Molecular Switches

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Coupling of the Decarboxylation of 2-Cyano-2-phenylpropanoic Acid to Large-Amplitude Motions: A Convenient Fuel for an Acid–Base-Operated Molecular Switch

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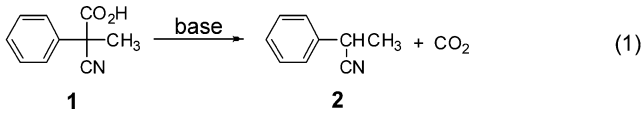
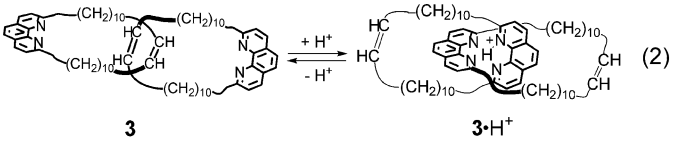
Abstract: *The decarboxylation of 2-cyano-2-phenylpropanoic acid is fast and quantitative when carried out in the presence of 1 molar equivalent of a [2]catenane composed of two identical macrocycles incorporating a 1,10-phenanthroline unit in their backbone. When decarboxylation is over, all of the catenane molecules have experienced large-amplitude motions from neutral to protonated catenane, and back again to the neutral form, so that they are ready to perform another cycle. This study provides the first example of the cyclic operation of a molecular switch at the sole expenses of the energy supplied by the substrate undergoing chemical transformation, without recourse to additional stimuli.*

The wide interest in molecular machines is evident from the large number of books[1] and review articles[2] that have been published in recent years. An important role has been played by catenanes and rotaxanes, in which the relative position of the components is controlled by the presence of switchable functions. Numerous examples of catalytic systems, in which the catalytic activity is triggered and controlled by the motion of one of the substructures with respect to the other, have been reported.[3] In all these cases, external stimuli, either chemical or physical, are required to switch the catalyst from the active to the inactive form, and vice versa.

Herein we report the decarboxylation of 2-cyano-2-phenylpropanoic acid [**1**, Eq. (1)] promoted by the acid–base-switchable [2]catenane **3**[4] [Eq. (2)], the structure of which consists of two identical interlocked 28-membered macrocyclic alkenes (*cis* and *trans*) featuring 1,10-phenanthroline units in their backbone. The unprecedented feature of this reaction is that the catenane is switched "off" and "on" solely through the protonation–deprotonation steps promoted by the substrate undergoing decarboxylation, without recourse to additional stimuli.



1 **2** (1)



3 **3**·H$^+$ (2)

The addition of 1 molar equivalent of trifluoroacetic acid (TFA) to a solution of **3** in CD_2Cl_2 causes significant changes in the ^{1}H NMR spectrum (Figure 1, compare trace a with trace b). These changes are very similar to those caused by complexation with Cu^+ (Figure 1, trace c);[4a] notably, the signals of the methylene protons are shifted upfield, apart from those which are close to the double bond (see Figure S7 in the Supporting Information), as a result of exposure to the shielding effect of the phenanthroline unit of the other macrocycle. A deeper investigation based on COSY and ROESY 2D NMR spectroscopy (see Figures S1–S4) fully confirmed the close structural analogy between **3**·Cu^+ and

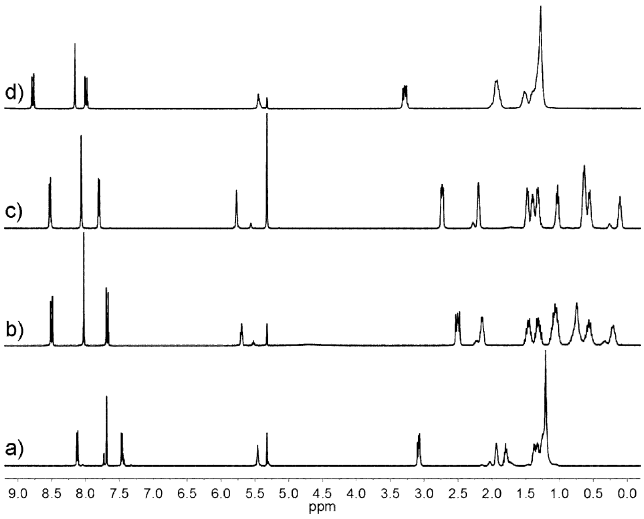


Figure 1. ^{1}H NMR spectra (CD_2Cl_2, 25 °C) of a) **3**, b) **3**·H$^+$ (trifluoroacetate salt), c) **3**·Cu^+ (hexafluorophosphate salt), and d) **3**·$(H^+)_2$ (trifluoroacetate salt). The spectra show signals of phenanthroline protons (8.8–7.3 ppm), double-bond protons (5.7–5.5 ppm), and methylene protons at higher field. The signal at 5.3 ppm is due to $CHDCl_2$. See Figure S7 for the full assignment of ^{1}H NMR signals.

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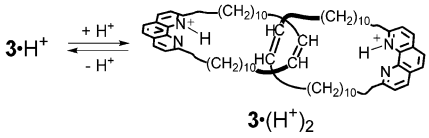
3·H$^+$, thus strongly supporting the proton catenate structure expected for **3**·H$^+$ on the basis of the behavior of similar catenanes.[5] The presence of only one set of signals in the aromatic region indicates that **3**·H$^+$ is a symmetrical species in which scrambling of the proton among the four nitrogen atoms is fast on the ^{1}H NMR time scale.[5a] Treatment with an excess of an aliphatic amine (Et_3N, $pK_a = 10.75$; Bu_2NH, $pK_a = 11.25$) failed to restore **3**·H$^+$ to the neutral form **3**, in keeping with the notion advanced by Sauvage and co-workers of the topological enhancement of basicity[5a] in phenanthroline-based catenanes. Indeed ^{1}H NMR and UV/Vis spectroscopic titrations of **3** with $Bu_2NH_2PF_6$ (see Figure S9) showed that **3** is no less than 5 orders of magnitude more basic than Bu_2NH. Consistent with the exceptionally high stability of **3**·H$^+$ is the finding that a large excess of TFA (20 equiv) was required to transform **3**·H$^+$ into the dication **3**·(H$^+$)$_2$ [Eq. (3)].



(3)

Comparison of the spectrum of **3**·(H$^+$)$_2$ (Figure 1 d), in which the protonated phenanthroline units are presumably held apart by electrostatic repulsion, with that of **3**, strongly suggests that these catenanes have similar structures. Apart from the phenanthroline protons, which are shifted to lower fields in **3**·(H$^+$)$_2$, prominent features common to both spectra are the lack of signals in the high-field region above 1.2 ppm and the upfield shifts of the double-bond protons (see Figure S8 for details) as compared to the proton catenate **3**·H$^+$. Again, comparison of the COSY and ROESY 2D NMR spectra of **3**·(H$^+$)$_2$ (see Figures S5 and S6) with those of **3** strongly indicates very similar structures.

The choice of the substrate for the present investigation was suggested by the report[6] that acid **1** undergoes smooth decarboxylation in the presence of tertiary bases under mild conditions. In a control experiment, we found that the decarboxylation of **1** (CD_2Cl_2, 10 mM, 25 °C) in the presence of Et_3N (1 equiv) was indeed quantitative and complete in about 5 h ($t_{1/2} = 43$ min; see Figure S11). Monitoring of the reaction progress by ^{1}H NMR spectroscopy afforded a number of spectra (see Figure S12) indicating quantitative proton transfer from **1** to Et_3N (step I in Scheme 1), followed by rate-determining decomposition of the carboxylate anion, presumably in the form of a hydrogen-bonded ion pair **4**$^-$ BH$^+$ (step II). Fast proton transfer to the carbanion intermediate (step III) leads to the final product **2** and restores the base to its neutral form. When 1,8-bis(dimethylamino)naphthalene (proton sponge, $pK_a = 12.1$) was used instead of Et_3N, quantitative conversion into **2** was observed in about 10 min. The much lower effectiveness of Et_3N as a promoter is not surprising, as Et_3NH^+ is expected to stabilize carboxylate **4**$^-$ by hydrogen bonding much more strongly than the protonated proton sponge, in which the proton is covalently bound to one nitrogen atom and hydrogen bonded to the other.[7] An experiment in which acid **1** was treated with half a molar equivalent of Et_3N is fully consistent with the idea that strong H-bonding donors exert a retarding effect on the rate of CO_2 liberation from carboxylate anion **4**$^-$ (see the Supporting Information for details).

When the decarboxylation of **1** (5 mM) was carried out in the presence of 1 molar equivalent of **3**, quantitative conversion into **2** was observed in about 50 min.[8] The ^{1}H NMR spectra recorded during the course of the reaction (Figure 2, Scheme 2) revealed a number of unexpected features, notably, the presence of three signals in the range of 4.8–3.8 ppm, whose intensities corresponded to five protons in a 1:3:1 ratio.[9] No traces of these peaks were detected when the decarboxylation of **1** was carried out in the presence of Et_3N (see Figure S12) or proton sponge. They must belong to a reaction intermediate, as their disappearance was paralleled by an increase in intensity of the signal of the benzylic proton of **2** at 3.95 ppm, as well by the gradual transformation of **3**·H$^+$

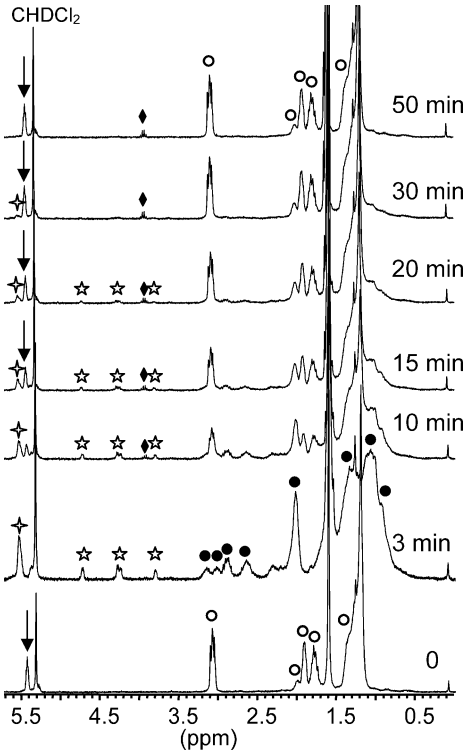
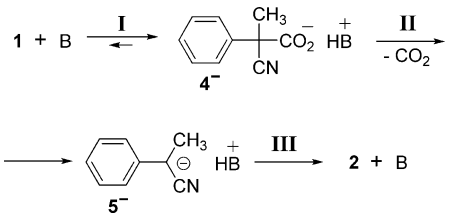
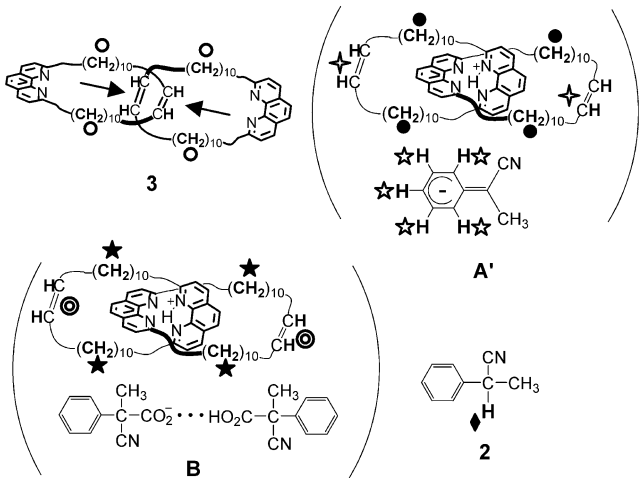


Figure 2. ^{1}H NMR monitoring of the reaction between **3** (5 mM) and **1** (5 mM) in CD_2Cl_2 at 25 °C. Marked signals are assigned to the protons with the corresponding symbol in Scheme 2. The trace at $t = 0$ is the spectrum of **3**. See Figure S13 for full spectra.



Scheme 1. Three-step base-promoted decarboxylation of acid **1**.



Scheme 2. Compounds and ion pairs involved in reactions of **1** with **3**. Key hydrogen atoms for the identification of these species in the ^{1}H NMR spectra in Figures 2 and 3 are marked with the symbols used to label the corresponding peaks.

into **3**,[10] as clearly shown by the disappearance of the peak at 5.53 ppm of the double-bond protons of the major geometrical isomer and the concomitant appearance of the corresponding peak at 5.46 ppm of the neutral catenane **3**, among other indications. The only feasible conclusion is that the reaction intermediate responsible for the three signals in the range from 4.8 to 3.8 ppm is carbanion $\mathbf{5}^-$. This conclusion is corroborated by a previous report[11] on the non-equivalence of the five aromatic protons of α-methylbenzyl carbanion (K^+ salt), as characterized by five distinct chemical shifts in the range from 6.2 to 4.6 ppm in [D_8]THF.[12]

The peculiar features displayed by the decarboxylation of **1** as promoted by **3** arise from the structure of $\mathbf{3}\cdot H^+$, in which the proton is embedded in the tetrahedral arrangement of the four N atoms. This structural arrangement has important consequences: The lack of any stabilizing effect of the carboxylate anion by H-bonding explains why step **II** (Scheme 1) is faster than when the countercation is the protonated proton sponge, and is complete within the short time required to record the first spectrum. Furthermore, the proton of $\mathbf{3}\cdot H^+$ is sterically hindered to such an extent that proton transfer to $\mathbf{5}^-$ becomes rate-determining. Accordingly, in the early stages of the reaction, the system should be almost exclusively composed of a 1:1 mixture of $\mathbf{5}^-$ and $\mathbf{3}\cdot H^+$. However, the ^{1}H NMR spectrum recorded 3 min after the start of the reaction (Figure 2) bears little resemblance to the spectra of the $CF_3CO_2^-$ (Figure 1b) and PF_6^- salts (see Figure S10) of $\mathbf{3}\cdot H^+$, notably in the high-field region, in which the highly structured signal pattern of the methylene protons is replaced with a broad signal at 1.2–0.7 ppm. As a possible explanation, we suggest that the driving force for the association of $\mathbf{5}^-$ with $\mathbf{3}\cdot H^+$ is not a simple cation–anion attraction as that involved in the ion pairs of $\mathbf{3}\cdot H^+$ with $CF_3CO_2^-$ and PF_6^- anions. It seems likely that the pair $\mathbf{5}^-\cdot(\mathbf{3}\cdot H^+)$, **A′** in Scheme 2, is better described as an electron-donor–acceptor (EDA) complex[13] between the presumably strong π-donor $\mathbf{5}^-$ and the protonated phenanthroline core of $\mathbf{3}\cdot H^+$, which acts as a strong π-acceptor.[14] In other words, $\mathbf{5}^-$ acts as a very effective shift reagent towards $\mathbf{3}\cdot H^+$, thus dramatically affecting its ^{1}H NMR spectrum.

Deeper insight into the reaction mechanism came from decarboxylation experiments carried out in the presence of substoichiometric amounts of catenane **3**. Excess acid is expected, on the one hand, to retard the loss of CO_2 from the carboxylate anion, as was found to be the case in the reaction carried out in the presence of Et_3N (see the Supporting Information). On the other hand, however, excess acid should accelerate the rate of protonation of the carbanion intermediate. ^{1}H NMR spectra for an experiment in which the molar ratio between acid **1** and catenane **3** was 2:1 are shown in Figure 3. Inspection of the spectrum recorded after 3 min, particularly in the double-bond region around 5.5 ppm, shows that the reaction mixture is composed of two distinct $\mathbf{3}\cdot H^+$ species, namely, the complex **A′** and a new species, whose spectrum displays features very similar to those of $CF_3CO_2^-\cdot(\mathbf{3}\cdot H^+)$ (Figure 1b), notably, the signal at 5.70 ppm and the set of signals in the high-field region. No trace of the latter species appears in the spectrum at 8 min. At this time, the reaction has reached 50% conversion, excess acid is no longer

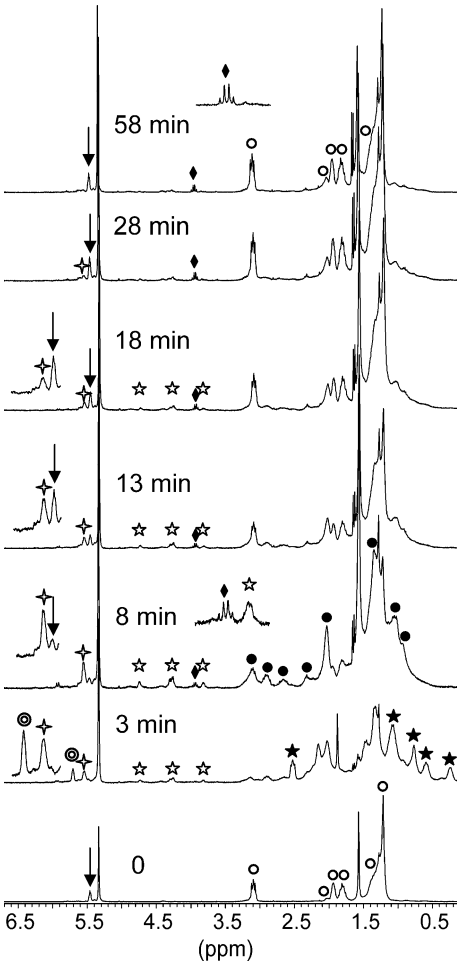
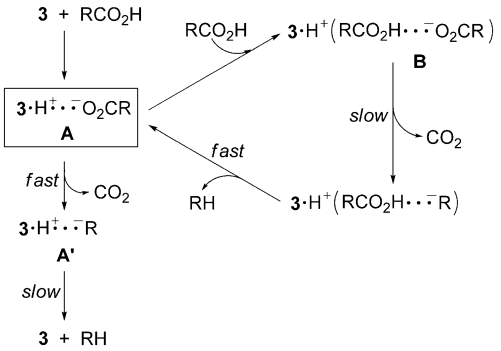


Figure 3. ^{1}H NMR monitoring of reaction between **1** (4 mM) and **3** (2 mM) in CD_2Cl_2 at 25 °C. Marked signals are assigned to the protons with the corresponding symbol in Scheme 2. The trace at $t = 0$ is the spectrum of **3**. See Figure S15 for full spectra.

present, and free catenane **3** begins to reappear, as shown by the tiny peak at 5.56 ppm. From then onwards, the second half of the reaction proceeds exactly as in the case in which the 1:1 molar ratio was set from the start (Figure 2). Excess acid in the first half of the reaction is clearly responsible for the appearance of the transient species. The observed phenomena are accounted for by the reaction pathways in Scheme 3:



Scheme 3. Reaction pathways for the reaction of **1** with **3**. The reaction sequence in Scheme 1 is shown on the left-hand side from top to bottom. An alternative pathway involving the rate-limiting liberation of CO_2 from the ternary adduct **B** is made available by excess acid.

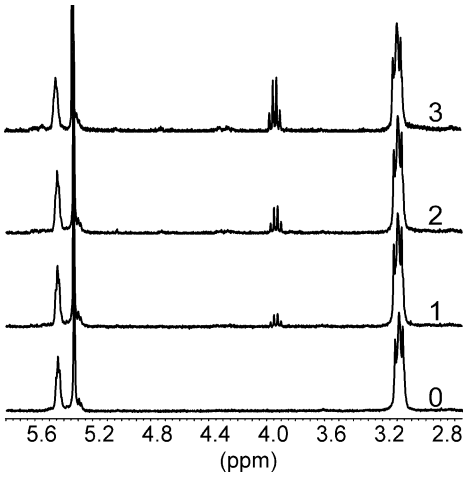


Figure 4. ^{1}H NMR spectra (CD_2Cl_2, 25 °C; peaks in the range 2.8–5.8 ppm) showing the results of three cycles of the reaction of **1** with **3**. Trace 0 is the spectrum of 5 mM catenane in the neutral form **3** and shows the signals of the double-bond protons and the triplet of the CH_2 groups bound to the phenanthroline moieties. Each cycle was started by the addition of 1 molar equivalent of acid **1**, and the corresponding spectrum was recorded after a reaction time of 50 min. The quartet centered at 3.95 ppm is due to the benzylic proton of **2**.

Excess acid transforms adduct **A** into the ternary complex **B**, thus causing a diversion of the reaction mechanism from a sequence in which the rate-determining step is the intramolecular proton transfer within **A′**, to one in which the rate-determining step is the liberation of CO_2 from the ternary complex **B**, which is the transient species detected in the ^{1}H NMR spectrum recorded after 3 min (Figure 3).

Consistent results were obtained from a reaction with a 10-fold molar excess of acid (see Figure S16 for ^{1}H NMR spectra). In this case, the ^{1}H NMR signals of **B** were clearly visible during a much longer period of time. After 102 min, the concentration of **B** was still larger than that of **A′**, and it was still significant after 110 min, thus showing that only in the very late stages of reaction **A′** is the predominant intermediate. The ^{1}H NMR spectra clearly indicate that the fractional contribution of the pathway proceeding via **B** was much larger in this case than in the reaction in which a twofold excess of acid was used.[15]

So far our attention has been concentrated on the peculiar features of the decarboxylation of **1** as promoted by **3**. We now focus on the large-amplitude motions experienced by **3** in going from the neutral catenand to the proton catenate state when the reaction is carried out with a 1:1 molar ratio. These motions are coupled to decarboxylation in such a way that each time a reactant molecule is transformed into the product, a catenane molecule switches from the neutral to the protonated state, and back again to the neutral state (Scheme 3, left). Thus, if another molar equivalent of acid **1** is added to the system, catenane **3** performs another cycle, and so on. The results of three full cycles are shown by the ^{1}H NMR spectra in Figure 4. It is apparent that the sole difference in the composition of the solutions obtained in the various cycles is the accumulation of the reaction product **2**. Consequently, the switchable catenane undergoes large-amplitude motions at the expense of the chemical energy supplied by the substrate undergoing decarboxylation.

In conclusion, we have shown that the mechanical motions experienced by an acid–base switchable catenane between two distinct states do not require the intervention of additional stimuli, but are intrinsically associated with the ability of the catenane itself to act as an effective base promoter of the decarboxylation of acid **1**. In general, we believe that any molecular switch[3] or motor that moves between two states under the influence of protonation/deprotonation could utilize acid **1**, or any other acid that undergoes base-promoted decarboxylation at a convenient rate, as a fuel.

Acknowledgements

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Keywords: catenanes · chemical fuels · decarboxylation · molecular devices · molecular motions

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[8] In a control experiment, a 5 mM solution of acid **1** was treated with 10 mM neocuproine (2,10-dimethyl-1,9-phenanthroline, $pK_a = 6.15$) in CD_2Cl_2 at 25 °C. After a reaction time of 50 min, the yield of product **2** did not exceed 1 %. The poor effectiveness of neocuproine can be ascribed to its low basicity and contrasts sharply with the behavior of **3**, which arises from the topological enhancement of basicity.
[9] Identical results were observed when the concentration of both reactants was raised to 10 mM (see Figure S14).
[10] Proton exchange between **3** and **3**·H^+ is slow on the ^{1}H NMR time scale.
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[12] The chemical shifts of the K^+ salt of α-methylbenzyl carbanion cannot be directly compared with those of the reaction intermediate for a number of reasons: 1) the structure of the two carbanions is not the same, 2) the ^{1}H NMR spectra were recorded in different solvents, and more importantly, 3) the carbanions are ion-paired to different counterions. In the study in Ref. [11], it was shown that the resonances of benzylic carbanions are strongly countercation-dependent. For example, the aromatic signals of $C_6H_5CH_2^-$ in [D_8]THF were shifted upfield when the high-charge-density countercation Li^+ (peaks in the range from 6.30 to 5.50 ppm) was replaced by lower-charge-density K^+ (peaks from 5.59 to 4.79 ppm). An even stronger upfield-shifting effect is expected for a much bigger countercation, such as **3**·H^+.
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[14] The non-equivalence of the two subunits of **3**·H^+ in **5**$^-$·(**3**·H^+) is particularly evident in the aromatic proton region (see Figure S13, trace at 3 min) and contrasts with the perfect equivalence revealed by the spectrum of the trifluoroacetate salt (Figure 1 b; see also Figure S7). This difference indicates that **3**·H^+ interacts with **5**$^-$ much more strongly than with $CF_3CO_2^-$, and that any rearrangement within the complex that would produce a time-averaged equivalence of the subunits is slow on ^{1}H NMR time scale.
[15] A catalyst can be defined as a substance which accelerates the rate of a chemical reaction without itself undergoing any chemical change. There is no doubt that the bases used in this study strictly comply with that definition from an operational point of view, independent of whether they are used in stoichiometric or substoichiometric amounts. From a mechanistic point of view, however, the situation is more complex, as shown by the experiment in which 10 mol % of catenane **3** was used. In this case, catenane **3** is not a catalyst in a strict sense, because it does not turn over. It rather behaves as the initiator of the secondary pathway proceeding via ternary adduct **B**, which is a chain reaction. Admittedly, catenane **3** is a very peculiar initiator, as it is recovered unchanged when the reaction has come to an end.

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