Synthesis of Deuterium-Labeled Cryptophane-A and Investigation of Xe@Cryptophane Complexation Dynamics by 1D-EXSY NMR Experiments

Thierry Brotin,* Thomas Devic, Anne Lesage, Lyndon Emsley,* and André Collet[a]

Abstract: We present the synthesis of a series of deuterated cryptophanes **2**–**6** by a slightly modified procedure used for cryptophane-A. We show that for [Xe@cryptophane] complexes the use of variable-temperature one-dimensional ^{129}Xe magnetization transfer (1D-EXSY) allows the measurement of exchange rates. From these data the decomplexation activation energy E_a has been estimated to be 37.5 ± 2 kJ mol^{-1}. The decomplexation activation enthalpy, $\Delta H^{\neq} = 35.5 \pm 2$ kJ mol^{-1}, and entropy, $\Delta S^{\neq} = -60 \pm 5$ J mol^{-1} K^{-1}, have also been calculated. The calculated negative activation entropy suggests that the activated complex associated with decomplexation is conformationally more strained than the complex in its ground state.

Keywords: cryptophanes · deuterium · isotopic labeling · molecular recognition · NMR spectroscopy · xenon

Introduction

Two-dimensional exchange (2D-EXSY) NMR experiments have been widely used for the study of host–guest complexation dynamics in many chemical systems with more than two exchanging sites.[1] For instance, this method has recently been extensively used in ^{129}Xe high-field NMR spectroscopy to study xenon exchange processes in various media.[2] In a recent example we have shown that high-field ^{129}Xe NMR spectroscopy is sensitive enough to distinguish at low temperature two cryptophanes differing only by their degree of deuteration (Figure 1).[3] Although smaller, a similar effect was observed for derivatives **2**–**5**. This unusual and intriguing effect, which is the sole example reported in the literature for host–guest complexes, can only be observed at low temperature (238 K), because of the slowing of the exchange dynamics. By way of demonstration, the effect was then used to extract rate constants from a 2D-EXSY experiment. Rate constants were obtained from several independent experiments (eight mixing times were used) by fitting the experimental data to a model. However, the large chemical shift difference observed between the free and complexed xenon, combined with the long relaxation time of monoatomic xenon, make these experiments extremely time-consuming (for each mixing time, a spectrum requires about 24 h), and these prohibitively long acquisition times prevented the determination of the activation parameters of this system. This problem could possibly be overcome by the use of, for instance, isotopically enriched ^{129}Xe, which would decrease

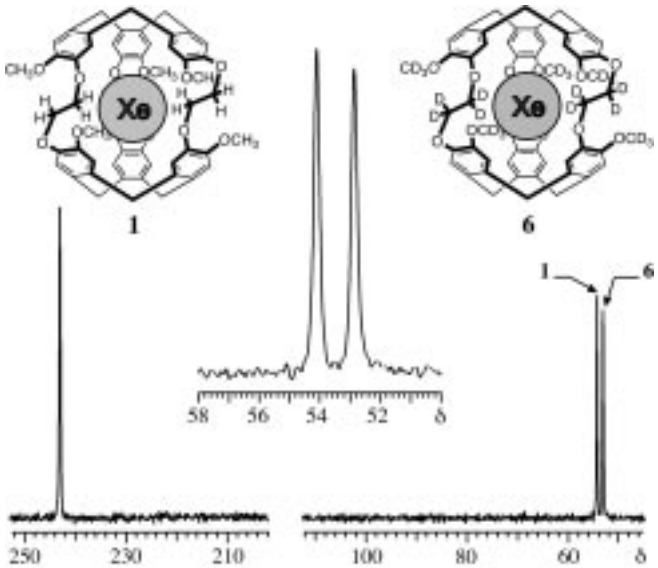

Figure 1. ^{129}Xe NMR spectrum, recorded at 238 K, of an approximately 0.07 M solution of cryptophanes **1** and **6** in $(CDCl_2)_2$, [^{129}Xe]/[**1** or **6**] ≈ 2 (462 scans, pw = 8 μs, d1 = 4.0 s; a Gaussian apodization (gf = 0.045) was applied). An expansion of this spectrum is depicted in the insert.

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the acquisition time required approximately by a factor 16. However the cost of this material makes these experiments expensive (though not impossible). An alternative solution would be to improve the NMR method used. The use of a single (relatively short) mixing time at a given temperature is also an option, but the resulting rate constant values may be inaccurate owing to the low signal-to-noise ratio of the cross-peak intensities observed for the 2D-NMR experiments, and uncertainties as large as 50% may result. Herein we show that one-dimensional magnetization transfer experiments involving selective irradiation of the three sites are particularly well adapted to this problem and result in a substantial decrease of the instrumentation time required to obtain the data. This has allowed us, for the first time in this type of system, to obtain rate constants as a function of temperature, thereby permitting the determination of the decomplexation activation energy E_a and the associated activation parameters $\Delta H^{\neq}$ and $\Delta S^{\neq}$. We also present the details of the new synthetic approach to the synthesis of the novel deuterated cryptophanes used in this study.

Results and Discussion

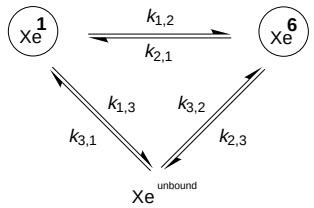
^{129}Xe 1D-EXSY NMR experiments: One-dimensional magnetization transfer is one of the simplest NMR techniques used in organic chemistry to obtain information on chemical exchange.[4] Selective inversion of one peak followed by examination of this effect on the other sites allows the determination of rate constants. The selective irradiation is then applied systematically to each of the other sites to yield the complete set of rate constants. This technique is of particular interest when the number of sites is relatively low, as observed in our case (monoatomic xenon exchanges between only three sites: two bound states and unbound xenon). However, the two bound states resonate at very similar frequencies, whose chemical shift difference is only 1.2 ppm, for a total chemical shift range of 200 ppm. Therefore the selective pulses must be chosen and calibrated with care. Also, since the chemical shift of the three sites is strongly temperature-dependent, and since very narrow-band excitation pulses are required, care must be taken to obtain sufficient temperature stability. Thus the sample was kept for about three hours at 238 K before 1D-EXSY experiments were commenced. Over about 24 hours of acquisition time, variations of the chemical shift of as little as 10–15 Hz were observed for the peaks corresponding to xenon in solution or xenon trapped in cages **1** and **6**. Since the observed chemical shift difference [Xe@**1** – Xe@**6**] is about 165 Hz, the variation observed as a function of slight temperature fluctuations is small enough to permit the successful performance of EXSY experiments.

A Gaussian 180° shaped pulse was used to carry out these experiments.[5] The pulse length and power were adjusted in order to irradiate selectively one site at a time, and a time domain pulse of 4.45 ms was found to be suitable. In our case, note that the need to use such a long pulse affects the signal-to-noise ratio. Indeed, the pulse length is of the same order of magnitude as the exchange rates for this system observed at 238 K between xenon in solution and xenon trapped in cages **1** and **6**. Therefore, significant chemical exchange occurs during the pulse; this will tend to decrease the polarization difference created by the pulse, and thus reduce the sensitivity of the experiment. However, we were able to achieve sufficient polarization differences to obtain adequate spectra. One should note that apart from the sensitivity, exchange or relaxation processes during the pulse do not affect the quantification and analysis of the spectra.

The magnetization of the three sites involved in the exchange obeys the modified Bloch equations, and the amplitude of each resonance as a function of the mixing time is given by the following matrix equation [Eq. (1)],

$$I_i(\tau_{mix}) = \exp(\mathbf{L}\tau)(I_0^i - I_{eq}^i) + I_{eq}^i \quad (1)$$

where I_0^i is the initial magnetization of the nucleus i at $\tau_{mix} = 0$, and I_{eq}^i is the magnetization at this site for infinite relaxation time. The matrix $\boldsymbol{L}$ is a function of the rate constants k_{ij} and the longitudinal relaxation times T_{1i} of each site for a given kinetic model. As previously reported, the following pseudo-first-order model may be proposed (Scheme 1) for exchange



Scheme 1. Pseudo-first-order kinetic model assumed to describe the 1D-EXSY experiments.

between xenon in solution and xenon encapsulated in cages **1** and **6**. This model assumes that exchange between the three sites may occur independently in two different ways. Firstly, exchange of xenon between cage **1** and **6** is likely to proceed through solution. Although less probable, monoatomic xenon may also move from one cage to another by direct collision between **1** and **6**. Therefore, using the pseudo-first-order model proposed in Scheme 1, the matrix $\boldsymbol{L}$ can be written as in Equation (2).

Abstract in French: *Des modifications apportées à la synthèse du cryptophane-A ont permis d'obtenir les cryptophanes-A deutérés **2**–**6**. Nous montrons pour le système [Xe@cryptophanes] que des expériences de transfert d'aimantation par RMN du ^{129}Xe (1D-EXSY) permettent la détermination des vitesses d'échange à différentes températures. A partir de ces données nous avons déterminé l'énergie d'activation de décomplexation $E_a = 37.5 \pm 2$ kJ mol^{-1}. L'enthalpie d'activation de décomplexation $\Delta H^{\neq} = 35.5 \pm 2$ kJ mol^{-1} et l'entropie d'activation de décomplexation $\Delta S^{\neq} = -60 \pm 5$ J mol^{-1} K^{-1} ont également été calculées. La valeur négative de l'entropie d'activation de décomplexation suggère une conformation du complexe activé plus rigide qu'à l'état fondamental.*

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$$\boldsymbol{L}=\begin{pmatrix} -1/T_{11}-(k_{1,2}+k_{1,3}) & k_{2,1} & k_{3,1} \\ k_{1,2} & -1/T_{12}-(k_{3,1}+k_{2,3}) & k_{3,2} \\ k_{1,3} & k_{2,3} & -1/T_{13}-(k_{3,1}+k_{3,2}) \end{pmatrix} \quad (2)$$

Relaxation time properties of monoatomic xenon in solution lead to a simplification of the matrix $\boldsymbol{L}$. The spin–lattice relaxation time T_{13} of free xenon in [D$_2$]tetrachloroethane was found to be several hundred seconds.[6] The relaxation time T_{11} of ^{129}Xe trapped in cage **1** was measured in the same solvent and found to be shorter, 16 s. The longitudinal relaxation time T_{12} of [^{129}Xe@**6**] has not yet been measured, but longitudinal relaxation times of xenon in deuterated cryptophanes are expected to be greater than T_{11}, since the main relaxation process of ^{129}Xe is believed to occur through dipolar coupling between hydrogen and ^{129}Xe (though fluctuations of the Xe chemical shift anisotropy also play a role).[2a, 7] Thus, since the exchange occurs on the 10-millisecond time scale, a mean value of the spin–lattice relaxation time $\langle T_{1i}\rangle$ much longer than any of the k_{ij} of the system is expected to be valid for the three sites.[8] This leads therefore to the simplification of the $\boldsymbol{L}$ matrix to that given in Equation (3).

$$\boldsymbol{L}=\begin{pmatrix} -(k_{1,2}+k_{1,3}) & k_{2,1} & k_{3,1} \\ k_{1,2} & -(k_{2,1}+k_{2,3}) & k_{3,2} \\ k_{1,3} & k_{2,3} & -(k_{3,1}+k_{3,2}) \end{pmatrix} \quad (3)$$

Moreover, similar rate constants are expected for $k_{1,3}=k_{2,3}$, $k_{3,1}=k_{3,2}$, and $k_{1,2}=k_{2,1}$, since the physical properties of cages **1** and **6** towards xenon complexation are assumed to be the same to a very good degree of approximation. Finally, the equilibrium condition also implies $k_{3,1}/k_{1,3}=M_1^0/M_3^0$; $k_{3,2}/k_{2,3}=M_2^0/M_3^0$; and $k_{2,1}/k_{1,2}=M_1^0/M_2^0$ where M_1^0, M_2^0, and M_3^0 are, respectively, the initial magnetization ($\tau_m=0$) of xenon bound to cage **1**, xenon bound to cage **6**, and xenon in solution. Since magnetizations are modified during pulse excitation, M_1^0, M_2^0, and M_3^0 are measured by integrating peaks in the 1D ^{129}Xe NMR spectrum.

A first set of experiments was performed at 238 K, using 16 scans for each acquisition. The same selective 180° pulse of 4.45 ms was applied successively to each site. A long delay of 30 s was applied between each scan to allow efficient relaxation of magnetizations, and seventeen values for mixing times ranging from 10 μs to 5 s were used for the three independent experiments. This required about eight hours of instrumentation time. The intensity of each signal was then measured, and the rate constants were obtained by iteratively fitting the observed intensities versus τ_m to the model of Equation (1).[9] This yielded values for the rate constants $k_{1,3}=52\ s^{-1}$ and $k_{2,3}=86\ s^{-1}$, whereas $k_{1,2}$ and its reverse constant were found to be negligible. Even though these values are close to those previously reported, there is a clear difference between them, although $k_{1,3}$ and $k_{2,3}$ are expected to be the same. Since the determination of all rate constants requires three independent experiments, 15 independent parameters (nine for initial magnetizations, three for magnetization at equilibrium, and three for rate constants) must be used to fit the experimental data. Therefore, the accurate determination of initial magnetizations, which is strongly dependent on the signal-to-noise ratio, must be determined with increased precision to fit the experimental data better. Thus, a second set of experiments was performed with 64 scans per spectrum under the same experimental conditions. About 28 hours of instrumentation time were needed to complete the experiment. Figure 2 shows the redistribution of magnetization as a function of mixing time for the three sites when the sites corresponding to [Xe@**1**] or [Xe@**6**] have been selectively irradiated. It also gives an idea of the signal-to-noise ratio obtained for the three sites. The two NMR spectra displayed for $\tau_m=0$ in Figure 2 show two peaks of the same intensity with opposite sign, thus demonstrating that the pulse width has been well calibrated to selectively irradiate one site at a time without affecting the other. The selective irradiation may affect the intensity of the second peak a little, as evidenced by the decrease in its intensity. However, even though the signal-to-noise ratio is modified, the fit of the experimental data is not affected, since initial magnetizations are used as variables.

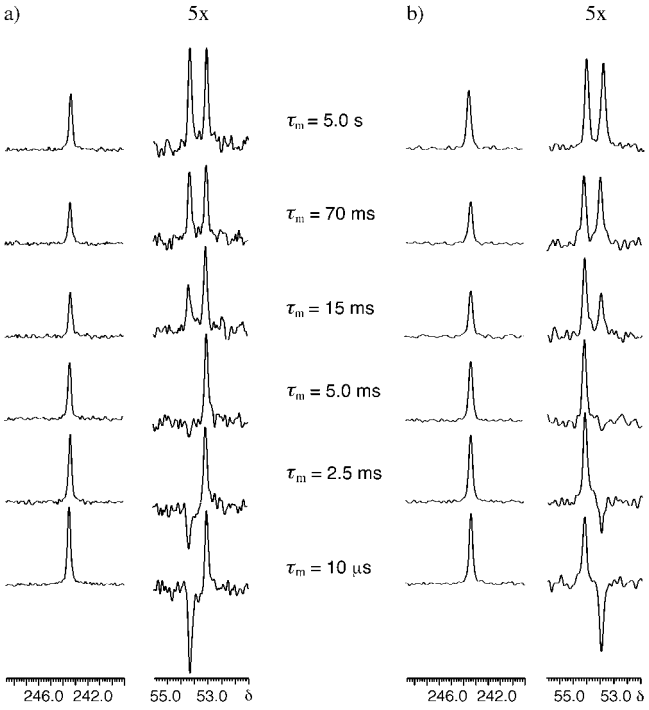

Figure 2. Evolution of the magnetization of the three sites (1D-EXSY experiments at 238 K) as a function of the mixing time. a) After selective excitation of the peak corresponding to [^{129}Xe@**1**]. b) After selective excitation of the peak corresponding to [^{129}Xe@**6**].

After the intensity of all peaks had been measured, the rate constants were determined by fitting the experimental data as a function of τ_m. Figure 3 shows nine panels corresponding to the evolution of magnetization of the three sites when each peak has been selectively irradiated (negative intensity at $\tau_m=0$), and the effect of that perturbation on the two other sites. The experiments were repeated twice to evaluate the experimental error. In both cases, the fits agree fairly well (see Figure 3) with experimental data, and the resulting rate constant values are given in Table 1.

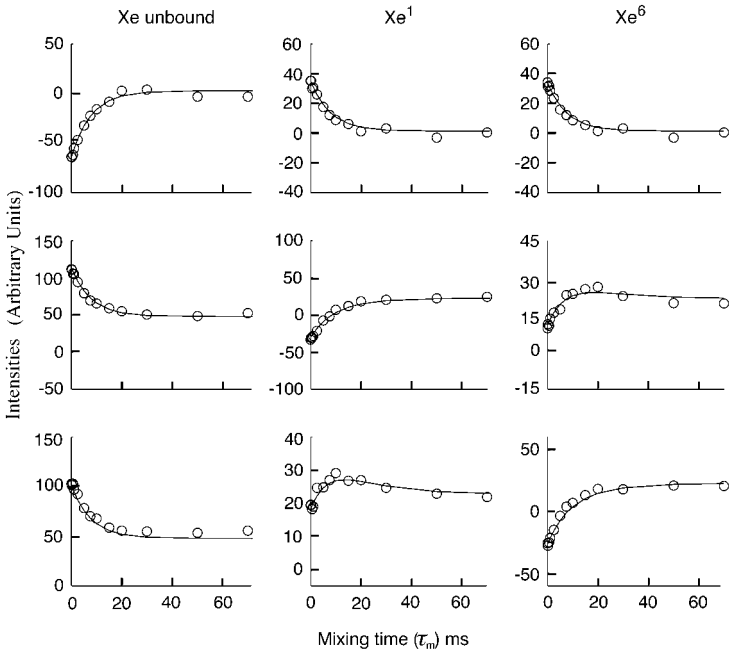

Figure 3. Evolution of magnetization as a function of mixing time, after selective irradiation of one of the three sites (negative intensity). Each panel represents a particular site and its evolution with τ_m (only mixing times ranging from 10 μs to 0.075 s are shown). Experimental data are represented by dots and the solid lines represent the best fit of the data (obtained by least-squares fitting).

Table 1. Rate constants k_{ij} (s^{-1}) obtained from 1D-EXSY experiments (Exp. 1 and 2) at 238 K in [D_2]1,1,2,2-tetrachloroethane in the presence of a 1:1 mixture of hosts **1** and **6** (0.07 mM), [^{129}Xe]/[**1** or **6**] ≈ 2.

	Exp. 1	Exp. 2
$k_{1,2}$	0	0
$k_{2,1}$	0	0
$k_{1,3}$	62 ± 10	58 ± 10
$k_{2,3}$	62 ± 10	56 ± 10
$k_{3,1}$	31 ± 5	29 ± 5
$k_{3,2}$	31 ± 5	28 ± 5

Rate constants deduced from experiments 1 and 2 give similar results and are in good agreement with those previously reported. Although it is difficult to evaluate the experimental error precisely, the estimate of ±10 s^{-1} given in Table 1 is conservative. The main sources of error are temperature variations during the experiment and the signal-to-noise ratio. Both experiments yield similar rates for either cages **1** or **6** as expected for this system. The constant $k_{1,2}$ and the reverse constant were found to be very close to zero, suggesting that these values were overestimated in the previous paper.[3] Therefore our result suggests that xenon *only exchanges between cages **1** and **6** through solution* and that other exchange mechanisms between xenon and both cages **1** and **6** are negligible.

Better precision in the results was probably obtained for 1D-EXSY experiments for the following reasons. First, the signal-to-noise ratio of signals recorded for 1D-EXSY experiments is better than those for cross-peak intensities measured in the previous paper, especially for small mixing times. In addition the fits of the experimental data were performed with 17 values for mixing times instead of eight, as previously reported for 2D-EXSY experiments, thus improving the quality of the fitting procedure and giving more accurate data. A substantial decrease of the instrumentation time was also observed between experiments **1** and **2** and 2D-EXSY experiments; the former were performed approximately seven times faster than the latter, with a consequently improved precision in the final results (note that when available, the use of isotopically enriched Xe in combination with 1D-EXSY will of course further reduce the instrumentation time required to perform these experiments and may allow their extension to even more complex or dilute systems than those considered here).

Variable-temperature ^{129}Xe 1D-EXSY NMR experiments: The significant decrease of the instrumentation time obtained for ^{129}Xe 1D-EXSY with respect to ^{129}Xe 2D-EXSY experiments allows the determination of rate constants at several temperatures. In addition, since $k_{1,2}$ and its reverse constant have been found to be negligible, this leads to a possible simplification of the ^{129}Xe 1D-EXSY experiment in which both [^{129}Xe@**1**] and [^{129}Xe@**6**] signals can now be irradiated at the same time, thus further decreasing the instrumentation time. Under the experimental conditions described in the Experimental Section, the complete set of rate constants can now be measured with high precision at a given temperature in approximately 6 h 30 min.

The physical characteristics of our system prevent us from measuring rate constants over a very large temperature range. At temperatures higher than 253 K, peak resolution and the signal-to-noise ratio decrease significantly as a result of an increase in the exchange rates and below 238 K the solvent solidifies. In order to enlarge the temperature window used for variable-temperature experiments, we used a sealed tube containing equimolar amounts of derivatives **1** and **6** dissolved in a mixture of solvents (tetrachloroethane/toluene: 75/25). Toluene was chosen because it cannot be encapsulated by host **1** and **6** and therefore it does not compete with monoatomic xenon, and because cryptophanes are also moderately soluble in this solvent. Since direct exchange is negligible and, as both cages **1** and **6** show similar complexation properties to a very good degree of approximation, the use of a solution containing a mixture of cryptophanes is not really necessary. However, the use of a mixture of cage **1** and **6** in the solution appears useful since it duplicates the data and thus yields an idea of the precision of the measurements. It was found that the rate constants $k_{2,3}$ and $k_{1,3}$ calculated from a series of ^{129}Xe 1D-EXSY experiments change by roughly one order of magnitude when the temperature varies from 253 K to 228 K (see Table 2). We have also noticed that the use of a mixture of solvents does not change the complexation dynamics significantly since similar rate constant values were obtained at 253 K and 238 K with the sample containing only tetrachloroethane as a solvent.

The Arrhenius plot shown in Figure 4 yields a straight line which allows the determination of the decomplexation

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Table 2. Rate constants $k_{2,3}$ and $k_{1,3}$ [s^{-1}] obtained from 1D-EXSY experiments at several temperatures (T [K]) in a mixture of [D_2]1,1,2,2-tetrachloroethane and toluene (75/25) in the presence of hosts **1** and **6** (0.074 M), [^{129}Xe]/[**1** or **6**] ≈ 2.0.

T	253	248	243	238	233	228
$k_{2,3}$	182.0 ± 10	134.0 ± 8	104.0 ± 6	67.0 ± 10	43.0 ± 4	26.0 ± 2
$k_{1,3}$	200.0 ± 10	136.0 ± 8	102.0 ± 6	66.0 ± 10	44.0 ± 4	26.0 ± 2

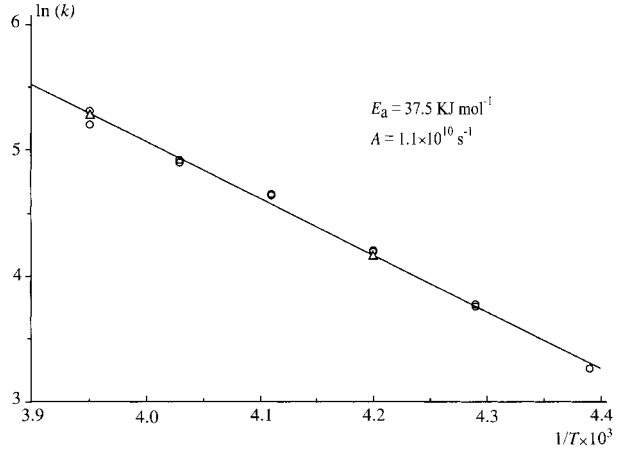


Figure 4. Arrhenius plot of $\ln(k_{1,3})$ and $\ln(k_{2,3})$ vs $1/T$ ($r^2 = 0.995$). ○: Values of $k_{1,3}$ and $k_{2,3}$ obtained from ^{129}Xe 1D-EXSY NMR experiments at various temperatures (ranging from 253 K to 228 K) in a sealed tube containing a mixture of solvent ([D_2]1,1,2,2-tetrachloroethane/toluene: 75/25); △: values of $\ln(k_{1,3})$ and $\ln(k_{2,3})$ obtained at two temperatures in a sealed tube containing only [D_2]1,1,2,2-tetrachloroethane as a solvent, [^{129}Xe]/[**1** or **6**] ≈ 2.

activation energy $E_a = 37.5 \pm 2$ kJ mol^{-1} and the corresponding preexponential factor $A = 1.1 \times 10^{10}$ s^{-1}. The experimental error given for E_a was calculated by propagating the experimental error obtained for the rate constants $k_{1,3}$ and $k_{2,3}$. Since this is the first measurement of the kind for this type of host–guest system a discussion of the measured activation energy seems difficult in the absence of comparative values for related systems, but we observe that the value reported for this system is close to that obtained by Ripmeester and coworkers for diffusional process of xenon in a zeolite.[2a] As mentioned by those authors, the magnitude of E_a depends strongly on the size of the intercage windows (in our case the size of cryptophane windows) used by xenon to go from one site to another.

A linear relationship was also obtained by plotting $\ln(k/T)$ versus $1/T$ (activated complex theory, Eyring plot) over the temperature range studied. This result allows the determination of both the decomplexation activation enthalpy $\Delta H^{\neq} = 35.5 \pm 2$ kJ mol^{-1} and entropy $\Delta S^{\neq} = -60 \pm 5$ J mol^{-1} K^{-1} (see Figure 5) and thus the Gibbs activation energy $\Delta G^{\neq} = 50$ kJ mol^{-1} at 238 K. The calculated $\Delta S^{\neq}$ value suggests a significant change of conformation between the activated complex and the [Xe@cryptophane] complex in its ground state. This result is not surprising, since the exit of a xenon atom from the cryptophane cavity probably requires a significant conformational reorganization of the cryptophane

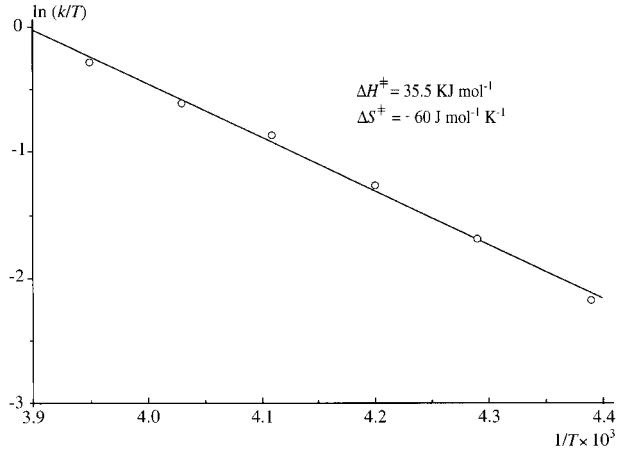
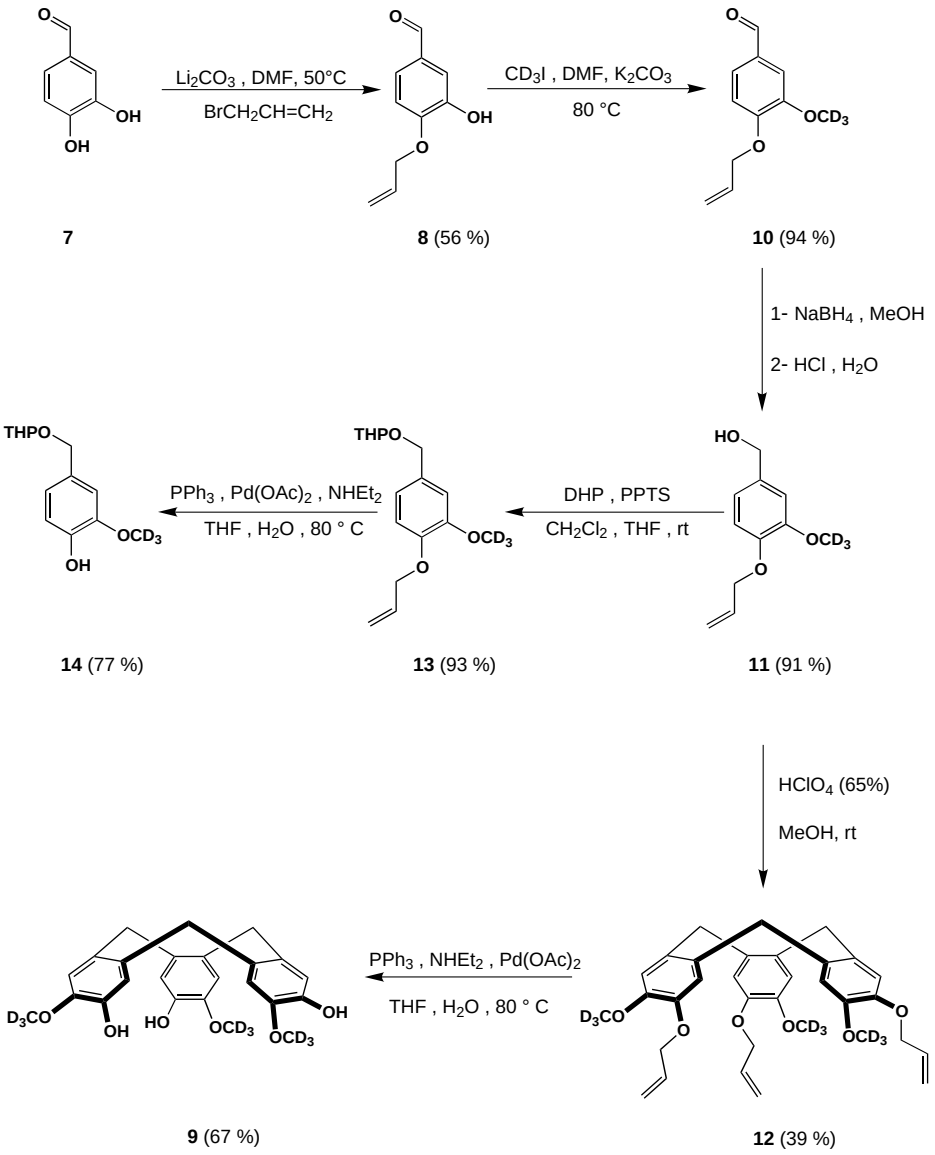


Figure 5. Eyring plot of $\ln(k/T)$ vs $1/T$ ($r^2 = 0.996$). For each temperature a mean value was used for $k_{1,3}$ and $k_{2,3}$.

windows. Additional interactions such as organization of solvent molecules around the activated complex, which is thought to be more polar than the complex in the ground state (it has no permanent dipole moment owing to its symmetry), also probably contribute significantly to the measured negative activation entropy, and to the stabilization of the activated complex.

Synthesis and characterization: The synthesis of cryptophane-A and related compounds has already been described in the literature.[10] Briefly, it may be obtained in two different ways. *The direct method or two-step method* allows the formation of cryptophane-A by trimerization of dimers of vanillic alcohol linked by an ethylenedioxy moiety under acidic conditions.[11] This method furnishes cryptophane-A with a yield of a few per cent and is therefore not appropriate for the synthesis of deuterium-labeled cryptophanes. Although more time-consuming, *the template method* has been successfully applied for the preparation of cryptophane-A and related derivatives.[12] This multistep synthesis based on the formation of the two cyclotriveratrylene moieties at different stages of the synthesis allows the preparation of cryptophane-A with a fair yield. An improvement of the template method is described in the following for the preparation of deuterated cryptophanes **2**–**6**. These derivatives were first prepared from 3,4-dihydroxybenzaldehyde (**7**), with [D_3]methyl iodide and [D_4]1,2-dibromoethane as sources of deuterium. Molecule **7** was first selectively protected by an allyl group in the *para* position in the presence of lithium carbonate as base to give compound **8** in 56% yield (Scheme 2).[13] Monoprotection in the *para* position was required to avoid production of a mixture of regioisomers which would be more difficult to separate at a later stage, and the preparation of cyclotriveratrylene compound **9** as well. Alkylation of **8** with [D_3]methyl iodide was then achieved with potassium carbonate as base resulting in compound **10** with a 90% yield. Benzyl alcohol **11**, obtained by reduction of **10** with sodium borohydride in methanol, was then used as a precursor to prepare molecules **9** and **12**. Molecule **11** was then protected with a tetrahydropyranyl ether moiety to give compound **13**. The introduction of a protecting group such as the tetrahydropyranyl ether moiety,



Scheme 2. Synthesis of deuterated cyclotriveratrylene **9** and phenol **14**.

which is required to achieve the deallylation step successfully, was also found to play an important role in the purification of intermediates of deuterated cryptophanes **2**–**6**. Deallylation of derivative **13** was finally carried out with a palladium catalyst ($[Pd(OAc)_2]$, PPh_3) in the presence of diethylamine and water according to a known procedure.[14]

The experimental conditions used leave the tetrahydropyranyl ether moiety unaltered and derivative **14** can thus be used directly to prepare molecule **15**, which was obtained by treating **14** with excess $[D_4]$1,2-dibromoethane in the presence of potassium carbonate (Scheme 3). Similarly, vanillic alcohol (**16**) gives derivative **17** in 48% yield under the same experimental conditions. A significant increase of this yield was observed for molecules **15** and **17** because of a deuterium isotope effect, whereas molecule **18**, prepared according to a known procedure, was only obtained with a 20–30% yield under the same experimental conditions.[15] The protection of the alcoholic function of molecules **17** and **18** with a tetrahydropyranyl ether group for the synthesis of compounds **19** and **20** was necessary to allow the purification of cryptophane precursors as described below. Then the conversion of molecules **15, 19**, and **20** into their corresponding iodo derivatives **21, 22**, and **23** was easily achieved in the presence of an excess of iodine in acetone with excellent yield. Several attempts to prepare pure cryptophanes **2** and **4** from starting materials **23** and **21** led us to the conclusion that the unprotected derivative **24**, obtained by deprotection of the tetrahydropyranyl ether moiety with pyridinium *p*-toluenesulfonate in methanol, was also needed.

Cyclotriveratrylene derivatives **9** and **25** were then used as starting materials for the preparation of cages **1**–**6**. Molecules **26**, **27, 28**, and **29** used as precursors of cryptophanes **1**, **3, 5**, and **6** were prepared respectively from compounds **25** or **9** (Scheme 4) and the appropriate iodo derivatives **21**, **22**, or **23** in presence of cesium carbonate. The tetrahydropyranyl ether group was found to be very useful in improving the purification procedures for the final materials by decreasing their polarity and thus allowing their purification on silica gel. In addition it was found that the introduction of these protecting groups does not alter the cyclization step under acidic conditions in the preparation of cryptophanes **1**–**6**. The synthesis of cages **2** and **4** is more difficult. Indeed, the use of an equimolar amount of starting materials **21** and **23** with cyclotriveratrylenes **9** and **25**, respectively, resulted in an inseparable mixture of mono-, bi-, and trisubstituted compounds. In order to improve the purification procedure, the nonprotected derivatives **24** and **30** were used. This allowed us to purify monosubstituted derivatives **31** and **32** by column chromatography on silica gel, because of the better separation of the desired compounds and the side-products (consisting mainly of bi- and trisubstituted derivatives). However, the low selectivity observed for this reaction led to a poor yield (20–30%) of monosubstituted derivatives **31** and **32** even though a non-negligible amount of starting material **9** or **25** can be collected by column chromatography (first eluted spot) and reused for another experiment. Compounds **33** and **34** were then obtained by treating molecules **31** and **32** with derivative **22** (Scheme 4), in order to increase the solubility of the desired product and thus

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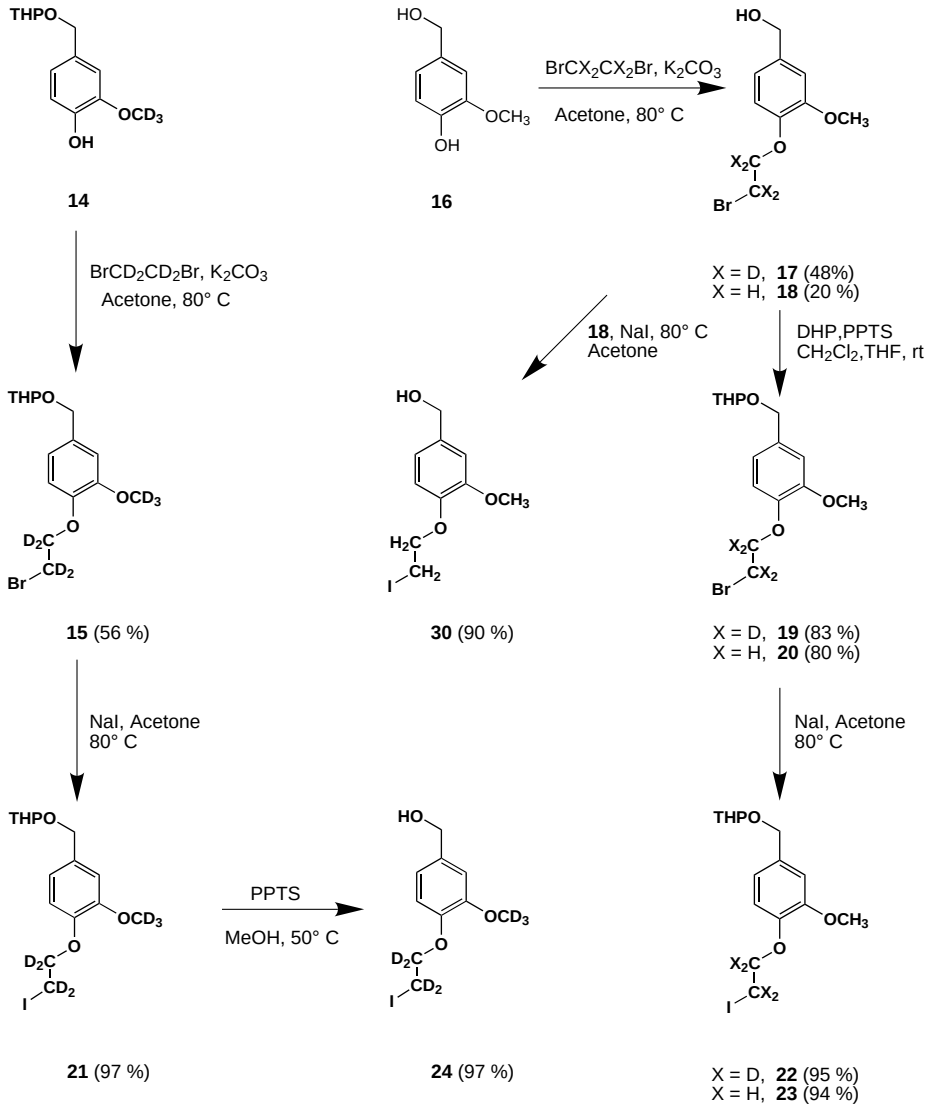


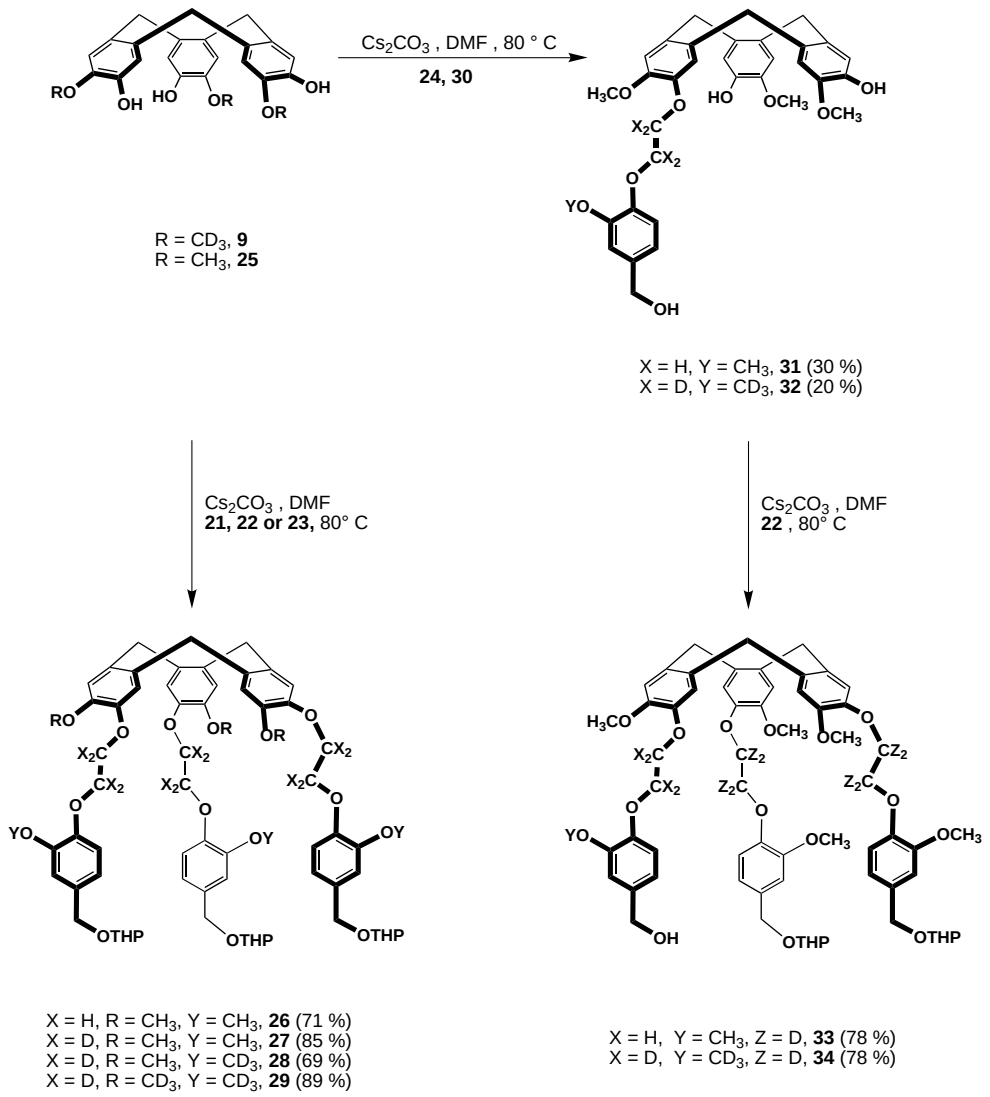
Scheme 3. Synthesis of compounds **22**–**24**.

facilitating the purification procedure. The cyclization steps for compounds **26**, **27**, **28**, **29**, **33**, and **34** were subsequently carried out in formic acid at 55 °C, and produced the desired cryptophanes **1**–**6** in fair yields (Scheme 5).

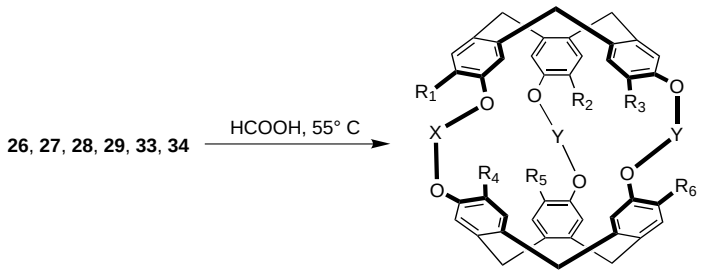
Compounds **7**–**25** were characterized by the usual techniques. Cyclotriveratrylene derivatives **26**–**34** were isolated with a purity exceeding 95 % (by NMR). However, they were obtained as glassy products and they still contained solvent after purification by column chromatography; this prevented their full characterization by elemental analysis. They were successfully characterized by means of ^{1}H and ^{13}C high-field NMR techniques and by mass spectroscopy. ^{1}H NMR spectra of derivatives **31** and **32** show four independent signals located between $\delta = 3.84$ and 3.71 characteristic of the four methoxy groups, and two peaks of the same intensity located at $\delta = 5.4$ and 5.38, characteristic of the two unreacted hydroxy groups. Whereas both ^{1}H and ^{13}C NMR spectra of compounds **26**, **27**, **28**, and **29** were easy to interpret owing to their symmetry, the low symmetry of derivatives **33** and **34** complicated their ^{1}H and ^{13}C NMR spectra significantly. The latter were found especially difficult to analyze, but their interpretation was possible through a close examination of the ^{13}C NMR spectra of their congeners. Cryptophanes **1**–**6**, also isolated as glassy products, have been obtained as [$CHCl_3$@**1**–**6**] complexes after purification. The symmetry of cryptophanes **1**–**6** combined with an increasing degree of deuteration led to very simple ^{1}H NMR spectra, depicted for compounds **2**, **4**, and **6** in Figure 6.

Molecule **6**, for example, displays only four signals, two for the aromatic rings located at $\delta = 6.65$ and 6.75 and two coupled signals for the methylene bridge protons. We have also observed for compounds **4** and **5** that the replacement of a methoxy group by its deuterated congener affects the aromatic proton signals. For instance, the aromatic proton signals of compound **5**, usually located at $\delta = 6.65$, split into two signals of the same intensity located very close to each other. This effect is also observed to a lesser extent for compound **4** where only one methoxy group has been replaced by its deuterated congener.

More interestingly, we have observed that the liquid secondary ion mass spectroscopy (LSIMS) technique leads to very simple mass spectra. Although a complicated mass spectrum was expected for each cryptophane precursor, all the spectra reveal the presence of only two major peaks. One peak corresponds to the cryptophane precursor molecular ion; the mass of the second peak was found to increase with the degree of deuteration, and it has been unambiguously identified as the molecular peak of the corresponding cryptophanes $[M+H]^+$. The ability of the LSIMS technique to reproduce some results observed in solution makes it extremely useful for the organic chemist, and numerous examples dealing with the use of this or related techniques in the field of supramolecular chemistry have already been reported.[16] In our particular case, LSIMS seems to be an easy method with which to investigate the formation of new cryptophanes from their precursors. We have recently shown, with a series of examples, that LSIMS could be used to study analytically the formation of new cryptophanes with more complicated structures.[17]



Scheme 4. Synthesis of cryptophane precursors **26**–**29** and **33**–**34**.



1 : X = CH_2CH_2 ; Y = CH_2CH_2 ; R_1 = OCH_3 ; R_2 — R_6 = OCH_3
2 : X = CH_2CH_2 ; Y = CD_2CD_2 ; R_1 = OCH_3 ; R_2 — R_6 = OCH_3
3 : X = CD_2CD_2 ; Y = CD_2CD_2 ; R_1 = OCH_3 ; R_2 — R_6 = OCH_3
4 : X = CD_2CD_2 ; Y = CD_2CD_2 ; R_1 = OCD_3 ; R_2 — R_6 = OCH_3
5 : X = CD_2CD_2 ; Y = CD_2CD_2 ; R_1 — R_3 = OCD_3 ; R_4 — R_6 = OCH_3
6 : X = CD_2CD_2 ; Y = CD_2CD_2 ; R_1 — R_6 = OCD_3

Scheme 5. Synthesis of cryptophanes **1**–**6**.

Conclusion

We have described the synthesis of deuterated cryptophanes **3**, **5**, and **6** based on a modification of the experimental procedure given for compound **1**. The use of the tetrahydropyranyl ether moiety as a protecting group for the benzyl alcohol moiety allowed us to facilitate significantly the purification of the intermediates, and to introduce selectively two deuterated alkyl chains connecting the two cyclotriveratrylene units, or to add a single deuterated methyl group to prepare pure crypto-

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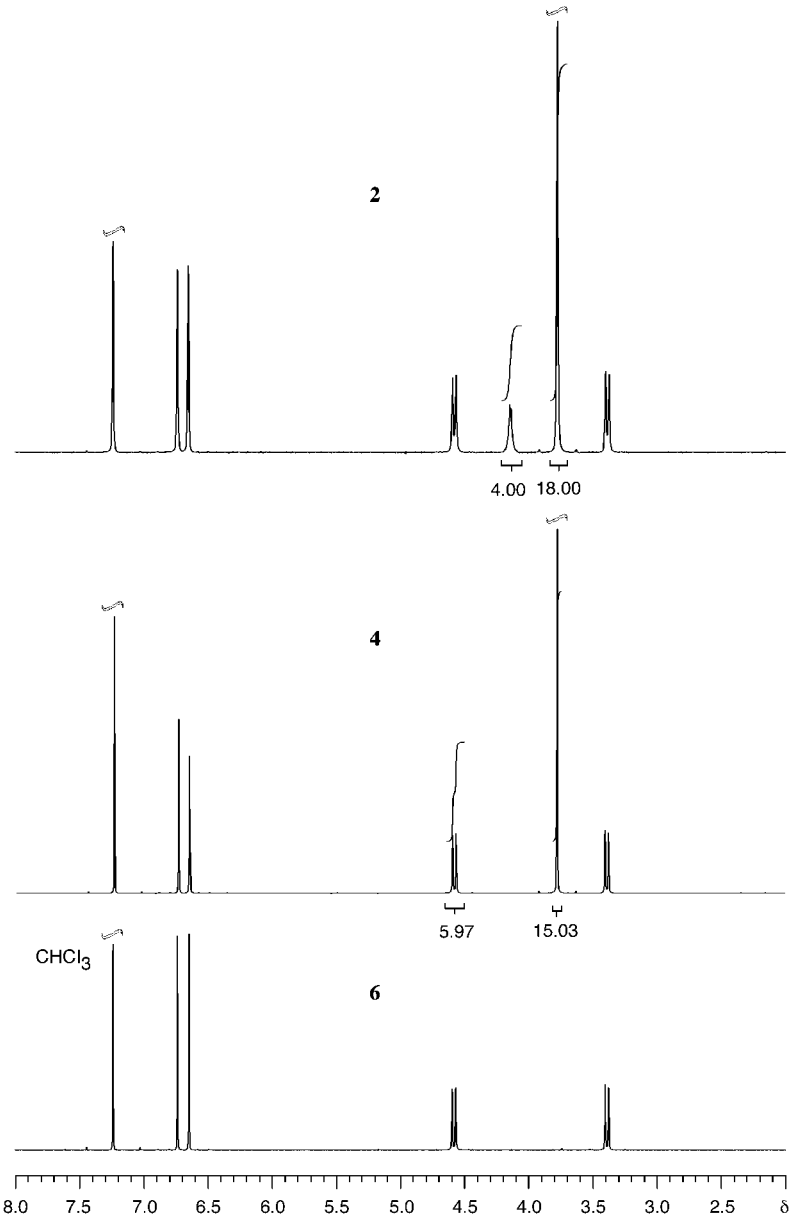

Figure 6. ^{1}H NMR spectra of cryptophanes **2**, **4**, and **6** in deuterated chloroform, recorded at 293 K. Integration of some peaks for compounds **2** and **4** is also shown.

phanes **2** and **4**. More generally, this new synthetic approach has allowed us to synthesize "asymmetric cryptophanes" (i.e. having different linker chains) for the first time. Indeed, this experimental procedure was also found to be very useful in preparing new cryptophanes with interesting properties towards xenon complexation, and these results will be published in due course.[18]

We have further shown that in [Xe@cryptophane] complexes, one-dimensional ^{129}Xe magnetization transfer (1D-EXSY NMR spectroscopy) could be used to measure exchange rate constants. This technique presents several advantages with respect to 2D-EXSY experiments, and renders practical for the first time the quantitative determination of the kinetic parameters for this exchange. We show that there is no direct exchange between cages, and we obtain from an Arrhenius plot the decomplexation energy of activation $E_a = 37.5 \pm 2\,\mathrm{kJ\,mol^{-1}}$. The activation enthalpy and entropy associated with this process were estimated to be $\Delta H^{\neq} = 35.5 \pm 2\,\mathrm{kJ\,mol^{-1}}$ and $\Delta S^{\neq} = -60 \pm 5\,\mathrm{J\,mol^{-1}\,K^{-1}}$, suggesting the formation of a more rigid activated complex than the complex in its ground state.

Experimental Section

[D_3]Methyl iodide (99–99.5% deuteration) and [D_4]1,2-dibromoethane (>99% deuteration) were purchased from Eurisotop. 3,4-Dihydroxybenzaldehyde was purchased from Aldrich. 1,2-dibromoethane, allyl bromide and pyridinium *p*-toluenesulfonate (PPTS) were purchased from Acros Organics. Cesium carbonate and potassium carbonate were dried under vacuum before use. All the solvents were distilled before use (DMF from calcium hydride under reduced pressure, acetone and CH_2Cl_2 from calcium chloride, THF from benzophenone ketyl). Column chromatographic separations were carried out over Merck silica gel 60 (0.040–0.063 mm). Analytical thin-layer chromatography (TLC) was performed on Merck silica gel TLC plates F254. Melting points were measured on a Perkin–Elmer DSC7 microcalorimeter. The NMR sample, containing an equimolar amount of cages **1** and **6** in the presence of monoatomic xenon in [D_2]tetrachloroethane, is as described in ref. [3].

NMR measurements: ^{129}Xe-NMR experiments were carried out at 138.4 MHz (proton frequency 500 MHz) on a Varian Unity$^+$ spectrometer using a 10 mm double resonance probe. ^{129}Xe-NMR spectra were recorded at 238 K, and the sample was kept for about three hours before starting 1D-EXSY experiments. The mixing times were varied in the range 0.01 ms to 5 s (17 values of τ_m were used). A Gaussian pulse was used for the 180° selective pulse (pulse width of 4.45 ms). A long relaxation delay of 30 s was used for each increment. Each spectrum was recorded with 64 scans for a given mixing time value for experiments 1 and 2. The length of the 90° pulse was 25 μs. Prior to the Fourier transform a Gaussian apodization (gf = 0.03) was applied. The intensity of each peak was then measured for a given vertical scale value, which was kept the same for all experiments.

Complexation dynamics as a function of temperature: The NMR sample used for variable-temperature experiments was prepared by mixing equal amounts of cages **1** and **6** (115 mg of each) in a minimum quantity of 1,1,2,2-tetrachloroethane. The solvent was stripped off, and the operation was repeated to remove any bound substrate (mostly $CHCl_3$). Then a mixture of [D_2]1,1,2,2-tetrachloroethane and toluene (75/25) was added, and the solution was poured into a 10 mm NMR tube. Xenon gas (^{129}Xe, natural abundance, 26.4%) was bubbled through the solution. The NMR tube was frozen in liquid nitrogen and sealed under vacuum. The overall cryptophane concentration was $[C] \approx 0.074$ M (using a mean molecular weight for **1** and **6**, $M = 910.105\,\mathrm{g\,mol^{-1}}$).

^{129}Xe 1D-EXSY experiments were performed from 253 K to 228 K (step 5 K, 6 experiments), using 12 mixing times for each given temperature. This requires about 6 h 30 min to complete an experiment. After each change of temperature the sample was left for 30 min before starting another experiment. In order to follow the evolution of rate constants with temperature and thus to obtain a better fit, a different set of mixing times was chosen for each temperature. A Gaussian pulse was used for the 180° selective pulse (pw = 556 μs). A relaxation delay of 30 s was used for each increment. Each spectrum was recorded with 32 scans for each mixing time. The length of the 90° pulse was 25 μs. Prior to the Fourier transform an exponential apodization (lb = 20.0) was applied.

4-Allyloxy-3-hydroxybenzaldehyde (8):[19] Allyl bromide (30.24 g, 0.25 mol) was added in one portion to a stirred solution of 3,4-dihydroxybenzaldehyde (**7**, 13.81 g, 0.1 mol), lithium carbonate (18.47 g, 0.25 mol), and freshly distilled DMF (250 mL). The mixture was then stirred overnight at 55 °C under argon. The mixture was poured into acidic water and the product extracted with ethyl acetate. The combined organic extracts were washed three times with a diluted HCl solution, then with brine. After drying over Na_2SO_4 the solvent was stripped off under reduced pressure and the oily residue chromatographed twice on silica gel (eluent: AcOEt/CH_2Cl_2; 20/80) to give **8** as white crystals (10 g, 56 %). These were washed three times with a few mL of a mixture of pentane and diethyl ether (60/40) and collected on a frit. M.p. 57–58 °C (by DSC); ^{1}H NMR (200 MHz, $CDCl_3$, 20 °C): δ = 9.82 (s, 1H; CHO), 7.43 (d, ^4J(H,H) = 1.9 Hz, 1H), 7.39 (dd, ^4J(H,H) = 1.9 Hz, ^3J(H,H) = 8.2 Hz, 1H), 6.95 (d, ^3J(H,H) = 8.2 Hz, 1H), 6.05 (m, 1H), 5.77 (s, 1H; OH), 5.4 (m, 2H), 4.68 (m, 2H; OCH_2); additional information: ^{13}C NMR (125.67 MHz, $CDCl_3$): δ = 191.12, 150.86, 146.2, 131.72, 130.43, 124.41, 119.03, 114.20, 111.35, 69.76.

4-Allyloxy-3-[D_3]methoxybenzaldehyde (10): [D_3]Methyl iodide (12.2 g, 84.2 mmol, 1.5 equiv) was added under argon to a stirred solution of **8** (10 g, 56.1 mmol), potassium carbonate (15.5 g, 0.112 mol) in 80 mL of freshly distilled DMF. The mixture was stirred overnight at 80 °C under an argon atmosphere. The product was extracted with ethyl acetate and the combined organic layers were washed several times with a dilute HCl solution, then with brine, and were finally dried over Na_2SO_4. Evaporation of the solvent under reduced pressure left a yellow, oily residue. Column chromatography (silica gel, eluent: AcOEt/pentane; 60/40) yielded **10** (10.26 g, 94 %) as a slightly yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$, 20 °C): δ = 9.83 (s, 1H; CHO), 7.41 (d, ^3J(H,H) = 8.5 Hz, 1H), 7.39 (s, 1H), 6.95 (d, ^3J(H,H) = 8.5 Hz, 1H), 6.05 (m, 1H), 5.37 (m, 2H), 4.68 (m, 2H; OCH_2); ^{13}C NMR (125.67 MHz, $CDCl_3$): δ = 190.44, 153.05, 149.44, 131.91, 129.79, 126.13, 118.31, 111.53, 108.84, 69.33, 54.77 (h, 1C, ^{1} J(C,D) = 22.0 Hz; O*C*D_3); elemental analysis calcd (%) for $C_{11}H_9D_3O_3$ (195.2): C 67.67, H 4.65; found C 67.86, H 4.38.

(4-Allyloxy-3-[D_3]methoxyphenyl)methanol (11): Sodium borohydride (2.6 g, 0.069 mol) was added in portions to a cooled solution of **10** (9.56 g, 0.049 mol) in 55 mL of methanol. Then the solution was allowed to warm to room temperature and was stirred overnight at this temperature under an argon atmosphere. Most of the solvent was removed under reduced pressure and the solution was then acidified at 0 °C with portionwise addition of a concentrated HCl solution. The product was then extracted with ethyl acetate. The combined organic extracts were washed three times with brine and dried over Na_2SO_4. The solvent was then stripped off to give **11** (8.79 g, 91 %) as a colorless solid. These crystals were recrystallized in 75 mL of isopropanol ether. M.p. 68.0–69.0 °C (by DSC); ^{1}H NMR (200 MHz, $CDCl_3$, 20 °C): δ = 6.87 (m, 3H; Ar), 6.05 (m, 1H), 5.33 (m, 2H), 4.59 (m, 4H; 2 × OCH_2), 1.64 (t, 1H, ^3J(H,H) = 5.6 Hz; OH); ^{13}C NMR (125.67 MHz, $CDCl_3$): δ = 149.37, 147.30, 133.88, 133.17, 119.11, 117.90, 113.13, 110.62, 69.79, 65.06, 55.1 (h, 1C, ^1J(C,D) = 22.0 Hz; O*C*D_3); elemental analysis calcd (%) for $C_{11}H_{11}D_3O_3$ (197.3): C 66.98, H 5.62; found C 66.86, H 5.74.

2-(4-Allyloxy-3-[D_3]methoxybenzyloxy)tetrahydropyran (13): A solution of pyridinium *p*-toluenesulfonate (1.0 g, 3.95 mmol) in 16 mL of CH_2Cl_2 was poured into a solution of **11** (7.8 g, 39.5 mmol) and dihydropyran (5.0 g, 59.3 mmol, 1.5 equiv) in dry THF (125 mL). The solution was stirred overnight at room temperature under argon. The solvent was then stripped off under reduced pressure to leave a residue, which was extracted with diethyl ether. The combined organic extracts were washed twice with brine and then dried over Na_2SO_4. After the solvent had been evaporated, the oily residue was purified by chromatography on silica gel (eluent: diethyl ether/pentane; 50/50) to give **13** as a slightly yellow oil (10.36 g, 93 %). ^{1}H NMR (200 MHz, $CDCl_3$, 20 °C): δ = 6.84 (m, 3H; Ar), 6.05 (m, 1H), 5.32 (m, 2H), 4.70 (d, 1H, ^2J(H,H) = 11.7 Hz), 4.68 (m, 1H), 4.59 (m, 2H), 4.42 (d, 1H, ^2J(H,H) = 11.7 Hz), 3.91 (m, 1H), 3.51 (m, 1H), 1.90–1.48 (m, 6H); ^{13}C NMR (125.67 MHz, $CDCl_3$): δ = 149.30, 147.40, 133.31, 131.03, 120.33, 117.89, 113.08, 111.60, 97.53, 69.84, 68.75, 62.25, 55.01 (h, 1C, ^1J(C,D) = 23.0 Hz; O*C*D_3), 30.57, 25.43, 19.45; elemental analysis calcd (%) for $C_{16}H_{19}D_3O_4$ (281.4): C 68.30, H 6.81; found C 68.57, H, 6.52.

2-[D_3]Methoxy-4-(tetrahydropyran-2-yloxymethyl)phenol (14): A solution of **13** (3.0 g, 10.7 mmol), palladium acetate (0.180 g, 0.8 mmol), triphenylphosphine (0.3 g, 1.16 mmol), diethylamine (60 mL), THF (150 mL), and H_2O (30 mL) was stirred at 80 °C under argon for about three hours. The dark solution was then stripped off under reduced pressure to leave a dark residue, which was extracted with ethyl acetate. The organic layer was washed once with water followed by filtration with filter paper to remove insoluble dark material. The combined organic extracts were then washed three times with brine and dried over Na_2SO_4. After removal of the solvent under reduced pressure the oily residue was purified twice by chromatography on silica gel (eluent: CH_2Cl_2/ Et_2O; 85/15) to give **14** as a yellow oil (2.01 g, 77 %). ^{1}H NMR (200 MHz, $CDCl_3$, 20 °C): δ = 6.87 (m, 3H; Ar), 5.57 (s, 1H; OH), 4.69 (d, ^2J(H,H) = 11.5 Hz, 1H), 4.64 (m, 1H), 4.40 (d, ^2J(H,H) = 11.5 Hz, 1H), 3.89 (m, 1H), 3.53 (m, 1H), 1.90–1.48 (m, 6H); ^{13}C NMR (125.67 MHz, $CDCl_3$): δ = 146.42, 145.16, 130.01, 121.32, 114.09, 110.75, 97.50, 68.91, 62.31, 55.06 (h, 1C, ^1J(C,D) = 22.0 Hz; O*C*D_3), 30.61, 25.45, 19.50; elemental analysis calcd (%) for $C_{13}H_{15}D_3O_4$, 0.1 H_2O (243.1): C 64.23, H 6.30; found C 64.02, H 6.14.

2-[4-(2-Bromoethoxy)-3-methoxybenzyloxy]tetrahydropyran (20): A solution of PPTS (0.33 g, 1.3 mmol) in 5 mL of CH_2CL_2 was added in one portion to a mixture of **18** (3.4 g, 13 mmol) and dihydropyran (1.64 g, 20 mmol) in 40 mL of THF. The solution was stirred overnight at room temperature under argon. The solvent was stripped off to leave a residue, which was extracted with diethyl ether. The combined organic layers were washed twice with brine, dried over Na_2SO_4 and evaporated to leave an oily residue. Chromatography on silica gel (diethyl ether/pentane; 40/60) yielded compound **20** (3.6 g, 80 %) as a white solid. M.p. 46 °C (by DSC); ^{1}H NMR (200 MHz, $CDCl_3$, 20 °C): δ = 6.91–6.87 (m, 3H; Ar), 4.70 (d, ^2J(H,H) = 11.8 Hz, 1H), 4.65 (m, 1H), 4.42 (d, ^2J(H,H) = 11.8 Hz, 1H), 4.30 (t, ^3J(H,H) = 7.0 Hz, 2H; OCH_2), 3.90 (m, 1H), 3.86 (s, 3H; OCH_3), 3.62 (t, ^3J(H,H) = 7.0 Hz, 2H; CH_2Br), 3.55 (m, 1H), 1.90–1.40 (m, 6H); ^{13}C NMR (125.67 MHz, $CDCl_3$): δ = 149.75, 146.81, 132.34, 120.45, 114.60, 112.09, 97.61, 69.25, 68.63, 62.26, 55.94, 30.56, 28.84, 25.41, 19.44; elemental analysis calcd (%) for $C_{15}H_{21}O_4Br$ (345.2): C 52.19, H 6.13; found: C 52.46, H 5.92.

2-[4-(2-[D_4]Bromoethoxy)-3-[D_3]methoxybenzyloxy]tetrahydropyran (15): [D_4]1,2-Dibromoethane (5.01 g, 26.1 mmol) was added to a stirred solution of **14** (1.98 g, 8.2 mmol) and potassium carbonate (2.37 g, 17.2 mmol) in 40 mL of dry acetone. The mixture was stirred overnight at 80 °C under an argon atmosphere. The solvent was stripped off to leave a residue, which was extracted with diethyl ether. The combined organic layers were washed three times with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave a yellow, oily residue. Chromatography on silica gel (diethyl ether/pentane: 40/60) yielded **15** (1.63 g, 56 %) as a white solid. M.p. 45–46 °C (by DSC); ^{1}H NMR (500 MHz, $CDCl_3$, 20 °C): δ = 6.91 (s, 1H; Ar), 6.86 (m, 2H; Ar), 4.70 (d, ^2J(H,H) = 12.0 Hz, 1H), 4.67 (m, 1H), 4.42 (d, ^2J(H,H) = 12.0 Hz, 1H), 3.91 (m, 1H), 3.53 (m, 1H), 1.90–1.80 (m, 1H), 1.78–1.66 (m, 1H), 1.66–1.46 (m, 4H); ^{13}C NMR (125.67 MHz, $CDCl_3$): δ = 149.76, 146.81, 132.33, 120.46, 114.55, 112.08, 97.64, 68.67, 68.42 (p, ^1J(C,D) = 22.0 Hz, 1C; O*C*D_2), 62.30, 55.15 (h, ^1J(C,D) = 22.0 Hz, 1C; O*C*D_3), 30.58, 28.34 (p, ^1J(C,D) = 22.0 Hz, 1C; Br*C*D_2), 25.44, 19.47; elemental analysis calcd (%) for $C_{15}H_{14}O_4D_7Br$ (352.3): C 51.14, H 4.01; found C 50.94, H 4.22.

2-[4-(2-[D_4]Bromoethoxy)-3-methoxybenzyloxy]tetrahydropyran (19): The workup described for the synthesis of **20** was applied. Derivative **19** (1.1 g, 83 %) was obtained from compound **17** (1.0 g, 3.8 mmol) in 20 mL of THF, dihydropyran (0.48 g, 5.7 mmol) and PPTS (95 mg, 0.38 mmol) dissolved in 3 mL of CH_2CL_2. M.p. 45–46 °C (by DSC); ^{1}H NMR (500 MHz, $CDCl_3$, 20 °C): δ = 6.91 (s, 1H; Ar), 6.86 (m, 2H; Ar), 4.70 (d, ^2J(H,H) = 11.5 Hz, 1H), 4.66 (m, 1H), 4.42 (d, ^2J(H,H) = 11.5 Hz, 1H), 3.90 (m, 1H), 3.86 (s, 3H; OCH_3), 3.53 (m, 1H), 1.90–1.80 (m, 1H), 1.78–1.66 (m, 1H), 1.66–1.46 (m, 4H); ^{13}C NMR (125.67 MHz, $CDCl_3$): δ = 149.72, 146.78, 132.30, 120.44, 114.53, 112.07, 97.60, 68.62, 68.36 (p, ^1J(C,D) = 22.5 Hz, 1 C; O*C*D_2), 62.26, 55.93, 30.55, 28.13 (p, ^1J(C,D) = 22.5 Hz, 1 C,

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BrCD$_2$), 25.40, 19.43; elemental analysis calcd (%) for $C_{15}H_{17}O_4D_4Br$ (349.3): C 51.58, H 4.91; found C 51.65, H 4.77.

2-[4-(2-Iodoethoxy)-3-methoxybenzyloxy]tetrahydropyran (23)

General procedure A: Sodium iodide (18 g, 0.12 mol, 10 equiv) was added in one portion to a stirred solution of **20** (4.15 g, 12.0 mmol) in dry acetone (55 mL). The solution was refluxed overnight under argon atmosphere. After it had cooled to room temperature, the solvent was stripped off under reduced pressure to leave a yellow residue. Chromatography on silica gel (eluent: diethyl ether/pentane; 60/40) yielded **23** as a white solid (4.40 g, 94%). M.p. 47–48 °C (by DSC); ^{1}H NMR (500 MHz, $CDCl_3$, 20 °C): δ = 6.91 (s, 1H; Ar), 6.85 (m, 2H; Ar), 4.70 (d, ^2J(H,H) = 11.5 Hz, 1H), 4.67 (m, 1H), 4.42 (d, ^2J(H,H) = 11.5 Hz, 1H), 4.27 (t, ^3J(H,H) = 7.5 Hz, 2H; OCH_2), 3.91 (m, 1H), 3.86 (s, 3H; OCH_3), 3.53 (m, 1H), 3.41 (t, ^3J(H,H) = 7.5 Hz, 2H; CH_2I), 1.90–1.80 (m, 1H), 1.78–1.66 (m, 1H), 1.66–1.46 (m, 4H); ^{13}C NMR (125.67 MHz, $CDCl_3$): δ = 149.72, 146.63, 132.29, 120.48, 114.57, 112.10, 97.63, 70.19, 68.66, 62.29, 55.97, 30.57, 25.42, 19.45, 1.06; elemental analysis calcd (%) for $C_{15}H_{21}O_4I$ (392.2): C 45.93, H 5.40; found C 45.74, H 5.42.

2-[4-(2-[D$_4$]Iodoethoxy)-3-methoxybenzyloxy]tetrahydropyran (22): According to general procedure A, compound **22** (1.67 g, 95%) was obtained from **19** (1.55 g, 4.4 mmol) and sodium iodide (6.6 g, 44 mmol) in dry acetone (40 mL). M.p. 47–48 °C (by DSC); ^{1}H NMR (500 MHz, $CDCl_3$, 20 °C): δ = 6.915 (d, ^4J(H,H) = 2.0 Hz, 1H; Ar), 6.87 (dd, ^4J(H,H) = 2.0 Hz, ^3J(H,H) = 8.0 Hz, 1H; Ar), 6.84 (d, ^3J(H,H) = 8.0 Hz, 1H; Ar), 4.71 (d, ^2J(H,H) = 12.0 Hz, 1H), 4.67 (m, 1H), 4.42 (d, ^2J(H,H) = 12.0 Hz, 1H), 3.91 (m, 1H), 3.86 (s, 3H; OCH_3), 3.53 (m, 1H), 1.90–1.80 (m, 1H), 1.76–1.68 (m, 1H), 1.65–1.48 (m, 4H); ^{13}C NMR (125.67 MHz, $CDCl_3$): δ = 149.67, 146.58, 132.23, 120.45, 114.48, 112.06, 97.59, 69.30 (p, ^1J(C,D) = 22.0 Hz, 1C; O*C*D$_2$), 68.62, 62.25, 55.93, 30.54, 25.40, 19.43, 0.56 (p, ^1J(C,D) = 22.0 Hz, 1C; *C*D$_2$I); elemental analysis calcd (%) for $C_{15}H_{17}O_4D_4I$ (396.3): C 45.47, H 4.32; found C 45.20, H 4.13.

2-[4-(2-[D$_4$]Iodoethoxy)-3-[D$_3$]methoxybenzyloxy]tetrahydropyran (21): According to general procedure A, compound **21** (1.16 g, 97%) was obtained from **15** (1.02 g, 3.0 mmol) and sodium iodide (4.43 g, 30 mmol) in dry acetone (30 mL). M.p. 47–48 °C (by DSC); ^{1}H NMR (500 MHz, $CDCl_3$, 20 °C): δ = 6.91 (s, 1H; Ar), 6.86 (m, 2H; Ar), 4.70 (d, ^2J(H,H) = 11.5 Hz, 1H), 4.66 (m, 1H), 4.42 (d, ^2J(H,H) = 11.5 Hz, 1H), 3.91 (m, 1H), 3.53 (m, 1H), 1.90–1.80 (m, 1H), 1.76–1.68 (m, 1H), 1.65–1.48 (m, 4H); ^{13}C NMR (125.67 MHz, $CDCl_3$): δ = 149.68, 146.58, 132.24, 120.43, 114.49, 112.04, 97.60, 69.31 (p, ^1J(C,D) = 22.0 Hz, 1C; O*C*D$_2$), 68.64, 62.27, 55.11 (h, ^1J(C,D) = 22.0 Hz, 1C; O*C*D$_3$), 30.55, 25.41, 19.44, 0.56 (p, ^1J(C,D) = 22.0 Hz, 1C; *C*D$_2$I); elemental analysis calcd (%) for $C_{15}H_{14}O_4D_7I$ (399.3): C 45.12, H 3.53; found C 45.37, H 3.30.

[4-(2-[D$_4$]Iodoethoxy)-3-[D$_3$]methoxyphenyl]methanol (24): Pyridinium *p*-toluenesulfonate (83 mg, 0.33 mmol) was added in one portion to a stirred solution of **21** (1.3 g, 3.3 mmol) in ethanol (15 mL). The solution was heated at 55 °C for 5 hours. The solvent was stripped off under reduced pressure to leave a residue, which was extracted with ethyl acetate. The combined organic extracts were washed with brine and then dried over Na_2SO_4. Evaporation of the solvent under reduced pressure left a solid, which was purified by chromatography on silica gel (AcOEt/pentane: 50/50), yielding **24** (0.99 g, 97%) as a white solid. M.p. 85 °C (by DSC); ^{1}H NMR (200 MHz, $CDCl_3$, 20 °C): δ = 6.93–6.85 (m, 3H; Ar), 4.62 (d, ^3J(H,H) = 5.1 Hz, 2H; CH_2), 1.60 (t, ^3J(H,H) = 5.1 Hz, 1H; OH); ^{13}C NMR (125.67 MHz, $CDCl_3$): δ = 149.82, 146.62, 134.99, 119.29, 114.55, 111.09, 69.31 (p, ^1J(C,D) = 22.1 Hz, 1C; O*C*D$_2$), 65.10, 54.94 (h, ^1J(C,D) = 22.0 Hz, 1C, O*C*D$_3$), 0.68 (p, ^1J(C,D) = 22.0 Hz, 1C; *C*D$_2$I); elemental analysis calcd (%) for $C_{10}H_6O_3D_7I$ (315.2): C 38.11, H 1.92; found C 38.30, H 1.97.

[4-(2-[D$_4$]Bromoethoxy)-3-methoxyphenyl]methanol (17): [D$_2$]1,2-dibromoethane (6.4 g, 33.3 mmol) was added to a stirred solution of vanillic alcohol (1.5 g, 9.73 mmol) and potassium carbonate (2.69 g, 19.5 mmol) in acetone (40 mL). The mixture was stirred overnight at 80 °C under an argon atmosphere. The solvent was stripped off under reduced pressure to leave a residue, which was extracted with ethyl acetate. The combined organic layers were washed twice with water, dried over Na_2SO_4, and evaporated under reduced pressure. Chromatography on silica gel (CH_2Cl_2/AcOEt: 70/30) yielded **17** as a white solid (1.23 g, 48%). The solid was then recrystallized in a mixture of diethyl ether and pentane. M.p. 71.5 °C; ^{1}H NMR (200 MHz, $CDCl_3$, 20 °C): δ = 6.94 (s, 1H; Ar), 6.865 (m, 2H; Ar), 4.62 (d, ^3J(H,H) = 6.0 Hz, 2H; CH_2), 3.87 (s, 3H; OCH_3), 1.60 (t, ^3J(H,H) = 6.0 Hz, 1H; OH); ^{13}C NMR (125.67 MHz, $CDCl_3$): δ = 149.79, 146.74, 135.06, 119.26, 114.55, 111.10, 68.36 (p, ^1J(C,D) = 22.0 Hz, 1C; O*C*D$_2$), 64.96, 55.87, 28.14 (p, ^1J(C,D) = 22.5 Hz, 1C; *C*D$_2$Br); elemental analysis calcd (%) for $C_{10}H_9O_3D_4Br$ (265.1): C 45.30, H 3.42; found C 45.39, H 3.71.

2,7,12-Tris(allyloxy)-3,8,13-[D$_3$]trimethoxy-10,15-dihydro-5*H*-tribenzo-[a,d,g]cyclononene (12): This compound was prepared according to a known procedure.[20] Deuterated starting material **11** (21.1 g, 0.107 mmol) gives derivative **12** (7.5 g, 39%) as a white solid after chromatography on silica gel (CH_2Cl_2/Et_2O: 97/3). M.p. 171–172 °C; ^{1}H NMR (500 MHz, $CDCl_3$, 20 °C): δ = 6.83 (s, 3H; Ar), 6.77 (s, 3H; Ar), 6.04 (m, 3H), 5.28 (m, 6H), 4.72 (d, ^2J(H,H) = 13.6 Hz, 3H), 4.58 (m, 6H), 3.49 (d, ^2J(H,H) = 13.6 Hz, 3H); ^{13}C NMR (125.67 MHz, $CDCl_3$): δ = 148.06 (3C), 146.60 (3C), 133.65 (3C), 132.22 (3C), 131.59 (3C), 117.47 (3C), 115.37 (3C), 113.38 (3C), 70.08 (3C), 55.16 (h, ^1J(C,D) = 22.0 Hz, 3C; O*C*D$_3$), 36.45 (3C); elemental analysis calcd (%) for $C_{33}H_{27}O_6D_9$ (537.7): C 73.72, H 5.06; found C 73.69, H 5.41.

3,8,13-[D$_3$]Trimethoxy-10,15-dihydro-5*H*-tribenzo[a,d,g]cyclononene-2,7,12-triol (9): A solution of **12** (2.2 g, 4.1 mmol), palladium acetate (61 mg, 0.28 mmol), triphenylphosphine (0.21 g, 0.8 mmol), diethylamine (20 mL), THF (50 mL), and H_2O (10 mL) was stirred at 80 °C under an argon atmosphere for about three hours. The dark solution was then stripped off under reduced pressure and the product extracted with ethyl acetate. The organic layer was washed once with water followed by filtration with filter paper to remove insoluble dark material. The combined organic layers were washed three times with brine and then dried over Na_2SO_4. Evaporation of the solvent under reduced pressure left a yellow solid, which was filtered on a frit and washed three times with diethyl ether to yield **9** (1.15 g, 67%) as white solid. M.p. > 300 °C; ^{1}H NMR (500 MHz, $CDCl_3$, 20 °C): δ = 6.86 (s, 3H; Ar), 6.76 (s, 3H; Ar), 5.39 (s, 3H; OH), 4.69 (d, ^2J(H,H) = 13.5 Hz, 3H), 3.48 (d, ^2J(H,H) = 13.5 Hz, 3H); ^{13}C NMR (125.67 MHz, $CDCl_3$): δ = 145.18 (3C), 144.07 (3C), 132.40 (3C), 131.18 (3C), 115.39 (3C), 112.19 (3C), 55.0 (h, ^1J(C,D) = 22.0 Hz, 3C; O*C*D$_3$), 36.27 (3C); elemental analysis calcd (%) for $C_{24}H_{15}O_6D_9$, 3/4 H_2O (431.0): C 66.88, H 3.86; found C 66.80, H 3.86; HRMS (LSIMS) exact mass calcd for $C_{24}H_{15}O_6D_9$ $[M]^+$ 417.2138, found 417.2144.

12-[2-(4-Hydroxymethyl-2-methoxyphenoxy)ethoxy]-3,8,13-trimethoxy-10,15-dihydro-5*H*-tribenzo[a,d,g]cyclononene-2,7-diol (31): Compound **30** (0.44 g, 1.43 mmol) was added in one portion to a stirred solution of **25** (0.6 g, 1.47 mmol) and cesium carbonate (0.96 g, 2.95 mmol) in dry DMF (35 mL). The solution was then heated for 18 h at 80 °C under argon. After cooling, the dark mixture was poured into water and the product extracted with ethyl acetate. The combined organic layers were washed several times with brine and then dried over Na_2SO_4. The solvent was stripped off by rotary evaporation to leave a residue, which was purified by chromatography on silica gel (eluent: AcOEt). The second spot observed by TLC was collected and identified, after evaporation of the solvent, as the expected derivative **31** (0.258 g, 30%). ^{1}H NMR (500 MHz, $CDCl_3$, 20 °C): δ = 6.98–6.77 (m, 9H; Ar), 5.40 (s, 1H; OH), 5.38 (s, 1H; OH), 4.72 (d, ^2J(H,H) = 13.5 Hz, 1H), 4.70 (d, ^2J(H,H) = 13.5 Hz, 2H), 4.605 (d, ^3J(H,H) = 6.0 Hz, 2H; OCH_2), 4.32 (m, 4H; OCH_2CH_2O), 3.84 (s, 3H; OCH_3), 3.81 (s, 3H; OCH_3), 3.79 (s, 3H; OCH_3), 3.71 (s, 3H; OCH_3), 3.50 (d, ^2J(H,H) = 13.5 Hz, 1H), 3.49 (d, ^2J(H,H) = 13.5 Hz, 2H), 1.60 (t, ^3J(H,H) = 6.0 Hz, 1H; OH); ^{13}C NMR (125.67 MHz, $CDCl_3$): δ = 149.62, 148.48, 147.55, 146.62, 145.21 (2C), 144.09, 144.06, 134.31, 133.05, 132.48, 132.20, 131.92, 131.22, 131.15, 119.39, 116.73, 115.52, 115.48, 113.73, 113.68, 112.15 (2C), 110.92, 68.14, 67.66, 65.23, 56.13, 56.02, 55.99, 55.76, 36.36, 36.26, 36.21; HRMS (LSIMS): exact mass calcd for $C_{34}H_{36}O_9$ $[M]^+$ 588.2366, found 588.2359.

12-[2-(4-Hydroxymethyl-2-[D$_3$]methoxyphenoxy)-[D$_4$]ethoxy]-3,8,13-trimethoxy-10,15-dihydro-5*H*-tribenzo[a,d,g]cyclononene-2,7-diol (32): Compound **24** (0.46 g, 1.46 mmol) was added in one portion to a stirred solution of **25** (0.6 g, 1.47 mmol) and cesium carbonate (0.96 g, 2.94 mmol) in DMF (35 mL). The mixture was stirred for 18 h at 80 °C under argon and then poured into water. The same workup used for compound **31** was applied to yield **32** as a white glassy solid (0.173 g, 20%). ^{1}H NMR (500 MHz, $CDCl_3$, 20 °C): δ = 6.97–6.77 (m, 9H; Ar), 5.42 (s, 1H; OH), 5.39 (s, 1H; OH), 4.72 (d, ^2J(H,H) = 13.5 Hz, 1H), 4.69 (d, ^2J(H,H) = 13.5 Hz, 2H), 4.605 (d, ^3J(H,H) = 5.0 Hz, 2H; OCH_2), 3.84 (s, 3H; OCH_3), 3.81 (s, 3H; OCH_3), 3.71 (s, 3H; OCH_3), 3.50 (d, ^2J(H,H) = 13.5 Hz, 1H), 3.49 (d, ^2J(H,H) = 13.5 Hz, 2H), 1.61 (t, ^3J(H,H) = 5.0 Hz, 1H; OH); ^{13}C NMR (125.67 MHz, $CDCl_3$): δ = 149.59, 148.45, 147.51,

146.59, 145.23, 145.21, 144.08, 144.05, 134.30, 133.03, 132.48, 132.19, 131.92, 131.22, 131.14, 119.35, 116.65, 115.54, 115.48, 113.74, 113.64, 112.17 (2C), 110.89, 68.0 (m, 2C; OCD_2CD_2O), 65.20 (s, 1C; CH_2OH), 56.11 (s, 1C; OCH_3), 56.01 (s, 1C; OCH_3), 55.98 (s, 1C; OCH_3), 55.0 (m, 1C; OCD_3), 36.34, 36.23 (2C); MS (LSIMS, NBA-Li^+): *m*/*z* (%): 602.1 (30.3) $[M+Li]^+$, 244.0 (18.5), 209.0 (20.0), 90.8 (35).

2,7,12-Trimethoxy-3,8,13-tris-{2-[2-methoxy-4-(tetrahydropyran-2-yloxymethyl)phenoxy]ethoxy}-10,15-dihydro-5*H*-tribenzo[a,d,g]cyclononene (26):

General procedure B: Derivative **23** (1.77 g, 4.5 mmol) was added to a stirred solution of **25** (0.46 g, 1.12 mmol) and cesium carbonate (2.20 g, 6.76 mmol) in dry DMF (20 mL). The mixture was heated for 18 h at 80 °C under argon. After cooling the mixture was poured into water and the product extracted with ethyl acetate. The combined organic layers were washed several times with brine and were then dried over Na_2SO_4. The solvent was stripped off by rotary evaporation to leave a yellow residue, which was purified by chromatography on silica gel ($AcOEt/CH_2Cl_2$: 50/50). Compound **26** was collected as a white, glassy solid (0.95 g, 71%). ^1H NMR (500 MHz, $CDCl_3$, 20 °C): $\delta = 7.01-6.83$ (m, 15H; Ar), 4.72 (d, $^2J(H,H) = 13.0$ Hz, 3H), 4.70 (d, $^2J(H,H) = 12.0$ Hz, 3H), 4.66 (m, 3H), 4.42 (d, $^2J(H,H) = 12.0$ Hz, 3H), 4.34 (m, 12H; OCH_2CH_2O), 3.90 (m, 3H), 3.85 (s, 9H; OCH_3), 3.72 (s, 9H; OCH_3), 3.525 (m, 3H), 3.52 (d, $^2J(H,H) = 13.0$ Hz, 3H), 1.90–1.80 (m, 3H), 1.78–1.66 (m, 3H), 1.66–1.46 (m, 12H); ^{13}C NMR (125.67 MHz, $CDCl_3$): $\delta = 149.41$ (3C), 148.42 (3C), 147.47 (3C), 146.78 (3C), 132.89 (3C), 131.75 (3C), 131.52 (3C), 120.46 (3C), 116.52 (3C), 113.70 (3C), 113.50 (3C), 111.83 (3C), 97.52 (3C), 68.65 (3C), 68.10 (3C), 67.58 (3C), 62.22 (3C), 56.11 (3C), 55.80 (3C), 36.33 (3C), 30.53 (3C), 25.38 (3C), 19.42 (3C); HRMS (LSIMS): exact mass calcd for $C_{69}H_{84}O_{18}$ $[M]^+$ 1200.5658, found 1200.5666.

2,7,12-Trimethoxy-3,8,13-tris-{2-[2-methoxy-4-(tetrahydropyran-2-yloxymethyl)phenoxy]-[D_4]ethoxy}-10,15-dihydro-5*H*-tribenzo[a,d,g]cyclononene (27): According to general procedure B, derivative **27** (0.98 g, 85%) was obtained from cyclotriveratrylene **25** (0.4 g, 0.98 mmol), compound **22** (1.4 g, 3.54 mmol), and cesium carbonate (1.92 g, 5.9 mmol) in DMF (20 mL). ^1H NMR (500 MHz, $CDCl_3$, 20 °C): $\delta = 7.00-6.83$ (m, 15H), 4.72 (d, $^2J(H,H) = 13.5$ Hz, 3H), 4.70 (d, $^2J(H,H) = 11.5$ Hz, 3H), 4.66 (m, 3H), 4.42 (d, $^2J(H,H) = 11.5$ Hz, 3H), 3.915 (m, 3H), 3.85 (s, 9H; OCH_3), 3.72 (s, 9H; OCH_3), 3.525 (m, 3H), 3.52 (d, $^2J(H,H) = 13.5$ Hz, 3H), 1.90–1.80 (m, 3H), 1.78–1.66 (m, 3H), 1.66–1.46 (m, 12H); ^{13}C NMR (125.67 MHz, $CDCl_3$): $\delta = 149.46$ (3C), 148.47 (3C), 147.53 (3C), 146.82 (3C), 132.92 (3C), 131.81 (3C), 131.56 (3C), 120.54 (3C), 116.51 (3C), 113.75 (3C), 113.50 (3C), 111.87 (3C), 97.60 (3C), 68.72 (3C), 68.0–66.0 (m, 6C; OCD_2CD_2O), 62.30 (3C), 56.18 (3C), 55.87 (3C), 36.41 (3C), 30.59 (3C), 25.44 (3C), 19.48 (3C); HRMS (LSIMS, NBA-Li^+): exact mass calcd for $C_{69}H_{72}O_{18}D_{11}Li_1$ 1217.6430 $[M-D+Li]^+$, found 1217.6471.

2,7,12-[D_3]Trimethoxy-3,8,13-tris-{2-[2-[D_3]methoxy-4-(tetrahydropyran-2-yloxymethyl)phenoxy]-[D_4]ethoxy}-10,15-dihydro-5*H*-tribenzo[a,d,g]cyclononene (29): According to general procedure B, derivative **29** (1.05 g, 89%) was obtained from deuterated cyclotriveratrylene **9** (0.4 g, 0.96 mmol), derivative **21** (1.38 g, 3.5 mmol), and cesium carbonate (1.88 g, 5.8 mmol) in dry DMF (20 mL). ^1H NMR (500 MHz, $CDCl_3$, 20 °C): $\delta = 7.00-6.82$ (m, 15H; Ar), 4.72 (d, $^2J(H,H) = 12.5$ Hz, 3H), 4.70 (d, $^2J(H,H) = 11.5$ Hz, 3H), 4.66 (m, 3H), 4.42 (d, $^2J(H,H) = 11.5$ Hz, 3H), 3.89 (m, 3H), 3.525 (m, 3H), 3.52 (d, $^2J(H,H) = 12.5$ Hz, 3H), 1.90–1.80 (m, 3H), 1.78–1.66 (m, 3H), 1.66–1.46 (m, 12H); ^{13}C NMR (125.67 MHz, $CDCl_3$): $\delta = 149.43$ (3C), 148.44 (3C), 147.50 (3C), 146.78 (3C), 132.91 (3C), 131.76 (3C), 131.54 (3C), 120.50 (3C), 116.49 (3C), 113.71 (3C), 113.48 (3C), 111.83 (3C), 97.58 (3C), 68.70 (3C), 68.0–66.0 (m, 6C; OCD_2CD_2O), 62.28 (3C), 56.0–54.0 (6C, m; OCD_3), 36.39 (3C), 30.58 (3C), 25.43 (3C), 19.46 (3C); MS (LSIMS, NBA): *m*/*z* (%): 1230.8 (60) $[M]^+$, 925.6 (100).

2,7,12-Trimethoxy-3,8,13-tris{2-[2-[D_3]methoxy-4-(tetrahydropyran-2-yloxymethyl)phenoxy]-[D_4]ethoxy}-10,15-dihydro-5*H*-tribenzo[a,d,g]cyclononene (28): According to general procedure B, compound **28** (0.83 g, 69%) was prepared from cyclotriveratrylene **25** (0.4 g, 0.98 mmol), compound **21** (1.38 g, 3.5 mmol), and cesium carbonate (1.88 g, 5.8 mmol) in DMF (20 mL). ^1H NMR (500 MHz, $CDCl_3$, 20 °C): $\delta = 7.00-6.83$ (m, 15H; Ar), 4.72 (d, $^2J(H,H) = 13.0$ Hz, 3H), 4.70 (d, $^2J(H,H) = 11.5$ Hz, 3H), 4.66 (m, 3H), 4.42 (d, $^2J(H,H) = 11.5$ Hz, 3H), 3.89 (m, 3H), 3.72 (s, 9H; OCH_3), 3.525 (m, 3H), 3.52 (d, $^2J(H,H) = 13.0$ Hz, 3H), 1.90–1.80 (m, 3H), 1.78–1.66 (m, 3H), 1.66–1.46 (m, 12H); ^{13}C NMR (125.67 MHz, $CDCl_3$): $\delta = 149.44$ (3C), 148.46 (3C), 147.51 (3C), 146.80 (3C), 132.90 (3C), 131.80 (3C), 131.55 (3C), 120.50 (3C), 116.49 (3C), 113.74 (3C), 113.49 (3C), 111.84 (3C), 97.59 (3C), 68.71 (3C), 68.0–66.0 (m, 6C; OCD_2CD_2O), 62.29 (3C), 56.17 (3C), 55.04 (h, 3C, ^1J (C,D) = 22.1 Hz; OCD_3), 36.40 (3C), 30.59 (3C), 25.43 (3C), 19.47 (3C); MS (LSIMS, NBA): *m*/*z* (%): 1221.1 (53.1) $[M]^+$, 916.4 (100).

{3-[D_3]Methoxy-4-[2-(3,8,13-trimethoxy-7,12-bis{2-[2-methoxy-4-(tetrahydropyran-2-yloxymethyl)phenoxy]-[D_4]ethoxy}-10,15-dihydro-5*H*-tribenzo[a,d,g]cyclononen-2-yloxy)-[D_4]ethoxy]phenyl}methanol (34): According to general procedure B, compound **34** (0.63 g, 78%) was obtained from derivative **32** (0.43 g, 0.71 mmol), compound **22** (0.68 g, 1.7 mmol, 2.4 equiv) and cesium carbonate (0.93 g, 2.85 mmol) in dry DMF (20 mL). ^1H NMR (500 MHz, $CDCl_3$, 20 °C): $\delta = 7.00-6.79$ (m, 15H; Ar), 4.72 (d, $^2J(H,H) = 13.0$ Hz, 3H), 4.70 (d, $^2J(H,H) = 11.5$ Hz, 2H), 4.66 (m, 2H), 4.59 (d, $^3J(H,H) = 6.0$ Hz, 2H; CH_2OH), 4.42 (d, $^2J(H,H) = 11.5$ Hz, 2H), 3.91 (m, 2H), 3.84 (s, 6H; OCH_3), 3.725 (s, 3H; OCH_3), 3.72 (s, 3H; OCH_3), 3.67 (s, 3H; OCH_3), 3.525 (m, 2H), 3.52 (d, $^2J(H,H) = 13.0$ Hz, 3H), 1.90–1.50 (m, 13H; THP + O*H*); ^{13}C NMR (125.67 MHz, $CDCl_3$): $\delta = 149.36$, 149.24 (2C), 148.27, 148.22, 148.16, 147.31 (2C), 147.07, 146.55 (2C), 146.53, 134.56, 132.75, 132.74, 132.71, 131.64 (2C), 131.58, 131.32 (2C), 120.31 (2C), 118.98, 116.43, 116.29, 116.24, 113.51 (4C), 113.33 (2C), 111.68 (2C), 110.62, 97.36 (2C), 68.48 (2C), 68.0–66.0 (m, 6C; OCD_2CD_2O), 64.65, 62.03 (2C), 55.93 (s, 1C; OCH_3), 55.90 (s, 1C; OCH_3), 55.87 (s, 1C; OCH_3), 55.62 (s, 2C; OCH_3), 54.48 (1C, h, ^1J(C,D) = 22.0 Hz; OCD_3), 36.09 (3C), 30.35 (2C), 25.21 (2C), 19.23 (2C); MS (LSIMS, NBA): *m*/*z* (%): 1131.7 (65.6) $[M]^+$, 910.4 (100).

{3-Methoxy-4-[2-(3,8,13-trimethoxy-7,12-bis{2-[2-methoxy-4-(tetrahydropyran-2-yloxymethyl)phenoxy]-[D_4]ethoxy}-10,15-dihydro-5*H*-tribenzo[a,d,g]cyclononen-2-yloxy)ethoxy]phenyl}methanol (33): According to general procedure B, derivative **33** (0.30 g, 78%) was prepared from derivative **31** (0.2 g, 0.34 mmol), compound **22** (0.30 g, 0.75 mmol), and cesium carbonate (0.44 g, 1.34 mmol) in DMF (15 mL). ^1H NMR (500 MHz, $CDCl_3$, 20 °C): $\delta = 6.99-6.78$ (m, 15H; Ar), 4.72 (d, $^2J(H,H) = 13.5$ Hz, 3H), 4.70 (d, $^2J(H,H) = 11.5$ Hz, 2H), 4.65 (m, 2H), 4.58 (d, $^3J(H,H) = 6.0$ Hz, 2H; CH_2OH), 4.41 (d, $^2J(H,H) = 11.5$ Hz, 2H), 4.32 (m, 4H; OCH_2CH_2O), 3.89 (m, 2H), 3.83 (s, 6H; OCH_3), 3.74 (s, 3H; OCH_3), 3.71 (s, 3H; OCH_3), 3.705 (s, 3H; OCH_3), 3.66 (s, 3H; OCH_3), 3.515 (m, 2H), 3.51 (d, $^2J(H,H) = 13.5$ Hz, 3H), 1.90–1.50 (m, 13H; THP + O*H*); ^{13}C NMR (125.67 MHz, $CDCl_3$): $\delta = 149.59$, 149.38 (2C), 148.47, 148.39, 148.32, 147.45 (2C), 147.34, 146.74, 146.72, 146.71, 134.54, 132.94, 132.88, 132.83, 131.78 (2C), 131.72, 131.49 (2C), 120.47 (2C), 119.25, 116.68, 116.43, 116.39, 113.74, 113.68 (2C), 113.45 (3C), 111.81 (2C), 110.84, 97.52 (2C), 68.65 (2C), 68.08, 68.0–66.0 (m, 4C; OCD_2CD_2O), 67.69, 65.02, 62.21 (2C), 56.11 (OCH_3), 56.08 (OCH_3), 56.04 (OCH_3), 55.79 (2C, OCH_3), 55.66 (OCH_3), 36.31 (3C), 30.51 (2C), 25.36 (2C), 19.39 (2C); MS (LSIMS, NBA): *m*/*z* (%): 1124.5 (72.7) $[M]^+$, 903.3 (100). HRMS (LSIMS): exact mass calcd for $C_{64}H_{68}O_{17}D_8$ 1124.5585 $[M]^+$, found 1124.5637.

(±)-Cryptophane-A (1): **General procedure C**: In a 1 L rotary evaporator flask, **26** (550 mg) was dissolved in chloroform (6 mL). Then 600 mL of formic acid was added in one portion and the solution was heated at 55–60 °C for three hours with slow rotation. Then the solvent was stripped off under reduced pressure and chloroform was added to remove residual formic acid by azeotropic distillation. The cryptophane was purified by column chromatography on silica gel (CH_2Cl_2/acetone: 90/10) and then washed with a few mL of diethyl ether on a frit. A second run of column chromatography (CH_2Cl_2/acetone: 90/10) yielded pure **1** (0.27 g, 60%). M.p. decomp above 300 °C.[11]

(±)-Cryptophane 2: According to general procedure C cryptophane **2** (0.30 g, 74%) was obtained from starting material **33** (0.51 g, 0.45 mmol) in 550 mL of formic acid. M.p. decomp above 300 °C; ^1H NMR (500 MHz, $CDCl_3$, 20 °C): $\delta = 6.74$ (s, 6H; Ar), 6.65 (s, 6H; Ar), 4.58 (d, $^2J(H,H) = 13.5$ Hz, 6H; CHa), 4.15 (m, 4H; OCH_2CH_2O), 3.78 (s, 18H; OCH_3), 3.39 (d, $^2J(H,H) = 13.5$ Hz, 6H; CHe); ^{13}C NMR (125.67 MHz, $CDCl_3$): $\delta =$ 149.50 (6C), 146.47 (6C), 134.02 (6C), 131.46 (6C), 120.68 (6C), 113.55 (6C), 69.21 (2C, OCH_2CH_2O), 69.0–68.0 (m, 4C; OCD_2CD_2O), 55.56 (s, 6C; OCD_3), 36.10 (s, 6C; CH_2); elemental analysis calcd (%) for $C_{54}H_{46}O_{12}D_8 \cdot 1.9CHCl_3$ (1129.9): C 59.42, H 4.27; found: C 59.25, H 4.24.

(±)-Cryptophane 3: According to general procedure C, cryptophane **3** (0.3 g, 73%) was obtained from starting material **27** (0.55 g, 0.47 mmol) in

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formic acid (550 mL). M.p. decomp above 300 °C; ^{1}H NMR (500 MHz, $CDCl_3$, 20 °C): $\delta = 6.74$ (s, 6H; Ar), 6.66 (s, 6H; Ar), 4.58 (d, ^2J(H,H) = 14.0 Hz, 6H; CHa), 3.78 (s, 18H; OCH_3), 3.39 (d, ^2J(H,H) = 14.0 Hz, 6H; CHe); ^{13}C NMR (125.67 MHz, $CDCl_3$): $\delta = 149.48$ (6C), 146.43 (6C), 133.99 (6C), 131.43 (6C), 120.65 (6C), 113.51 (6C), 68.37 (m, 6C; OCD_2CD_2O), 55.53 (6C), 36.06 (6C); elemental analysis calcd (%) for $C_{54}H_{42}O_{12}D_{12} \cdot 2.0\,CHCl_3$ (1145.8): C 58.70, H 3.87; found C 58.79, H 3.61.

(±)-Cryptophane 4: According to general procedure C, cryptophane **4** (0.35 g, 70%) was obtained from starting material **34** (0.625 g, 0.55 mmol) in formic acid (650 mL). M.p. decomp above 300 °C; ^{1}H NMR (500 MHz, $CDCl_3$, 20 °C): $\delta = 6.74$ (6H, s, Ar), 6.66 (2s, 5H + 1H; Ar), 4.58 (d, ^2J(H,H) = 13.5 Hz, 6H; CHa), 3.78 (s, 15H; OCH_3), 3.39 (d, ^2J(H,H) = 13.5 Hz, 6H; CHe); ^{13}C NMR (125.67 MHz, $CDCl_3$): $\delta = 149.56$ (6C), 146.52 (6C), 134.06 (6C), 131.52 (5C), 131.48 (1C), 120.73 (6C), 113.61 (5C), 113.57 (1C), 69.0–68.0 (p, ^1J(C,D) = 21.0 Hz, 6 C; OCD_2CD_2O), 55.61 (5C, OCH_3), 54.61 (h, ^1J (C,D) = 22.0 Hz, 1C; OCD_3), 36.16 (6C); elemental analysis calcd (%) for $C_{54}H_{39}O_{12}D_{15} \cdot 1.9\,CHCl_3$ (1136.9): C 59.06, H 3.63; found C 59.10, H 3.64.

(±)-Cryptophane 5: According to general procedure C, cryptophane **5** (0.375 g, 63%) was prepared from starting material **28** (0.8 g, 0.65 mmol) in formic acid (500 mL). M.p. decomp above 300 °C; ^{1}H NMR (500 MHz, $CDCl_3$, 20 °C): $\delta = 6.74$ (s, 6H; Ar), 6.65 (s, 3H; Ar), 6.648 (s, 3H; Ar), 4.58 (d, ^2J(H,H) = 13.5 Hz, 6H; CHa), 3.78 (s, 9H; OCH_3), 3.39 (d, ^2J(H,H) = 13.5 Hz, 6H; CHe); ^{13}C NMR (125.67 MHz, $CDCl_3$): $\delta = 149.51$ (6C), 146.47 (6C), 134.02 (6C), 131.48 (3C), 131.44 (3C), 120.68 (6C), 113.56 (3C), 113.53 (3C), 68.40 (m, 6C; OCD_2CD_2O), 55.57 (3C, OCH_3), 54.75 (h, ^1J(C,D) = 22.5 Hz, 3C, OCD_3), 36.11 (6C); elemental analysis calcd (%) for $C_{54}H_{33}O_{12}D_{21} \cdot 1.7\,CHCl_3$ (1119.1): C 59.78, H 3.13; found C 59.99, H 3.10.

(±)-Cryptophane 6: According to general procedure C, cryptophane **6** (0.30 g, 72%) was prepared from starting material **29** (0.556 g, 0.45 mmol) in formic acid (550 mL). M.p. decomp above 300 °C; ^{1}H NMR (500 MHz, $CDCl_3$, 20 °C): $\delta = 6.74$ (s, 6H; Ar), 6.65 (s, 6H; Ar), 4.58 (d, ^2J(H,H) = 14.0 Hz, 6H, CHa), 3.39 (d, ^2J(H,H) = 14.0 Hz, 6H; CHe); ^{13}C NMR (125.67 MHz, $CDCl_3$): $\delta = 149.51$ (6C), 146.46 (6C), 134.03 (6C), 131.45 (6C), 120.68 (6C), 113.53 (6C), 68.42 (m, 6C; OCD_2CD_2O), 54.57 (h, ^1J(C,D) = 22.0 Hz, 6C, OCH_3), 36.11 (6C); HRMS (LSIMS): exact mass calcd for $C_{54}H_{24}O_{12}D_{30}$ 924.5498 $[M]^+$, found 924.5491.

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