s^{-1})	K_{CD}^{T} (10^2 M^{-1})	$K_{CD}^{T}K_{CD}^{TCD}$ (10^5 M^{-2})
ACD	1.26 ± 0.01	7.4 ± 0.2	0.30 ± 0.05	51.2 ± 0.8	14 ± 2	7 ± 2
ACD[b]				36.3 ± 0.1	4.0 ± 0.8	1.4 ± 0.4
BCD	1.26 ± 0.01	9.1 ± 0.4		50.5 ± 0.5	29 ± 1	
	(0.077 ± 0.009)[c]			(1.1 ± 0.2)[c]		
HPBCD	1.26 ± 0.01	32.1 ± 0.8		49.1 ± 0.4	77 ± 2	
PMBCD	1.28 ± 0.01	10.9 ± 0.4		46.5 ± 0.9	22 ± 1	

[a] Solvent contains 2% (v/v) methanol (unless stated otherwise); $T = 21°C$; $\mu = 0.5$ M (NaCl); 0.05 M phosphate buffer (pH 6.16). Errors given correspond to the standard deviations.

[b] Solvent contains 2% (v/v) acetonitrile.

[c] Value for $k_{N2-N3}^{CD}[H^+]/K_a^{CD}$.

ACD as host. Based on the two-equilibria model depicted in Scheme 3, the expression corresponding to the observed rate constant for acid-promoted decomposition of target triazenes in the presence of ACD would be given by Eq. (4), where K_a^{CD2} and k_{N2-N3}^{CD2} represent, respectively, the acid dissociation equilibrium constant and the first-order rate constant for heterolytic cleavage of 2:1 cyclodextrin–TH^+ complexes.

$$k_{obs}^{CD} = \frac{\left\{(k_{N2-N3}/K_a) + \left(k_{N2-N3}^{CD}/K_a^{CD}\right) K_{CD}^{T}[CD] + \left(k_{N2-N3}^{CD2}/K_a^{CD2}\right) K_{CD}^{T}K_{CD}^{TCD}[CD]^2\right\}[H^+]}{1 + K_{CD}^{T}[CD] + K_{CD}^{T}K_{CD}^{TCD}[CD]^2} \quad (4)$$

Curve fittings reveal that $\{(k_{N2-N3}^{CD}/K_a^{CD})K_{CD}^{T}[CD] + (k_{N2-N3}^{CD2}/K_a^{CD2})K_{CD}^{T}K_{CD}^{TCD}[CD]^2\} \ll k_{N2-N3}/K_a$ in the numerator of Eq. (4), in agreement with linear $(1/k_{obs}^{CD} - 1/k_{obs})/[CD]$ vs. [CD] plots (not shown). Thus, Eq. (4) reduces to Eq. (5), from which nonlinear fittings yield association equilibrium constants for 1:1 and 2:1 ACD complexes (Table I).

$$k_{obs}^{CD} = \frac{(k_{N2-N3}/K_a)[H^+]}{1 + K_{CD}^{T}[CD] + K_{CD}^{T}K_{CD}^{TCD}[CD]^2} \quad (5)$$

In all cases, calculated first-order rate coefficients corresponding to reaction in the bulk solution lead to k_{N2-N3}/K_a values that agree very well with those determined from the pH-dependence series in the absence of CD. Furthermore, from the values for the three fitted parameters given in Table I for decomposition of **1** in the presence of BCD, one obtains $\{(k_{N2-N3}/K_a) + (k_{N2-N3}^{CD}/K_a^{CD})K_{CD}^{T}[CD]\}/(1 + K_{CD}^{T}[CD]) \approx 195$ M^{-1} s^{-1} (at [CD] = 11 mM), in excellent agreement with the slope value calculated from Fig. 2 (triangles) for the BCD series.

The fact that, for any given target substrate and regardless of the type of CD employed, decomposition of complexed triazenes is much slower than that of the free (uncomplexed) substrates, can be rationalized in terms of the dependence of the reaction on the polarity of the reaction medium. Second-order rate coefficients for acid-catalyzed N2—N3 bond cleavage of **1** and **2** in aqueous buffer solutions containing 30% (v/v) THF have been reported as being (21.3 ± 0.7) M^{-1} s^{-1} and (976 ± 9) M^{-1} s^{-1}, respectively [8],[†] i.e., significantly smaller than the values reported here for decomposition in 2% (v/v) MeOH aqueous buffer solutions. Protonation constants for anilines in dioxane–water solvent mixtures have been shown to (systematically) decrease as the concentration of the aprotic nonpolar organic co-solvent increases [18]. On the other hand, and based on the Hughes and Ingold theory [19], k_{N2-N3} values would be expected to increase (albeit only slightly) as the concentration of the organic cosolvent increases since the transition state for heterolytic cleavage of TH^+ involves charge dispersion. Thus, the (noticeable) decrease in reactivity on going from 2% MeOH to 30% THF would indicate that the rate of decomposition of

[†] Values were obtained from k_{obs} vs. 10^{-pH} plots and correspond indeed to $k_{N2-N3}/(\gamma_{H^+}K_a)$, where γ_{H^+} represents the proton activity coefficient.

target triazenes is dominated by their basicity. Inclusion in the cavity of CDs certainly renders a relatively nonpolar environment, at least in comparison with water, which leads to a decrease in triazene basicity and, ultimately, in the rate of decomposition. The fact that BCD is the only host, among those used in this study, for which reactivity of the cyclodextrin–TH^+ complex is detected suggests guest triazenes experience lesser environmental changes upon inclusion in BCD than upon inclusion in the narrower ACD (ultimately with two host units) or in any of the BCD derivatives (in which alkyl substituents elongate the cavity and increase the hydrophobicity of its edges [20,21]).

As indicated in Table I, K_{CD}^{T} values derived from the dependence of the observed first-order rate constants on CD concentration increase in the order ACD $<$ BCD $\sim$ PMBCD $<$ HPBCD. This trend is consistent with existing reports in the literature that show an increase in binding constants for aromatic guest species with increasing cavity size (ACD vs. BCD) as well as with increasing rim substitution (BCD vs. HPBCD and PMBCD) [22]. It is important to point out here that both target substrates **1** and **2** have two binding sites: N1-phenyl and N3-phenyl end groups; hence, isomeric 1:1 complexes can form in each case. The K_{CD}^{T} values kinetically determined would correspond to the complexes that more strongly influence the rate of decomposition. Interestingly, equilibrium constants for complexation of **2** are ca. twice as large as those for **1**, and values corresponding to BCD complexation are comparable to literature values for inclusion of azobenzene derivatives (X-Ph-N=N-Ph-$N(CH_3)_2^+Cl^-$), namely 860 and 1300 M^{-1}, respectively, for X = H and CH_3 [21].

Further evidence of inclusion complex formation was obtained by means of induced circular dichroism (ICD) and UV–visible absorption spectroscopy, using borax buffer solutions (pH 9.98) to minimize substrate decomposition while acquiring corresponding spectra. For instance, ICD spectra corresponding to solutions of **1** in the presence of ACD, BCD, or HPBCD show a single peak with positive sign in the 280–430 nm region (Fig. 6), while that of a solution of **1** in the presence of PMBCD displays a split-type pattern. Interestingly, these spectral characteristics are comparable to those reported for CD complexes of azobenzene derivatives; recent reports, for example, show a positive peak in the ICD spectra of 4-hydroxyazobenzene and 4-aminoazobenzene upon inclusion in BCD [23], and a splitting pattern in the case of complexation with PMBCD [24]. On the other hand, UV–visible absorption spectroscopy reveals that addition of CDs to solutions of **1** or **2** generally leads to a bathochromic (red) shift of the longest wavelength absorption band. While

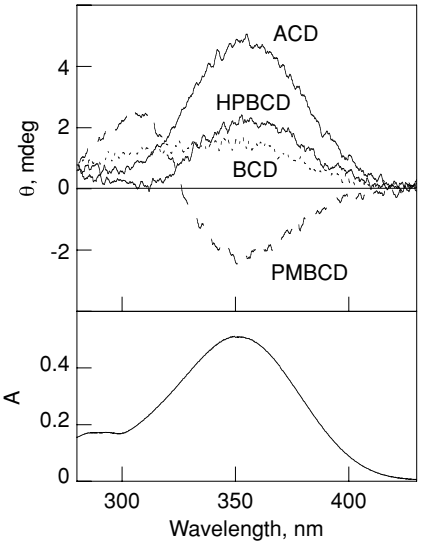


Figure 6 Induced circular dichroism spectra in the presence of 7 mM CD (top) and absorption spectrum (bottom) of **1** in 2% MeOH aqueous borax buffer (pH 9.94).

the wavelength shift (approximately 3–5 nm) and variations in signal intensity are rather small for native and substituted BCDs (spectra not shown), spectral changes are certainly noticeable in the case of ACD. Upon addition of increasing amounts of ACD, besides a bathochromic shift, a decrease in signal intensity is observed when using solutions of **1** (Fig. 7), whereas an increase in absorption ultimately results in the case of **2** (Fig. 8). Interestingly, no isosbestic point remains throughout the ACD concentration range employed ([ACD] $\leq$ 21 mM) in either case. Moreover, fittings

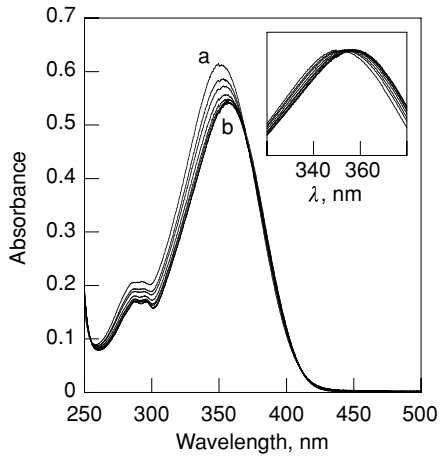


Figure 7 Absorption spectra of **1** in 2% MeOH aqueous borax buffer (pH 9.94) as a function of ACD concentration (0, 0.5, 1, 2, 4, 5, 10, 13.5, and 21 mM, from a to b). Inset: cutoff normalized spectra.

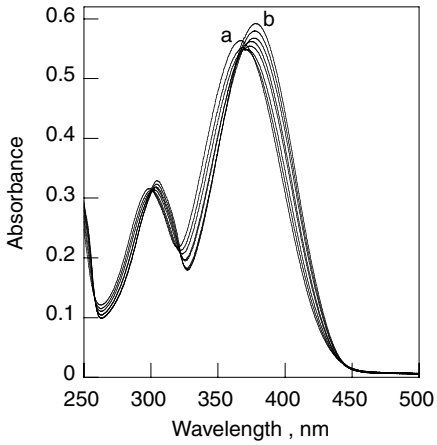


Figure 8 Absorption spectra of **2** in 2% MeCN aqueous borax buffer (pH 9.94) as a function of ACD concentration (0, 1, 2, 4, 5, 10, 13.5, and 21 mM, from a to b).

according to Eq. (6) of the change in absorbance (ΔA) resulting from addition of ACD,

$$\Delta A = \frac{\Delta\varepsilon K_{CD}^{T}[CD][T]_0}{1 + K_{CD}^{T}[CD]} \qquad (6)$$

where $\Delta\varepsilon$ and $[T]_0$ represent the difference in extinction coefficients between a 1:1 host–guest complex and free substrate and the total concentration of substrate, respectively, render K_{CD}^{T} values that are wavelength dependent. This result, together with the lack of isosbestic points, is a very clear indication of formation of higher complexes [25], consistent with the kinetic analysis presented above based on the involvement of 1:1 and 2:1 (host–guest) ACD complexes. Unfortunately, the small variations in signal intensity ($\Delta A < 0.1$) and limited number of ΔA values obtained precluded a statistically significant fitting to a function involving $\Delta\varepsilon$ and K_{CD} terms for 1:1 and 2:1 (host–guest) complexes (i.e., with four adjustable parameters) to determine equilibrium constants.

Absorption spectra displayed in Fig. 8 correspond indeed to aqueous solutions of **2** containing 2% MeCN instead of 2% MeOH, since appreciable decomposition of **2** stock MeOH solution would typically take place within the time period needed for completion of spectral titrations. Interestingly, during the course of these experiments it was noticed that for any given ACD concentration, spectral changes recorded for 2% MeCN aqueous solutions of **2** were less significant than those corresponding to 2% MeOH aqueous solutions, which suggests lower association equilibrium constants in the former solvent system. It is well established that binding properties of CDs can be significantly affected by the presence of (aprotic) organic cosolvents; competition for the CD cavity between guest and cosolvent may lead to a (significant) decrease in binding constant [21,26]. Methanol, among organic solvents, is the closest to water in structure and properties; thus, a decrease in binding affinity on going from 2% MeOH to 2% MeCN would not be unexpected. To verify this reasoning, observed first-order rate constants for decomposition of **2** were determined in 2% MeCN aqueous phosphate buffer solutions and from the dependence on ACD concentration (Fig. 5 inset; Eq. (5)) lower association equilibrium constants in comparison with values for 2% MeOH in fact result (Table I, second row). Also, the calculated first-order rate coefficient corresponding to decomposition of **2** in 2% MeCN aqueous solution is lower than that in 2% MeOH (but higher than in 30% THF), in excellent agreement with the dependence of the reaction on solvent polarity presented in a preceding paragraph.

In summary, acid-promoted decomposition of 1,3-diphenyltriazenes in aqueous solutions is strongly inhibited upon inclusion by cyclodextrins. For any given substrate, the inhibitory effect, attributed to the decrease in substrate basicity resulting from a decrease in the polarity of the reaction medium, depends both on the cavity size and the rim substituents of the host molecule. Data reported herein should prove valuable to applications requiring modulation of (aromatic) triazenes stability under acidic conditions.

Special thanks are due to Prof. G. Guillemette for the use of the spectropolarimeter.

BIBLIOGRAPHY

1. Kimball, D. B.; Haley, M. M. Angew Chem, Int Ed 2002, 41, 3338–3351.
2. For representative articles see (a) Marchesi, F.; Turriziani, M.; Tortorelli, G.; Avvisati, G.; Torino, F.; De Vecchis, L. Pharmacol Res 2007, 56, 275–287; (b) Carvalho, E.; Francisco, A. P.; Iley, J.; Rosa, E. Bioorg Med Chem 2000, 8, 1719–1725; (c) Rouzer, C. A.; Sabourin, M.; Skinner, T. L.; Thompson, E. J.; Wood, T. O.; Chmurny, G. N.; Klose, J. R.; Roman, J. M.; Smith, R. H., Jr.; Michejda, C. J. Chem Res Toxicol 1996, 9, 172–178; (d) Wilman, D. E. V. Cancer Treat Rev 1988, 15, 69–72; (e) Kolar, G. F. In Chemical Carcinogens, 2nd ed.; Searle, C. E., (Ed.); ACS Monograph 182; American Chemical Society: Washington, DC, 1984; Vol. 2, Ch. 14.
3. Tonelli, M.; Vazzana, I.; Tasso, B.; Boido, V.; Sparatore, F.; Fermeglia, M.; Paneni, M. S.; Posocco, P.; Pricl, S.;

La Colla, P.; Ibba, C.; Secci, B.; Collu, G.; Loddo, R. Bioorg Med Chem 2009, 17, 4425–4440.
4. Campbell, M.; Prankerd, R. J.; Davie, A. S.; Charman, W. N. J Pharm Pharmacol 2004, 56, 1327–1332.
5. Dodziuk, H. (Ed.). Cyclodextrins and Their Complexes: Chemistry, Analytical Methods, Applications; Wiley-VCH: Weinheim, Germany, 2006.
6. For recent review articles see (a) Stella, V. J.; He, Q. Toxicol Pathol 2008, 36, 30–42; (b) Vyas, A.; Saraf, S.; Saraf, S. J Inclusion Phenom Macrocyclic Chem 2008, 62, 23–42; (c) Cal, K.; Centkowska, K. Eur J Pharm Biopharm 2008, 68, 467–478; (d) Brewster, M. E.; Loftsson, T. Adv Drug Delivery Rev 2007, 59, 645–666; (e) Oshovsky, G. V.; Reinhoudt, D. N.; Verboom, W. Angew Chem, Int Ed 2007, 46, 2366–2393; (f) Villalonga, R.; Cao, R.; Fragoso, A. Chem Rev 2007, 107, 3088–3116.
7. (a) Roehrl, M. H. A.; Wang, J. Y.; Wagner, G. Biochem 2004, 43, 16067–16075; (b) Nifontov, V. I.; Belśkaya, N. P.; Krupnova, L. V.; Ershova, Y. A.; Fedorova, A. P. Pharm Chem J 1994, 28, 611–615.
8. Chen, N.; Barra, M.; Lee, I.; Chahal, N. J Org Chem 2002, 67, 2271–2277.
9. Harned, H. S.; Owen, B. B. The Physical Chemistry of Electrolytic Solutions; Reinhold: New York, 1958; p. 748.
10. (a) Hanusek, J.; Bělohlavová, H.; Přikryl, J.; Macháček, V. Dyes Pigm 2009, 80, 136–140; (b) Ludwig, M.; Bednářová, I; Pařík, P. Collect Czech Chem Commun 1999, 64, 1654–1672; (c) Pytela, O.; Nevěčná, T.; Kaválek, J. Collect Czech Chem Commun 1990, 55, 2701–2706; (d) Svodoba, P.; Pytela, O.; Večeřa, M. Collect Czech Chem Commun 1987, 52, 2217–2224.
11. (a) Beneš, J.; Beránek, V.; Zimprich, J.; Vetešník, P. Collect Czech Chem Commun 1977, 42, 702–710; (b) Zvěřina, V.; Remeš, M.; Diviš, J.; Marhold, J.; Matrka, M. Collect Czech Chem Commun 1973, 38, 251–256.
12. Chen, N. M. Sc. thesis, University of Waterloo, Waterloo, Canada, 2000.
13. (a) Rakotondradany, F.; Williams, C. I.; Whitehead, M. A.; Jean-Claude, B. J. J Molec Struct (Theochem) 2001, 535, 217–234; (b) Schmiedekamp, A.; Smith, R. H., Jr.; Michejda, C. J. J Org Chem 1988, 53, 3433–3436; (c) Nguyen, M-T.; Hoesch, L. Helv Chim Acta 1986, 69, 1627–1637.
14. Sutherland, J. W. J Phys Chem 1979, 83, 789–795.
15. Hansch, C.; Leo, A.; Taft, R. W. Chem Rev 1991, 91, 165–195.
16. Lide, D. R., (Ed.). CRC Handbook of Chemistry and Physics; CRC Press: Boca Raton, FL, 1996; (a) pp. 8–49, (b) pp. 8–52.
17. Svodoba, P.; Pytela, O.; Večeřa, M. Collect Czech Chem Commun 1986, 51, 553–563.
18. Demirelli, H.; Köseoğlu, F. J Sol Chem 2004, 33, 1501–1515.
19. Reichardt, C. Solvents and Solvent Effects in Organic Chemistry; Wiley-VCH: Weinheim, Germany, 2003; Ch. 5.
20. Immel, S.; Lichtenthaler, F. W. Starch/Stärke 1996, 48, 225–232.
21. Sueishi, Y.; Kasahara, M.; Inoue, M.; Matsueda, K. J Inclusion Phenom Macrocyclic Chem 2003, 46, 71–75.
22. (a) Connors, K. A. Chem Rev 1997, 97, 1325–1357; (b) Szejtli, J. Pure Appl Chem 2004, 76, 1825–1845.
23. Liu, Y.; Zhao, Y-L.; Chen, Y.; Guo, D-S. Org Biomol Chem 2005, 3, 584–591.
24. Shi, J., Guo, D-S., Ding, F. Liu, Y. Eur J Org Chem 2009, 923–931.
25. Connors, K. A. Binding Constants: The Measurement of Molecular Complex Stability; Wiley: New York, 1987; Ch. 4.
26. The detailed coverage of solvent effects on binding constants is beyond the scope of this article; only a few representative publications are listed here: (a) Lo Meo, P.; D'Anna, F.; Riela, S.; Gruttadauria, M.; Noto, R. Tetrahedron 2009, 65, 2037–2042; (b) García-Rio, L.; Hervés, P.; Leis, J. R.; Mejuto, J. C.; Pérez-Juste, J.; Rodríguez-Dafonte, P. Org Biomol Chem 2006, 4, 1038–1048; (c) Porras, S. P.; Sarmini, K.; Fanali, S.; Kenndler, E. Anal Chem 2003, 75, 1645–1651; (d) Partyka, M.; Au, B. H.; Evans, C. H. J Photochem Photobiol A: Chem 2001, 140, 67–74; (e) Connors, K. A.; Mulaki, M. J.; Paulson, A. J Org Chem 1992, 57, 1794–1798.