

Secondary Isotope Effects on the Deslipping Reaction of Rotaxanes: High-Precision Measurement of Steric Size

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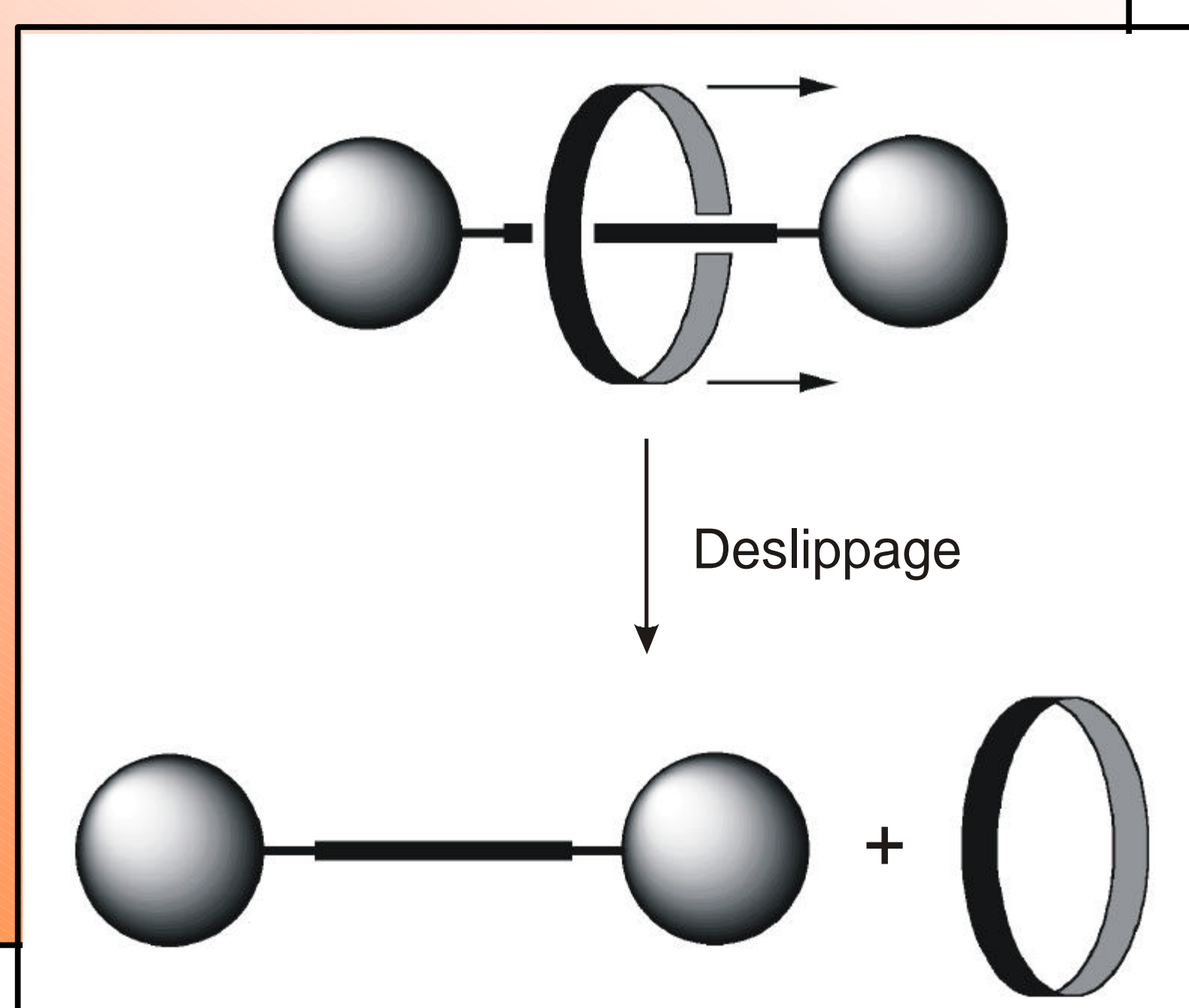
I. Introduction:

The measurement of steric size has been a controversial topic in organic chemistry which prompted a large number of different studies. Van-der-Waals radii can be used to define steric size as well as structure/reactivity correlations of suitable systems such as substituted cyclohexanes (A values).

The deslipping reaction of rotaxanes, in which the wheel slips over the stopper at elevated temperatures, should also provide insight into the steric demand of the stopper.

As shown earlier, small structural changes can cause huge effects on the deslipping kinetics of a rotaxane.

One of the smallest steric changes which can be made in a molecule is the replacement of hydrogen atoms by deuterium. Thus, rotaxanes with labeled stoppers may serve to evaluate the sensitivity of the deslipping reaction for steric changes.

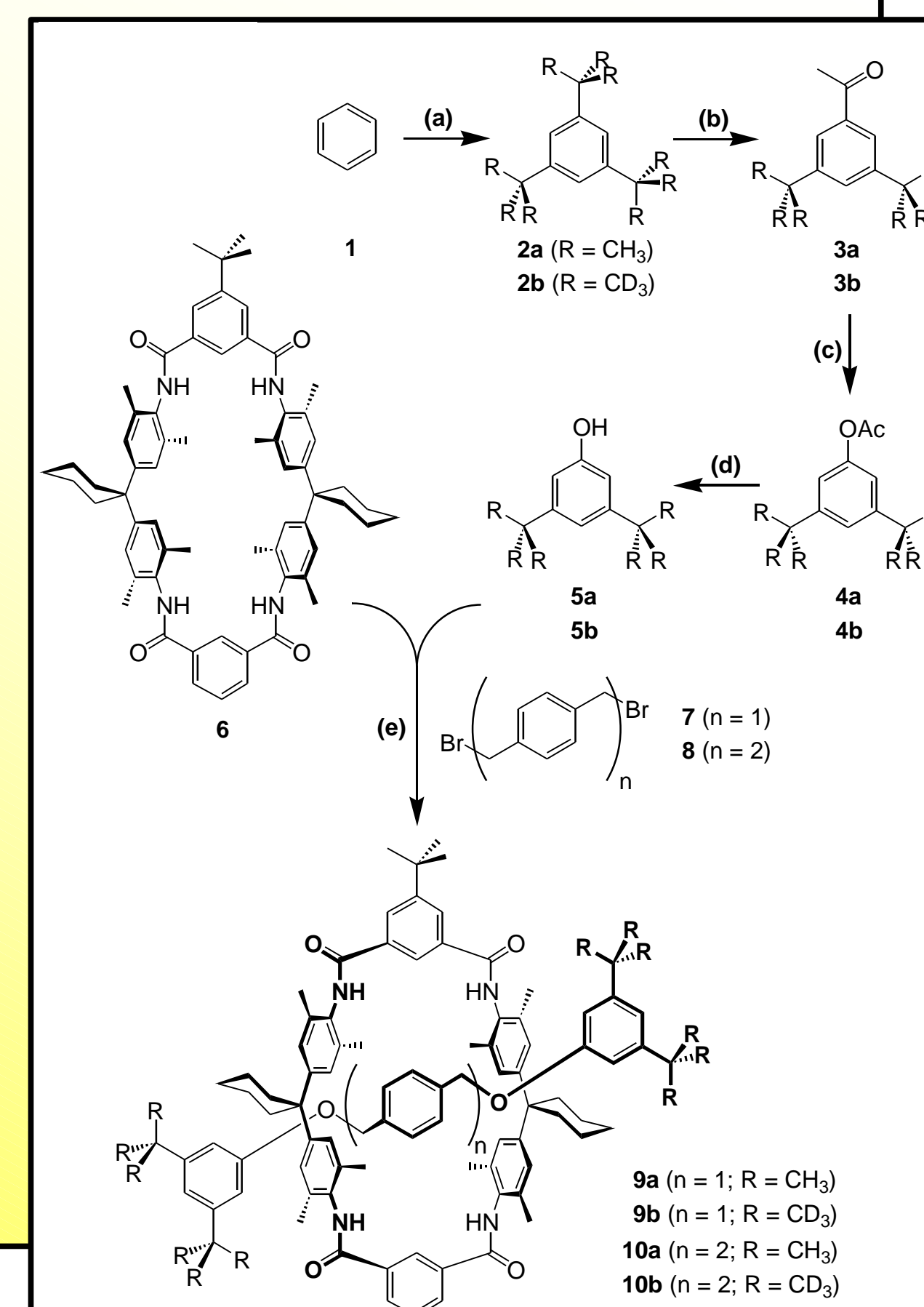


II. Labeled Rotaxanes: Synthesis

According to electron diffraction studies and calculations, in time average the C-D bond is shorter than the C-H bond by ca. 0.005 Å. Furthermore, the vibrational amplitude and the vibrational frequency of the C-D bond is lower in comparison with the C-H bond. This is reflected in a smaller Van-der-Waals radius.

The deuterated di-[D₉]-*t*-butyl phenol stopper was synthesized according to known procedures (Scheme 1). Threefold Friedel-Crafts alkylation of benzene **1** is followed by a Friedel-Crafts acylation and the replacement one of the *t*-butyl groups in **2b** by an acetyl substituent. The attachment of an acetyl substituent deactivates the aromatic system and prevents it from further reaction. Baeyer-Villiger oxidation of **3b** with *m*-chloroperbenzoic acid leads to the intermediate **4b**. The hydrolysis of ester **4b** yields stopper **5b**.

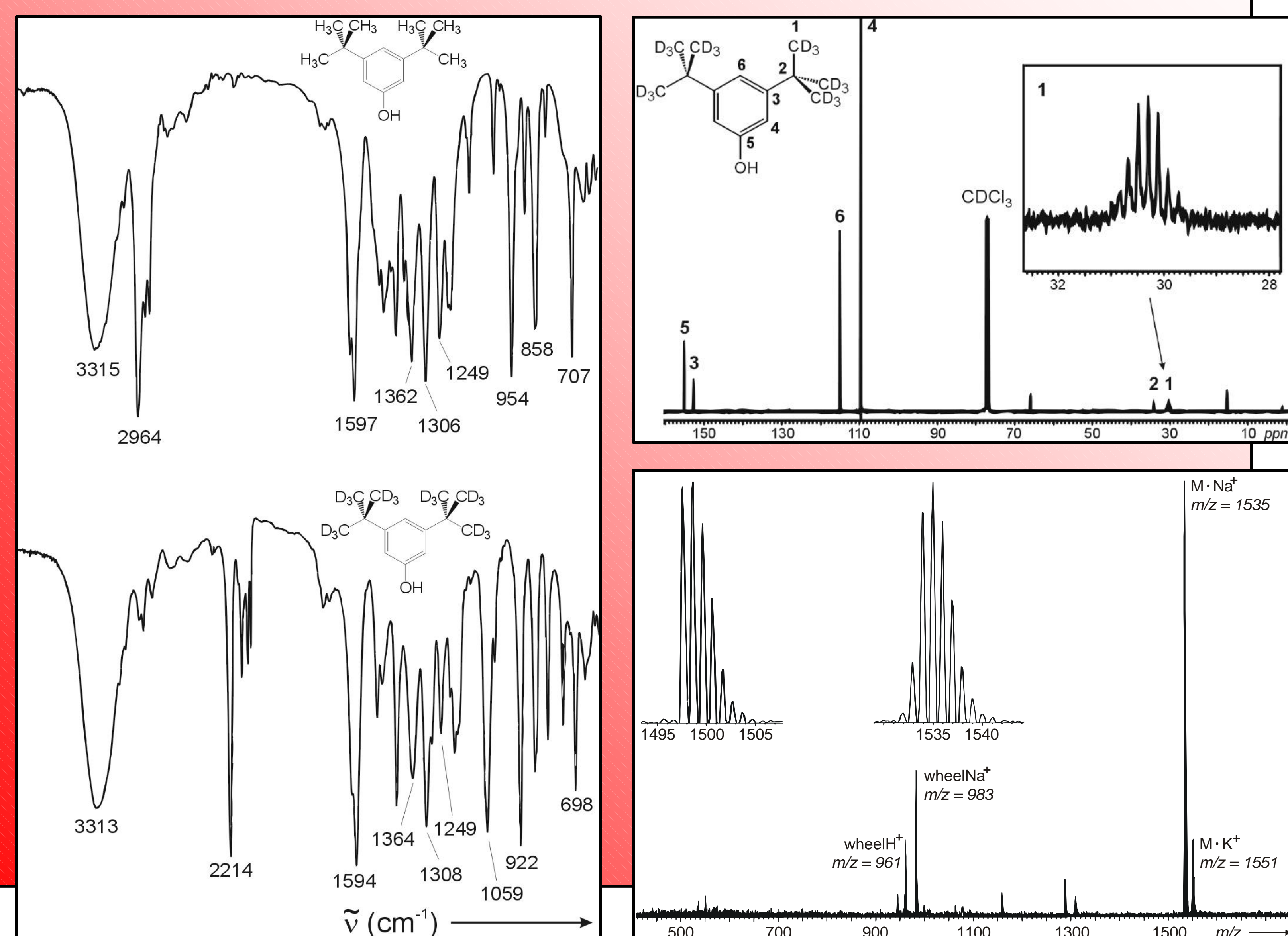
The rotaxanes **9a,b** and **10a,b** can be prepared from the corresponding stoppers **5a,b**, one of the axle center pieces **7** or **8** and the wheel component **6** by an anion template effect with 25-30% yield.



III. Characterization

Deuteration of stopper **5b** can be detected by ¹³C NMR (septet for the CD₃ groups at 30.2 ppm) as well as IR spectroscopy (C-D vibrations around 2200 cm⁻¹).

From the ¹H-NMR spectra of **9b** as well as from the isotope patterns (**9a** left and **9b** right) of the MALDI mass spectra, the degree of isotope labeling could be derived to be larger than 95%.



IV. Kinetic Measurements

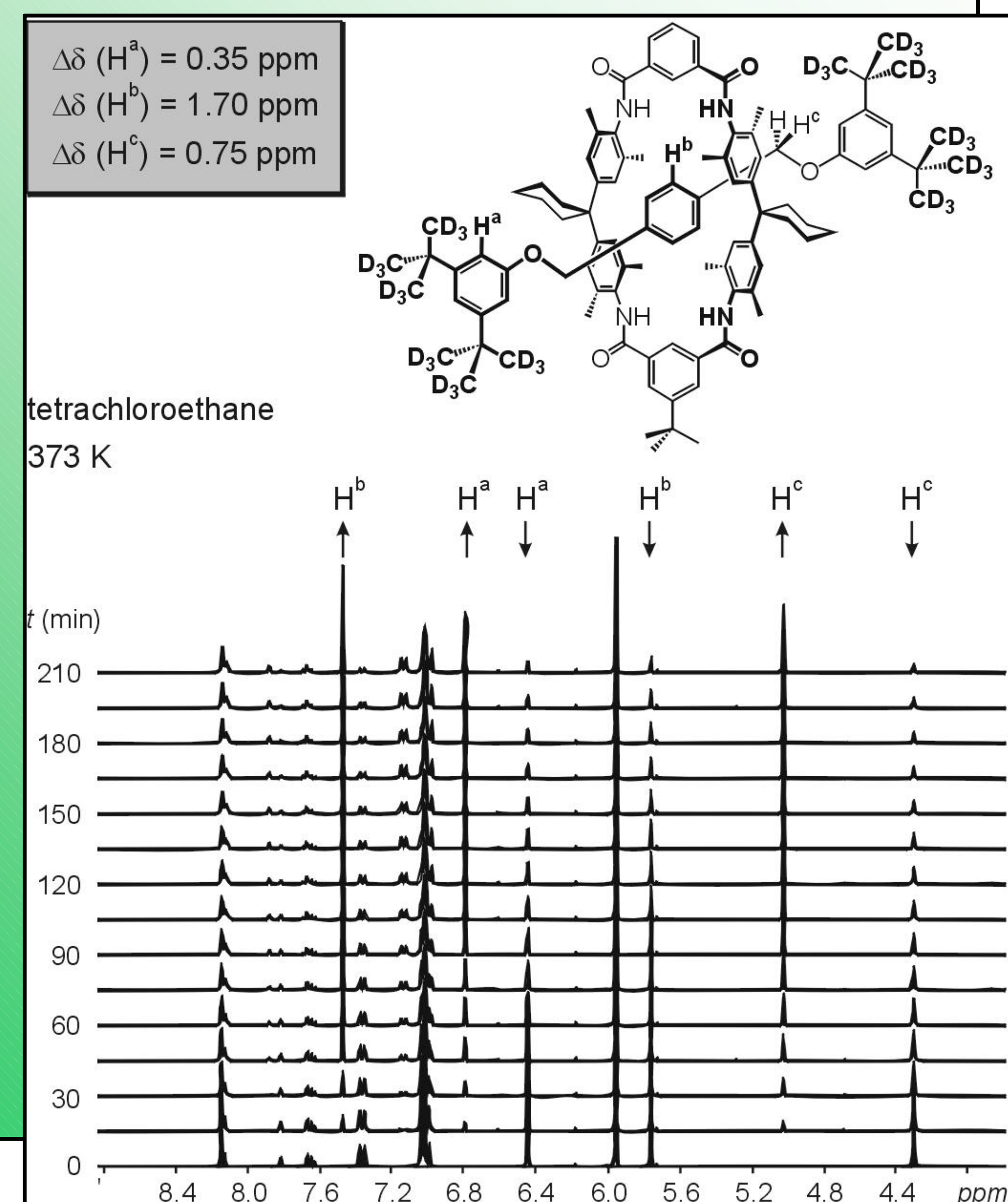
The deslipping reaction is a unimolecular process and follows a first rate law. It can easily be monitored by ¹H-NMR spectroscopy (Figure 1).

Over time, the rotaxane signals decrease and new signals of the liberated components i.e. the free axle and free wheel appear.

As a result of the anisotropy effect of the aromatic rings incorporated in the wheel, the largest value for Δδ is observed for the protons (H^b: Δδ = 1.70 ppm) of the axle center piece.

Smaller upfield shifts are found for protons more remote from the center (H^c: Δδ = 0.75 ppm; H^a: Δδ = 0.35 ppm).

The rate constants *k* of the deslipping processes can be determined from a plot of ln(*c*/*c*₀) versus reaction time *t*. The concentrations *c* and *c*₀ are derived from the integrations of the signal of rotaxane and free components.

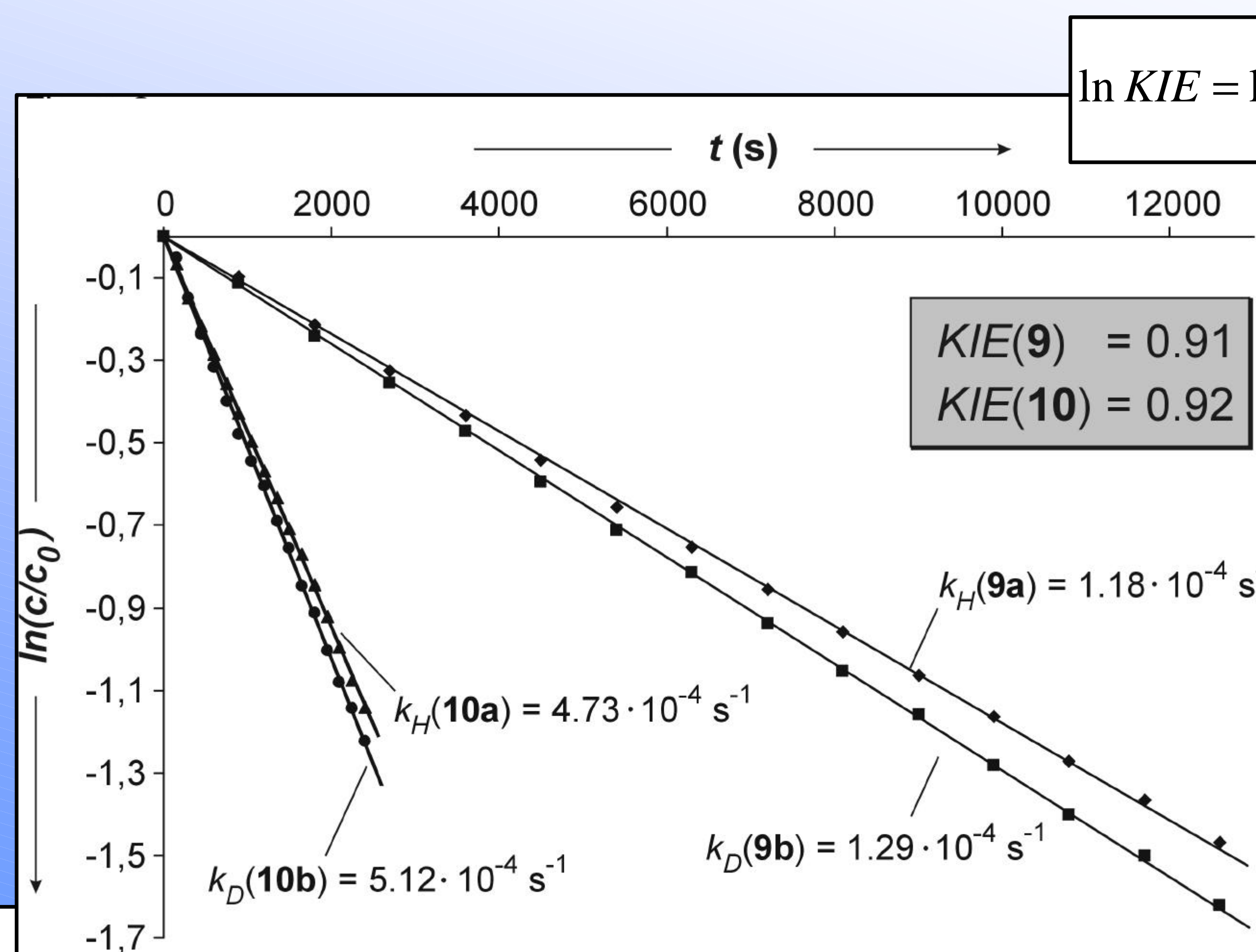


V. Results

The deuterated rotaxanes **9b** and **10b** liberate the free components at a rate 10% higher than the non-labeled analogues **9a** and **10a**. The fact that rotaxanes **10a,b** with the longer axle center piece deslip more quickly compared to their shorter counterpart has been analyzed in detail before.

Inverse, secondary kinetic isotope effects (*KIE* = *k_H*/*k_D*) of *KIE* = 0.9 were determined for **9a** versus **9b** and **10a** versus **10b**. This can be traced back to the smaller steric demand of the deuterated stopper groups.

The isotope effects were measured at four different temperatures between 313 K and 383 K and did not significantly change with temperature. This means, in a semiquantitative manner of speaking, that ΔΔ*H*[‡] should be equal or close to zero (see equation).



$$\ln KIE = \ln \frac{k_H}{k_D} = -\frac{\Delta\Delta G^\ddagger}{RT} = -\frac{\Delta\Delta H^\ddagger}{RT} + \frac{\Delta\Delta S^\ddagger}{R}$$

The isotope effects are thus mostly entropic in nature with ΔΔ*S*[‡] values of ca. -0.8 J K⁻¹ mol⁻¹ for **9a,b** and ca. -0.6 J K⁻¹ mol⁻¹ for **10a,b**.

The entropic nature can be understood when considering the vibrational freedom in the transition structures of the deslipping reaction. Because of the larger vibrational amplitude of the C-H bond, the vibration of the non-labeled stopper is more restricted in the transition structure compared to the deuterated stopper groups. The larger vibrational freedom is expressed in a slightly higher and thus more beneficial activation entropy for the deslipping reaction of the deuterated rotaxanes.

This work provides a novel supramolecular and highly precise approach to the classical problem of determining and comparing steric demand. The fact that the two reaction partners are just mechanically interlocked molecules before the reaction excludes all isotope effects due to hyperconjugative or inductive effects.

Acknowledgment

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