

Kinetic Control in the Chiral Recognition of Three-Bladed Propellers

Clément Bonnot,^[a] Emmanuel Aubert,^[b] Natalie Banerji,^[c] Jérôme Lacour,^[c]
Enrique Espinosa,*^[b] and Jean-Claude Chambron*^[a]

Dedicated to the memory of Dr. Christiane Dietrich-Buchecker

Abstract: The ion pair of the stereolabile C_3 -symmetric, i^+o proton complex $[1\cdot H]^+$ of diaza-macropentacycle **1** and the configurationally stable Δ -TRISPHAT ($[\Delta-3]^-$) anion exists in the form of two diastereomers, namely, $[\Delta-(1\cdot H)][\Delta-3]$ and $[\Lambda-(1\cdot H)][\Delta-3]$, the ratio of which, in terms of diastereomeric excess (*de*) decreases in the order $[D_8]THF$ (28%) > CD_2Cl_2 (22%) > $CDCl_3$ (20%) > $[D_8]toluene$ (16%) > C_6D_6 (7%) > $[D_6]acetone$ (0%) at thermodynamic equilibrium. Except in the case of $[D_6]acetone$, the latter is reached after a period of time that increases from 1 h ($[D_8]THF$) to 24 h ($CDCl_3$). Moreover, the initial value of the *de* of $[1\cdot H][\Delta-3]$ in $CDCl_3$,

before the thermodynamic equilibrium is reached, depends on the solvent in which the sample has been previously equilibrated (sample “history”). This property has been used to show that the crystals of $[1\cdot H][\Delta-3]$ formed by slow evaporation of CH_2Cl_2/CH_3OH mixtures had 100% *de*, which indicates that $[1\cdot H][\Delta-3]$ has enjoyed a crystallization-induced asymmetric transformation. Structural studies in solution (NMR spectroscopy) and in the gas phase by calculations at the semiempir-

ical PM6 level of theory suggest that the optically active anion is docked on the i^+ (*endo*) external side of the proton complex such that one of the aromatic rings of $[\Delta-3]^-$ is inserted into a groove of $[1\cdot H]^+$, a second aromatic ring being placed astride the outside i^+ pocket. Solvent polarity controls the thermodynamics of inversion of the $[1\cdot H]^+$ propeller. However, both polarity and basicity control its kinetics. Therefore, the rate-limiting steps correspond to the ion-pair separation/recombination and $[1\cdot H]^+/1$ deprotonation/protonation processes, rather than the inversion of $[1\cdot H]^+$, the latter being likely to take place in the deprotonated form (**1**).

Keywords: cryptands • helical structures • ion pairs • kinetics • solvent effects

Introduction

A racemate of a conformationally or configurationally stereolabile chiral compound can be enantiomerically enriched by supramolecular interactions with an optically active substance.^[1] This amply illustrated principle, which underlies

asymmetric transformation processes introduced by Kuhn in 1932,^[2] can be considered to be the generalization of the Pfeiffer effect, originally formulated a year before in the case of the ion pair formed between a labile chiral metal complex cation and an optically active anion.^[3] Such induction of optical activity is usually controlled thermodynamically. Kinetic control has been reported,^[4] mainly in the case of macromolecules that are able to take up chiral (usually helical) conformations,^[4b,d] and is at the root of “memory of chirality” effects, whereby the chiral bias created by intermolecular interactions is left unchanged upon replacement of the optically active inducer by an achiral analogue.^[5]

Previously, we reported that single protonation of diaza-macropentacycle **1** (Figure 1) affords an interesting geometrical construction of type i^+o - $[1\cdot H]^+$, in which the captured proton resides on the *endo* or *in* (*i*) bridgehead nitrogen, being hydrogen bonded with the three proximal thioether sulfur atoms, whereas the other bridgehead nitrogen has the *exo* or *out* (*o*) configuration.^[6a,b] The resulting proton complex is a C_3 -symmetric propeller,^[7] the sense of configura-

[a] Dr. C. Bonnot, Dr. J.-C. Chambron
ICMUB (CNRS, UMR no. 5260), Université de Bourgogne
9 Avenue Alain Savary, BP 47870, 21078 Dijon (France)
Fax: (+33)380-39-61-17
E-mail: jean-claude.chambron@u-bourgogne.fr

[b] Dr. E. Aubert, Prof. Dr. E. Espinosa
CRM2 (CNRS, UMR no. 7036), Nancy-Université
Boulevard des Aiguillettes, BP 239
54506 Vandœuvre-lès-Nancy (France)
E-mail: enrique.espinosa@crm2.uhp-nancy.fr

[c] N. Banerji, Prof. Dr. J. Lacour
Department of Chemistry, University of Geneva
Quai Ernest Ansermet 30, 1211 Geneva 4 (Switzerland)

Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/chem.200903058>.

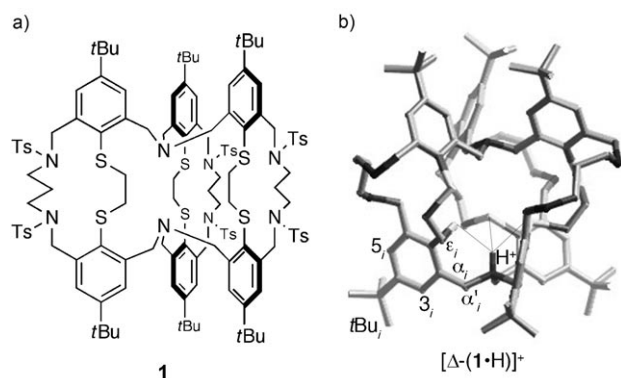
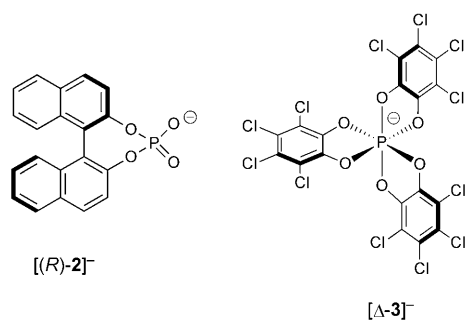


Figure 1. a) Chemical structure of **1** and b) Δ enantiomer of $[\mathbf{1}\cdot\mathbf{H}]^+$ in the X-ray crystal structure of $[\mathbf{1}\cdot\mathbf{H}][\text{OTf}]$ (side view).^[6a,8] Tosyl (Ts) groups and hydrogen atoms, except (N)H⁺ and selected *endo* (*i*) ones, are omitted for clarity.

tion^[8] of which can be thermodynamically controlled by ion pairing with the optically active C_2 -symmetric 1,1'-binaphthyl-2,2'-diyl phosphate anion ($[(R)\text{-}\mathbf{2}]^-$ or $[(S)\text{-}\mathbf{2}]^-$, Scheme 1), up to 24% diastereomeric excess (*de*) in CDCl_3 , thus consti-



Scheme 1. Chemical structures of optically active C_2 - and D_3 -symmetric anions $[(R)\text{-}\mathbf{2}]^-$ and $[\Delta\text{-}\mathbf{3}]^-$, respectively.

tuting an example of asymmetric transformation of the first kind.^[2] Now, using instead the D_3 -symmetric Δ -TRISPHAT anion ($[\Delta\text{-}\mathbf{3}]^-$), we report that not only thermodynamic but also kinetic control occurs. It is demonstrated, in different solvents, by the disparity in time evolution of the diastereomeric ratio (d.r.) before an equilibrated stereocontrol can be reached. Indeed, samples obtained in various solvents not only differ in the proportions of the diastereomers but also in the rates at which they reach the equilibrium. Through detailed NMR spectroscopic and computational studies, a rationale for the kinetic effects is suggested. It highlights the delicate interplay between solvent polarity and basicity, and competing interactions between solvent and optically active anions and also accounts for the intrinsic differences between anions of type $[\mathbf{2}]^-$ and $[\mathbf{3}]^-$.^[9]

Results

The salt $[\mathbf{1}\cdot\mathbf{H}][\Delta\text{-}\mathbf{3}]$ was obtained quantitatively by anion metathesis between $[\mathbf{1}\cdot\mathbf{H}][\text{CF}_3\text{CO}_2]$ and $[\textit{n}\text{Bu}_4\text{N}][\Delta\text{-}\mathbf{3}]$ in $\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$ biphasic solvent mixture, and was isolated in crystalline form by slow evaporation of $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ solutions. It was examined by ^1H and ^{13}C NMR spectroscopy in various solvents (Figures S3–S12 and Tables S1–S7 in the Supporting Information). In $[\text{D}_6]$ acetone, only four protons out of 31 show split signals: 3_i and $t\text{Bu}_i$, which are located on the external bottom side of the *endo* part of the complex, and the diastereotopic pair $\varepsilon_i\text{-CH}_2$ (Figure 1b). However, the diastereomers $[\Delta\text{-}(\mathbf{1}\cdot\mathbf{H})][\Delta\text{-}\mathbf{3}]$ and $[\Lambda\text{-}(\mathbf{1}\cdot\mathbf{H})][\Delta\text{-}\mathbf{3}]$ are formed in equal proportions (0% *de*). By contrast, in CDCl_3 , in which they are formed in 20% *de*, the signals of all the *endo* protons (except ε_i) plus a few *exo* protons are split, the $\Delta\delta$ exceeding 0.20 ppm in the case of neighboring protons 3_i and α'_i . ^{13}C NMR spectra of $[\mathbf{1}\cdot\mathbf{H}][\Delta\text{-}\mathbf{3}]$ obtained in CDCl_3 and $[\text{D}_8]$ THF also show numerous splittings, in addition to the signature of the $[\Delta\text{-}\mathbf{3}]^-$ anion (Figures S9–S12 and Tables S6 and S7). The *de* values decrease in the following order (Figure S13): $[\text{D}_8]$ THF (28%) > CD_2Cl_2 (22%) > CDCl_3 (20%) > $[\text{D}_8]$ toluene (16%) > C_6D_6 (7%) > $[\text{D}_6]$ acetone (0%). These data are collected in Table 1 together with the corresponding equilibrium constants $K_{\text{inv}}^{+/-}$ (=d.r.).

Table 1. Thermodynamics and kinetics of the equilibrium between the diastereomers of $[\mathbf{1}\cdot\mathbf{H}][\Delta\text{-}\mathbf{3}]$.

	C_6D_6	$[\text{D}_8]$ Toluene	CDCl_3	$[\text{D}_8]$ THF	CD_2Cl_2	$[\text{D}_6]$ Acetone
ε ^[a]	2.3	2.4	4.7	7.5	8.9	20.7
SB ^[b]	0.124	0.128	0.071	0.591	0.178	0.475
<i>de</i> ^[c] [%]	7	16	20	28	22	0
$K_{\text{inv}}^{+/-}$ ^[d]	1.16	1.38	1.50	1.78	1.56	1.00
k_i^{inv} ^[e]	n.d. ^[f]	0.13	0.03	1.61	0.21	n.d. ^[f]

[a] Dielectric constant. [b] Solvent basicity. See ref. [10]. [c] Diastereomeric excess. [d] Equilibrium constant of the major (M) and minor (m) diastereomers: $K_{\text{inv}}^{+/-} = [\text{M}]/[\text{m}] = \text{d.r.}$ (diastereomeric ratio). [e] Initial rate constant [h^{-1}] determined from the slope of the time variation of $\ln(1 - de)$, assuming that $[\text{m}]_t = [\text{m}]_0 \exp(-k_i t)$, in which m = minor diastereomer. [f] n.d. = not determined.

In another series of experiments, a sample of $[\mathbf{1}\cdot\mathbf{H}][\Delta\text{-}\mathbf{3}]$ was dissolved in $[\text{D}_6]$ acetone to set its *de* value to 0%. The solvent was evaporated and the residue dried in a vacuum at 35°C. It was subsequently dissolved in CDCl_3 and checked by ^1H NMR spectroscopy. In fact, the measured *de* was only 1% 30 min after sample preparation and 2.5% after 1 h. After 10 h it had reached 10%, and the equilibrium value of 20% was obtained after one day. The time dependence in different solvents (including CDCl_3) of the *de* of samples that have been preconditioned in $[\text{D}_6]$ acetone is shown in Figure 2. Extrapolation of the initial trends to $t=0$ invariably gives $de_0 = 0\%$. Whereas equilibration in $[\text{D}_6]$ acetone itself takes place on the ^1H NMR spectroscopic timescale, this is not the case for all the other solvents examined. The time necessary to reach the equilibrium value is the shortest

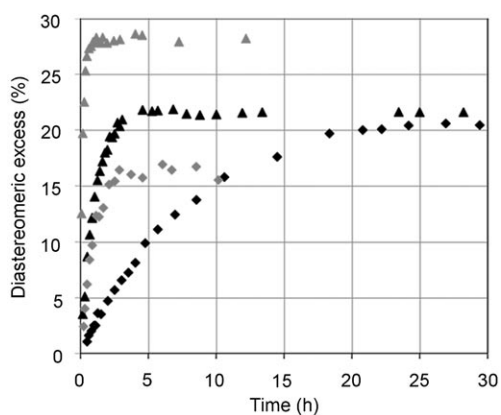


Figure 2. Time dependence of the diastereomeric excess of a solution of $[1\cdot H][\Delta-3]$ in $[D_8]$ THF (gray triangle), CD_2Cl_2 (black triangle), $[D_8]$ toluene (gray diamond), and $CDCl_3$ (black diamond) starting from a sample that has been conditioned in acetone (0% de).

in $[D_8]$ THF (1 h) and the longest in $CDCl_3$ (24 h). The corresponding initial rate constants (k_i) are collected in Table 1.

The next series of experiments examines by 1H NMR spectroscopy the time dependence of the de of samples of $[1\cdot H][\Delta-3]$ that have been preconditioned in various solvents (Figure 3). $CDCl_3$ was chosen in this study because the slow-

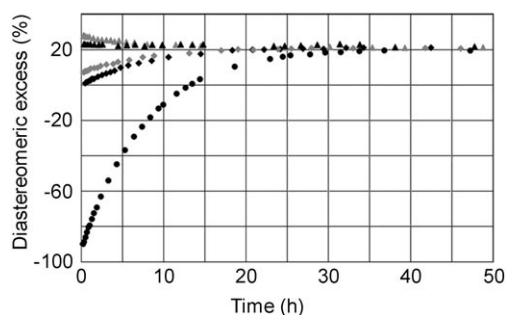


Figure 3. Time dependence of the diastereomeric excess of a solution of $[1\cdot H][\Delta-3]$ in $CDCl_3$ starting from different initial conditions (de_0): $[D_8]$ THF (gray triangle), CD_2Cl_2 (black triangle), C_6D_6 (gray diamond), and $[D_6]$ acetone (black diamond); crystals obtained from CH_2Cl_2/CH_3OH (black circle).

est kinetics are observed in this medium. For example, starting from a sample that has been equilibrated in $[D_8]$ THF leads to a slow de decrease from 28 to 20%, whereas preconditioning in $[D_6]$ benzene allows one to observe a de increase from 7 to 20%. The extrapolated de_0 values match the equilibrium values measured for the different solvents used for conditioning the samples.

We took advantage of this observation to examine the crystals of $[1\cdot H][\Delta-3]$ that formed upon slow evaporation of CH_2Cl_2/CH_3OH mixtures. As $[1\cdot H][\Delta-3]$ is not soluble in CH_3OH , its de cannot be directly measured in this solvent. However the relatively slow change of the de in $CDCl_3$ permits one to obtain by extrapolation and with good confidence the de value that the sample had in the crystalline

state before dissolution in this solvent (de_0). Well-shaped transparent needles of $[1\cdot H][\Delta-3]$ were washed with CH_3OH , carefully dried in a vacuum at $35^\circ C$, and subsequently dissolved in $CDCl_3$. The magnitude of the de decreases from -96% (15 min) to 0% (13 h), then increases until the 20% equilibrium value in $CDCl_3$ is reached (Figure 3). The extrapolated de_0 is very close to -100% , which shows that the crystals of $[1\cdot H][\Delta-3]$ are diastereomerically pure. Remarkably, its sign is opposite to that of the de_0 values obtained in all of the solvents investigated, which indicates opposite configurations of the predominant $[1\cdot H]^+$ propellers in solution at thermodynamic equilibrium, and in the solid state. Crystal growth therefore proceeds by means of the so-called asymmetric transformation of the second kind.^[2,11] Although this is not the only example of such a process being induced by $[\Delta-3]^-$,^[11] this anion has been mostly used for the resolution of chiral cationic transition-metal complexes by crystallization.^[12]

As the low crystalline quality of $[1\cdot H][\Delta-3]$ did not allow for X-ray diffraction (XRD) analysis, structural studies were carried out in solution by 1H and ^{13}C NMR spectroscopy (Tables S1–S7 in the Supporting Information) and in the gas phase by calculations at the semiempirical PM6 level of theory (Figures S14–S21 and Tables S8–S16).^[13] The results of the comparison of the 1H NMR spectra of $[1\cdot H][\Delta-3]$ and $[1\cdot H][CF_3CO_2]$ in four different solvents ($[D_8]$ THF, CD_2Cl_2 , $CDCl_3$, and $[D_6]$ acetone) are displayed graphically in Figure 4. This allowed us to evidence the anisotropic effects

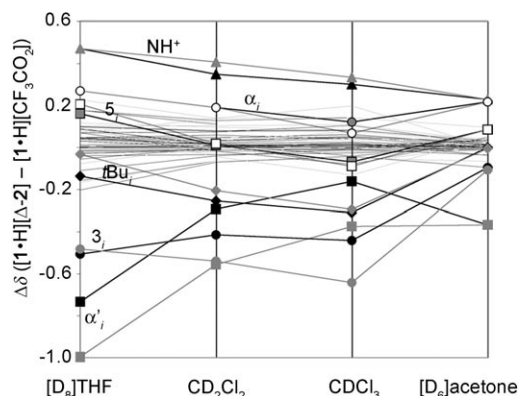


Figure 4. Plot of the chemical shift difference ($\Delta\delta$, ppm) between analogous protons of $[1\cdot H][\Delta-3]$ and $[1\cdot H][CF_3CO_2]$ in $[D_8]$ THF, CD_2Cl_2 , $CDCl_3$, and $[D_6]$ acetone. Lines corresponding to the protons undergoing the largest $\Delta\delta$ are marked with geometric figures. Lines in black correspond to the major diastereomers and lines in gray correspond to the minor diastereomers (see Figure S22 in the Supporting Information for the color version of Figure 4).

induced by the $[\Delta-3]^-$ anion on $[1\cdot H]^+$.^[11m] The directions of the shifts are practically solvent-independent and are the same in both diastereomers, which suggests that the binding mode of $[\Delta-3]^-$ to $[1\cdot H]^+$ does not depend on the configuration of the latter. Given that the optically active anion is likely to be located in the vicinity of the *endo* side of $[1\cdot H]^+$, as can be inferred from XRD studies of the triflate

and chloride salts,^[6b] this observation is in keeping with the fact that the twist of the *endo*-tribenzylamine propeller is small compared to that of the *exo* one.^[6b] Upon replacement of CF_3CO_2^- by $[\Delta\text{-3}]^-$, strong upfield shifts are observed for *endo* protons α'_i , 3_i , and *t*Bu_{*i*}, whereas NH^+ and α_i experience downfield shifts. The shifts are maximal in $[\text{D}_8]\text{THF}$ for NH^+ and α'_i , and in CDCl_3 for *t*Bu_{*i*}.

The most stable computed structures (I–IV) are all heterochiral ion pairs (Figures S14–S21), with ΔH values between the homo- and heterochiral ion pairs in the gas phase being 4.9, 10.2, 11.9, and 2.5 kJ mol^{-1} for I, II, III, and IV, respectively. Heterochiral and homochiral I are obtained by docking $[\Delta\text{-3}]^-$ onto the *endo* external side of $[\Lambda\text{-(1-H)}]^+$ and $[\Delta\text{-(1-H)}]$ (Figure 5a and b), so as to make the C_3 -symmetry

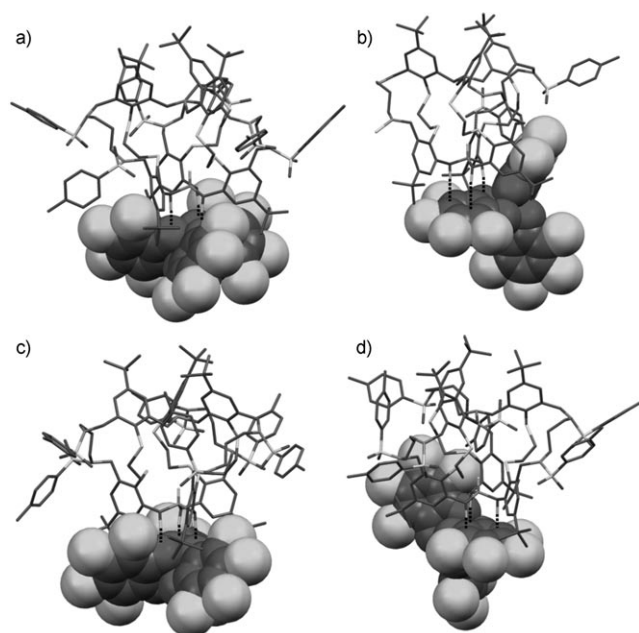


Figure 5. Computed molecular structures of $[\Lambda\text{-(1-H)}][\Delta\text{-3}]$ heterochiral ion pairs a) I and b) II, and $[\Delta\text{-(1-H)}][\Delta\text{-3}]$ homochiral ion pairs c) I and d) II.^[13] Some Ts groups and hydrogen atoms, except $(\text{N})\text{H}^+$ and α'_i , are omitted for clarity (see Figures S14–S17 in the Supporting Information for the color versions of the views shown in Figure 5).

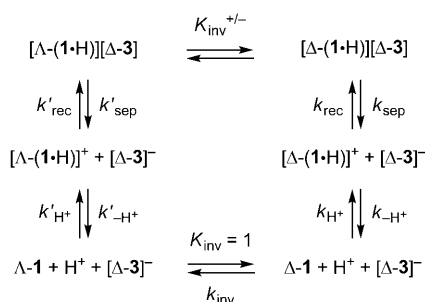
axes of the two propellers coincident. A similar docking mode has been previously invoked to describe the ion pair by means of π – π stacking interactions in $[\Delta\text{-Fe}\{4,4'\text{-Me}_2\text{-(bpy)}\}_3][[\Delta\text{-3}]_2]^{[1c]}$ ($\text{bpy} = 2,2'$ -bipyridine) and related complexes,^[14c] which are driven by a remarkable size and shape complementarity between the D_3 -symmetric metal complex and $[\Delta\text{-3}]^-$ homochiral propellers. In the case of $[\Lambda\text{-(1-H)}][\Delta\text{-3}]$, it allows for $\text{O}\cdots\text{H}$ (α'_i and 3_i) hydrogen bonds, in addition to $\pi\cdots\text{H}(\text{tBu})$ contacts, to be established. Indeed, XRD analysis of the triflate and chloride salts of $[\mathbf{1-H}]^+$ has shown that the anions enjoy close contacts with protons α'_i and 3_i .^[6b] However, if structure I could depict the ion pair in the solid state, such a model cannot account for the observations made in solution, as it is not consistent with the upfield shift of protons α'_i . Indeed the latter should, on the contrary,

be deshielded by hydrogen bonding with the phosphate oxygen atoms. The next lowest energy structures are 31.2 (II), 34.3 (III), and 44.6 kJ mol^{-1} (IV) less stable than structure I. All are obtained by insertion of one of the blades of $[\Delta\text{-3}]^-$ into a groove of $[\Lambda\text{-(1-H)}]^+$ (e.g., heterochiral II, Figure 5b), thereby giving rise to $\text{O}\cdots\text{H}$ and $\text{Cl}\cdots\text{H}$ bonds. This places a second aromatic ring of the anion astride the outside *endo* pocket, which allows for 3_i (and α'_i) $\text{CH}\cdots\pi$ interactions, and accounts for the observed upfield shifts. The third blade is offside and does not interact with $[\Lambda\text{-(1-H)}]^+$. As their relative energies are close to each other, averaging structures II–IV represents an acceptable model of the ion pair in the solid state. However, as observed by $^1\text{H NMR}$ spectroscopy (Figure 3), and by contrast to the case of the solid state, the solution structures result from homochiral ion pairing (e.g., homochiral II, Figure 5d). In connection with this model, we note that the side-on mode of interaction has been proposed in the case of the minor diastereomer of $[\text{Fe}(\text{diimine})_3]^{2+}$, in which the C_3 -symmetry axis of the anion and one of the three C_2 -symmetry axes of the cation are approximately coincident. This makes two blades of each propeller complementary with each other, with the third one being not engaged in the steric recognition process.^[1m]

Discussion

Because the thermodynamics of ion pairing ($K_{\text{inv}}^{+/-}$) are usually controlled by solvent polarity, the *de* should decrease with an increasing dielectric constant.^[1c,f,4b,6b] This trend is roughly followed here, as the highest *de* values (20–28%) are obtained in low-polarity solvents ($[\text{D}_8]\text{THF}$, CD_2Cl_2 , and CDCl_3), whereas 0% *de* is measured in polar acetone. It is not obeyed, however, in apolar aromatic solvents (e.g., 7% *de* in $[\text{D}_6]\text{benzene}$, 16% *de* in $[\text{D}_8]\text{toluene}$), which can possibly compete with the tetrachlorocatecholate rings of $[\Delta\text{-3}]^-$ for $\text{CH}\cdots\pi$ interactions.

The kinetics of chirality transfer within the ion pair $[\mathbf{1-H}][\Delta\text{-3}]$ depend also on basicity, as they are slow in less basic and low-polarity solvents (CDCl_3 , C_6D_6 , $[\text{D}_8]\text{toluene}$, and CD_2Cl_2), relatively fast in more basic and low-polarity $[\text{D}_8]\text{THF}$, and fast in more basic and polar $[\text{D}_6]\text{acetone}$.^[10] They would be first-order if they resulted from the unimolecular interconversion between $[\Delta\text{-(1-H)}]^+$ and $[\Lambda\text{-(1-H)}]^+$. As the experimental curves of Figure 2 and 3 cannot be fitted by single exponential functions, the inversion mechanism of the $[\mathbf{1-H}]^+$ propeller is not described solely by the equilibrium between the diastereomeric ion pairs $[\Delta\text{-(1-H)}][\Delta\text{-3}]$ and $[\Lambda\text{-(1-H)}][\Delta\text{-3}]$, but must involve other species and other equilibria. To explain the effects observed, we propose the following hypotheses to suggest a reasonable pathway for the interconversion between $[\Delta\text{-(1-H)}]^+$ and $[\Lambda\text{-(1-H)}]^+$ (Scheme 2): 1) Separation of the ion pair into $[\Delta\text{-(1-H)}]^+$ and $[\Delta\text{-3}]^-$; 2) deprotonation of $[\Delta\text{-(1-H)}]^+$ to form the transient species $\Delta\text{-1}$; 3) inversion of $\Delta\text{-1}$ into $\Lambda\text{-1}$; 4) protonation of $\Lambda\text{-1}$ into $[\Lambda\text{-(1-H)}]^+$; and 5) formation of



Scheme 2. Suggested mechanism for the inversion process.

the ion pair $[\Lambda-(\mathbf{1}\cdot\text{H})][\Delta\text{-}\mathbf{3}]$. Our key assumption is that propeller inversion takes place in the deprotonated state (step 3) of Scheme 2). The corresponding equilibrium has $K_{\text{inv}} = 1$, as $[\Delta\text{-}\mathbf{3}]^-$ is not engaged in diastereomeric interactions with $\Delta\text{-}\mathbf{1}$ and $\Lambda\text{-}\mathbf{1}$. Assuming that its rate (k_{inv}) is high and not solvent dependent, the kinetics of chirality transfer are controlled by the rates of the ion-pair separation/recombination ($k_{\text{sep}}/k_{\text{rec}}$ and $k'_{\text{sep}}/k'_{\text{rec}}$) and of the $[\mathbf{1}\cdot\text{H}]^+/\mathbf{1}$ deprotonation/protonation ($k_{-\text{H}^+}/k_{\text{H}^+}$ and $k'_{-\text{H}^+}/k'_{\text{H}^+}$) processes. The variables $k_{\text{sep}}/k_{\text{rec}}$ ($k'_{\text{sep}}/k'_{\text{rec}}$, respectively) increase with solvent polarity, whereas $k_{-\text{H}^+}/k_{\text{H}^+}$ ($k'_{-\text{H}^+}/k'_{\text{H}^+}$) increase with solvent basicity. In a first approximation, only the former are directly controlled by diastereomeric interactions (that is, within the ion pairs formed between $[\Delta-(\mathbf{1}\cdot\text{H})]^+$ or $[\Lambda-(\mathbf{1}\cdot\text{H})]^+$, and $[\Delta\text{-}\mathbf{3}]^-$). The latter are affected by these interactions when the anion competes with the solvent as a base, which, given the very low basicity of $[\Delta\text{-}\mathbf{3}]^-$,^[15] should happen in the case of acidic solvents such as CDCl_3 .

The kinetic effects presented here are in keeping with the earlier observation that single protonation of macropentacycle **1** by strongly acidic $\text{CF}_3\text{SO}_3\text{H}$ was in the hours range in CDCl_3 and CD_2Cl_2 ; it was faster in the latter solvent.^[6b] In the same work, we had studied the induction of chirality on $i^+o\text{-}[\mathbf{1}\cdot\text{H}]^+$ by ion pairing with the optically active $[(R)\text{-}\mathbf{2}]^-$ and $[(S)\text{-}\mathbf{2}]^-$ anions. The diastereomeric excess decreased with increasing solvent polarity and basicity: 24% (CDCl_3) > 16% (CD_2Cl_2) > 10% ($[\text{D}_6]\text{acetone}$). However, contrary to the present case ($[\text{D}_6]\text{acetone}$ excepted), the inversion of the $[\mathbf{1}\cdot\text{H}]^+$ propeller in its ion pair with $[\mathbf{2}]^-$ took place at the NMR spectroscopic timescale in all three solvents studied, as did single protonation of **1** by $\text{CF}_3\text{CO}_2\text{H}$, the $\text{p}K_{\text{a}}$ of which is higher than that of $\text{CF}_3\text{SO}_3\text{H}$ but similar to that of $[\mathbf{2}\cdot\text{H}]$.^[6a] Another noticeable difference when comparing $[\mathbf{3}]^-$ to $[\mathbf{2}]^-$ is that the former shows much stronger anisotropic effects, as evidenced by comparing the ^1H NMR spectroscopic shifts induced on $[\mathbf{1}\cdot\text{H}]^+$ by $[\mathbf{3}]^-$ ($\Delta\delta_{\text{max}} = 1$ ppm) to those induced by $[\mathbf{2}]^-$ ($\Delta\delta_{\text{max}} = 0.3$ ppm). Careful analysis of the latter indicated that $[\mathbf{2}]^-$ was located also on the *endo* side of $[\mathbf{1}\cdot\text{H}]^+$ but positioned in such a way that its C_2 -symmetry axis was coincident with the C_3 -symmetry axis of the $[\mathbf{1}\cdot\text{H}]^+$ propeller, a negatively charged oxygen atom of $[\mathbf{2}]^-$ being hydrogen-bonded to protons 3, and α'_i . Comparison of the anisotropic effects induced by $[\mathbf{2}]^-$ and $[\mathbf{3}]^-$, as well as of the proposed docking modes shows that the latter

anion forms a tighter ion pair with $[\mathbf{1}\cdot\text{H}]^+$ than $[\mathbf{2}]^-$. This is in keeping with the earlier observation that anions with a more dispersed charge, such as $[\mathbf{3}]^-$, increase the complex stability between quaternary ammonium guests and cyclopeptide receptors.^[16] The enforced interaction of $[\mathbf{3}]^-$ by comparison with $[\mathbf{2}]^-$ could explain why slow kinetics are observed in the case of $[\mathbf{1}\cdot\text{H}][\Delta\text{-}\mathbf{3}]$ but not in the case of $[\mathbf{1}\cdot\text{H}][(R)\text{-}\mathbf{2}]$. In summary, taken altogether, the observations discussed above indicate that the kinetic effects observed in the chiral recognition between $[\mathbf{1}\cdot\text{H}]^+$ and $[\Delta\text{-}\mathbf{3}]^-$ are the result of the delicate interplay between solvent polarity and basicity, and competing interactions between solvent and optically active anion.

Conclusion

The $i^+o\text{-}[\mathbf{1}\cdot\text{H}]^+$ proton complex of diaza-macropentacycle **1**, which is a stereolabile C_3 -symmetric chiral species, forms a tight ion pair with the Δ -TRISPHAT ($[\Delta\text{-}\mathbf{3}]^-$) anion, as shown by the strong NMR spectroscopic anisotropic effects induced by the latter on the former. Unlike stereolabile transition-metal complex cations, the interaction of which with $[\Delta\text{-}\mathbf{3}]^-$ and the resulting chirality transfer are under thermodynamic control, $[\mathbf{1}\cdot\text{H}]^+$ shows kinetic control for the same phenomenon. This observation suggests that the time dependence of the *de* of $[\mathbf{1}\cdot\text{H}]^+$ before the thermodynamic equilibrium is reached is connected to the very nature of the proton complex, which differs from that of the transition-metal complexes involved in earlier studies, as, unlike transition-metal cations such as Fe^{2+} and Co^{2+} , the proton can be exchanged between receptor and solvent or anion molecules. In spite of the fact that they affect the equilibrium between $[\Delta-(\mathbf{1}\cdot\text{H})][\Delta\text{-}\mathbf{3}]$ and $[\Lambda-(\mathbf{1}\cdot\text{H})][\Delta\text{-}\mathbf{3}]$, the observed kinetic effects are probably not directly due to the inversion of the $[\mathbf{1}\cdot\text{H}]^+$ propeller. Rather, they are a consequence of equilibrium phenomena taking place within the ion pair of a proton complex. In addition, from a mechanistic point of view, the behavior of $[\mathbf{1}\cdot\text{H}][\Delta\text{-}\mathbf{3}]$ is likely to be different from that of other species that show related kinetic effects, such as helically chiral polymers.

Experimental Section

General: The preparation of macropentacycle **1** is described in ref. [6c]. $[\text{D}_8]\text{toluene}$ excepted, deuterated solvents were dried on 4 Å molecular sieves (CDCl_3 , CD_2Cl_2 , C_6D_6 , and $[\text{D}_8]\text{THF}$) or MgSO_4 ($[\text{D}_8]\text{acetone}$) and stored in a glove box.

Preparation of $[\mathbf{1}\cdot\text{H}][\Delta\text{-}\mathbf{3}]$: Trifluoroacetic acid (0.68 μL , 8.79×10^{-6} mol) was added to a solution of **1** (0.0211 g, 8.79×10^{-6} mol) in CH_2Cl_2 (1 mL) and the solution was stirred at room temperature. After completion of the reaction (TLC), $[\text{nBu}_4\text{N}][\Delta\text{-}\mathbf{2}]$ (0.0084 g, 8.79×10^{-6} mol) in CH_2Cl_2 (1 mL) was added to the solution, followed by water (2 mL), and the biphasic reaction mixture was stirred vigorously for 24 h. The aqueous layer was extracted twice with CH_2Cl_2 , and the combined organic fractions were washed thoroughly with water. The solvent was evaporated and the residue retaken in a mixture of CH_2Cl_2 (3 mL) and CH_3OH (1 mL). Slow evaporation of the solution afforded colorless crystals,

which were collected, washed with methanol, and dried in vacuo at 35°C overnight. Yield: 0.0245 g (88%). The salt [1-H][Δ-3] has been characterized by ¹H and ¹³C NMR spectroscopy (see the Supporting Information).

Kinetic studies: A sample of [1-H][Δ-3] (12 mg) was dissolved in approximately 0.5 mL of deuterated solvent in the glove box. The NMR spectroscopy tube was capped and sealed with parafilm. NMR spectra were then recorded at intervals. The diastereomeric excesses were determined by integration of the signals of diastereomeric protons which showed the highest splittings, that is, 5_i ([D₈]THF) or 3_i (CDCl₃, CD₂Cl₂, [D₆]acetone), or γ_i (C₆D₆, [D₈]toluene). See Figures S1 and S13 in the Supporting Information.

Acknowledgements

We are grateful to Dr. Michel Meyer (ICMUB) for helpful discussions.

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Received: November 6, 2009
Published online: April 13, 2010