

PREFERENTIAL FORMATION OF HOMOCHIRAL SILVER(I) COMPLEXES UPON COORDINATION OF TWO AZA[6]HELICENE LIGANDS TO Ag⁺ IONS

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Received September 11, 2008

Accepted November 19, 2008

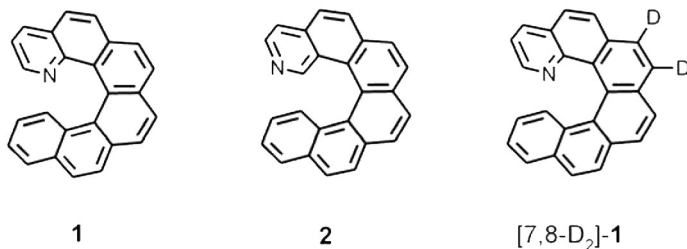
Published online February 16, 2009

By means of selective deuterium labeling of 1-aza[6]helicene combined with resolution of the enantiomers, chiral discrimination in silver(I)-bound dimers of the type [LAGL']⁺ is probed by electrospray mass spectrometry. The analysis of the results reveals a pronounced preference for the formation of homochiral dimers (*P,P* and *M,M*, respectively) over the statistically preferred heterochiral variant (*P,M*), which is fully consistent with previous data about the formation of homochiral dimers in the condensed phase. Further, competitive experiments with mixtures of 1- and 2-aza[6]helicene suggest a largely preferred coordination of 1-aza[6]helicene to the silver(I) cation.

Keywords: Fused pyridines; Helical heterocycles; Azahelicenes; Chiral discrimination; Mass spectrometry; Metal-bound dimers; Silver complexes.

Although the role of chiral ligands in organic and organometallic synthesis as well as biochemistry is enormous, gas-phase studies of chiral metal complexes are relatively scarce^{1,2}. This still limited amount of fundamental insight is primarily due to the fact that mass spectrometric methods – in addition to spectroscopy the central tool for mechanistic studies of gas-phase reactions – cannot discriminate between enantiomers unless the chiral information is translated into an appropriate mass difference. One possible approach to exploit the rich methodological repertoire of mass spectrometry for the analysis of chiral interactions accordingly is the preparation of selectively isotope-labeled chiral compounds in enantiomerically pure form. For reactions involving a single stereocenter, the stereochemical effects (SEs) found so far are often not very large with highest values of about four^{2–4}.

Inspired by the search for particularly large SEs, we have recently initiated mass spectrometric studies of the aza[6]helicenes **1** and **2** (Scheme 1) as a particular class of chiral compounds having a helically chiral backbone with an incorporated heteroatom⁵. The basic nitrogen atom in the framework may thus serve as a donor ligand in metal-ion complexes while the helical backbone may impose stereochemical restrictions. In our first report, we already have demonstrated notable enantioselective effects in the association of protonated aza[6]helicenes with secondary alkanols⁵, which are particularly suitable chiral substrates for the investigation of chiral discrimination in the gas phase^{6–10}. Here, we report an experimental study of the stereochemical effects in the formation of bisligated silver(I) complexes of the aza[6]helicenes **1** and **2** under the conditions of electrospray ionization (ESI) using the specifically deuterated compound [7,8-D₂]-**1** as an internal reference^{1,4,11–13}.



SCHEME 1
Compounds **1**, **2**, and [7,8-D₂]-**1**

EXPERIMENTAL

The mass spectrometric experiments were performed with a Waters Micromass ZQ mass spectrometer equipped with an ESI source. The silver(I)-bound dimers of the aza[6]helicene ligands, i.e. compounds **1**, **2**, and [7,8-D₂]-**1**, which were all available in enantiomerically pure form, were generated from mmolar acetone solutions of the aza[6]helicenes and silver(I) triflate, which were introduced to the ESI source via a syringe pump (ca. 5 $\mu\text{l min}^{-1}$) using nitrogen as a sheath gas. The ionization conditions were kept soft¹⁴ in order to enhance the formation of bisligated metal-cation complexes^{15,16}. For the evaluation of possible stereochemical effects in the formation of silver(I)-bound dimers of the aza[6]helicenes, the ion intensities of the corresponding mass region in the source spectra were modeled in a stepwise procedure as detailed elsewhere¹⁷. To this end, acetone solutions of the pure aza[6]helicenes were subjected to ESI in order to establish the isotope envelopes of the signals due to the protonated bases and for the determination of the deuterium content of the labeled samples. Next, an optically pure, non-labeled aza[6]helicene, either **1** or **2**, was mixed with one enantiomer of [7,8-D₂]-**1** was prepared and the mixing ratio was determined by numerical fitting of the overlapping isotope clusters of the protonated molecules. Finally,

silver(I) triflate was added to the solution and the resulting isotope cluster of the silver(I)-bound ions of the type $[LAgL']^+$ ($L, L' = \text{aza}[6]\text{helicenes}$) was analyzed by numerical modeling of the experimentally observed isotope patterns. High-resolution mass measurements^{18,19} would provide an alternative to the unconvolution of the isotope cluster pursued here, but for the problem at hand a mass resolution of $m/\Delta m > 10^5$ would have been required for a proper separation of the various isotopes in the dimers (i.e. ¹H, ²H, ¹²C, ¹³C, ¹⁴N, ¹⁵N, ¹⁰⁷Ag, and ¹⁰⁹Ag). Additional collision-induced dissociation experiments of the ions described below were recorded using a TSQ Classic mass spectrometer^{5,20} in order to confirm their assignment as genuine silver(I)-bound dimers.

The synthesis of the deuterated 1-aza[6]helicene, [7,8-D₂]-**1**, which is based on a metal-mediated cyclotrimerization of an appropriate triyne precursors followed by oxidative aromatization^{21,22}, its complete spectroscopic characterization as well as the racemate resolution into the enantiomers (+)-(*P*)-[7,8-D₂]-**1** and (-)-(*M*)-[7,8-D₂]-**1** have been described elsewhere¹⁷.

RESULTS AND DISCUSSION

Due to their extended π -skeletons, the azahelicenes **1** and **2** are rather strong bases in the gas phase being much more basic than the parent compound pyridine⁵. Accordingly, signals of the corresponding protonated molecules, i.e. $[(\mathbf{1})\text{H}]^+$ and $[(\mathbf{2})\text{H}]^+$, respectively, predominate the electrospray mass spectra of solutions of **1** and/or **2** in acetone. Under soft ionization conditions, also the corresponding proton-bound dimers, i.e. $[(\mathbf{1})\text{H}(\mathbf{1})]^+$, $[(\mathbf{1})\text{H}(\mathbf{2})]^+$, and $[(\mathbf{2})\text{H}(\mathbf{2})]^+$, respectively, are observed in significant abundance. In addition to these purely organic ions, reasonably abundant signals corresponding to the monoligated silver(I) complexes $[(\mathbf{1})\text{Ag}]^+$ and $[(\mathbf{2})\text{Ag}]^+$ as well as bisligated species of the type $[(\mathbf{1})\text{Ag}(\mathbf{1})]^+$, $[(\mathbf{1})\text{Ag}(\mathbf{2})]^+$, and $[(\mathbf{2})\text{Ag}(\mathbf{2})]^+$, respectively, are formed in the presence of silver(I) triflate. No higher adducts, e.g. trisligated species, are observed, which is consistent with the size of the aza[6]helicene ligands and the generally preferred coordination number 2 of silver(I)²³. Upon collision-induced dissociation (CID) of the mass-selected dimers, exclusive losses of a neutral helicene molecule to form $[(\mathbf{1})\text{Ag}]^+$ and $[(\mathbf{2})\text{Ag}]^+$, respectively, are observed, thus confirming the assignment of these species as bisligated Ag^+ complexes^{24,25}; we note in passing that loss of neutral AgH prevails²⁶ in the CID spectra of the monoligated cations $[(\mathbf{1})\text{Ag}]^+$ and $[(\mathbf{2})\text{Ag}]^+$. In this work, we focus on the possible diastereoselective discrimination in the complexes of the silver(I) cation with two aza[6]helicene ligands. Inherent chirality of helicenes in conjunction with the presence of heteroatom in the A-ring serving as an anchor for the metal cation may thus lead to a significant enantiomeric discrimination in the gas phase and possibly offer further perspectives for solution chemistry.

At first, the strategy to experimentally assess the possible discrimination in the formation of bisligated complexes of aza[6]helicenes with silver(I) is outlined briefly^{1,2,4}. Specifically, the mandatory translation of chiral information into a mass difference was achieved by specific deuterium labeling of 1-aza[6]helicene, **1**, followed by resolution of the enantiomers, (+)-(*P*)-[7,8-D₂]-**1** and (-)-(*M*)-[7,8-D₂]-**1**, respectively. Combination of one enantiomer of the labeled compound with the same or the opposite enantiomer of unlabeled **1** can hence be used to investigate the formation of the corresponding homo- and heterochiral dimers. ESI of a dilute acetone solution containing silver(I) triflate, (*P*)-[D₀]-**1**, and (*M*)-[7,8-D₂]-**1**, for example, leads to the bisligated homochiral complexes [((*P*)-[D₀]-**1**)Ag((*P*)-[D₀]-**1**)]⁺ (*m/z* 765 for the ¹⁰⁷Ag and *all*-¹²C isotope) as well as [((*M*)-[7,8-D₂]-**1**)Ag((*M*)-[7,8-D₂]-**1**)]⁺ (*m/z* 769) and the heterochiral variant [((*P*)-[D₀]-**1**)Ag((*M*)-[7,8-D₂]-**1**)]⁺ (*m/z* 767). Because silver has two isotopes, the ¹³C envelopes of **1** and **2** are appreciable, the deuterium incorporation in both enantiomers of [7,8-D₂]-**1** is incomplete (i.e. 80.5 ± 1.5 atom-% D)¹⁷, and the mass difference between the unlabeled and labeled sample is relatively small (Δ*m* = 2 amu), the resulting isotope patterns are quite complex. Provided sufficiently reproducible measurements, however, we have demonstrated previously that quantitative fitting of the isotope envelopes can provide the required insight at a molecular level and thereby *inter alia* reveal kinetic isotope effects (KIEs), equilibrium isotope effects (EIEs), or stereochemical effects (SEs)^{17,27,28}. A complication arises from the fact that only very small quantities of the chiral, deuterated samples are available for a series of experiments, such that a gravimetric mixing scheme is impractical. Instead, the mixtures were prepared only approximately and the actual mixing ratio has been determined by fitting the isotope envelopes of the signals due to the protonated bases upon ESI-MS as described elsewhere¹⁷. Thus, prior to the measurements in the presence of Ag⁺, the actual mixing ratio of the labeled and unlabeled sample is determined in an independent experiment, followed by analysis of the isotope pattern of the dimeric silver(I) complexes in a second step. Finally, it is noted explicitly that this kind of analysis is based upon equilibrium kinetics, while electrospray ionization is a highly dynamic process and may thus lead to a non-equilibrium distribution of the ions evolving from the solution via charged droplets to the gas phase. However, in the comparison of the unlabeled and labeled 1-aza[6]helicenes **1** and [7,8-D₂]-**1**, the only difference between the constituents of the silver(I)-bound dimers is their chirality since all non-equilibrium effects are likely to cancel. Nevertheless, the relevance of these dynamical aspects of the ESI process becomes apparent in the comparison

of 1-aza[6]helicene, **1**, and 2-aza[6]helicene, **2** (vide infra). Accordingly, the equilibrium constants K_i and equilibrium isotope effect (EIE) given below are to be considered as phenomenological parameters which describe the ratios of the respective sums of individual rates under non-equilibrium con-

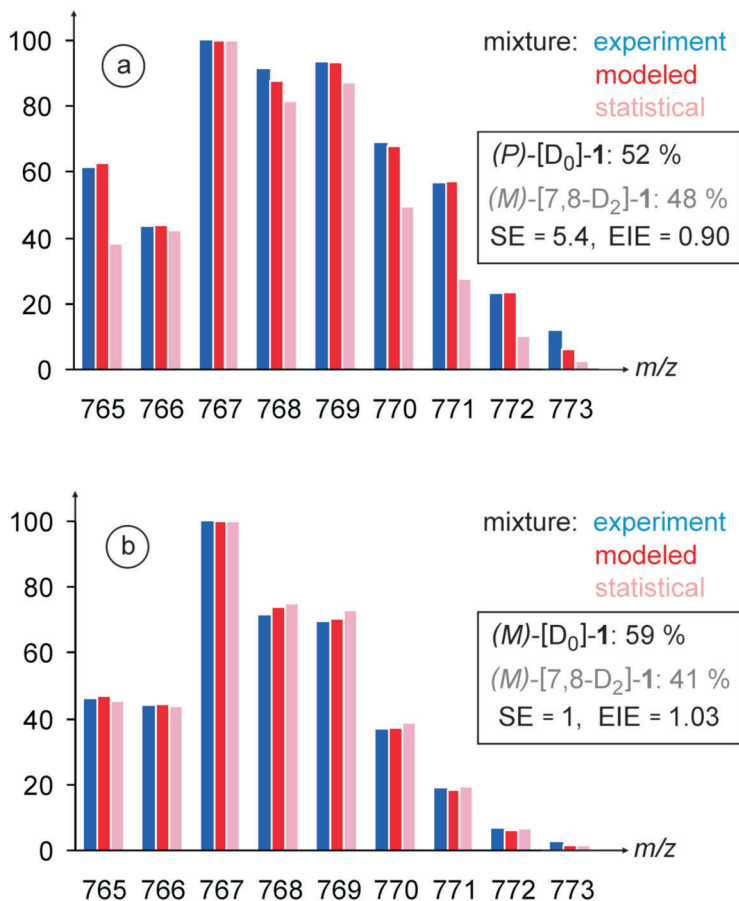


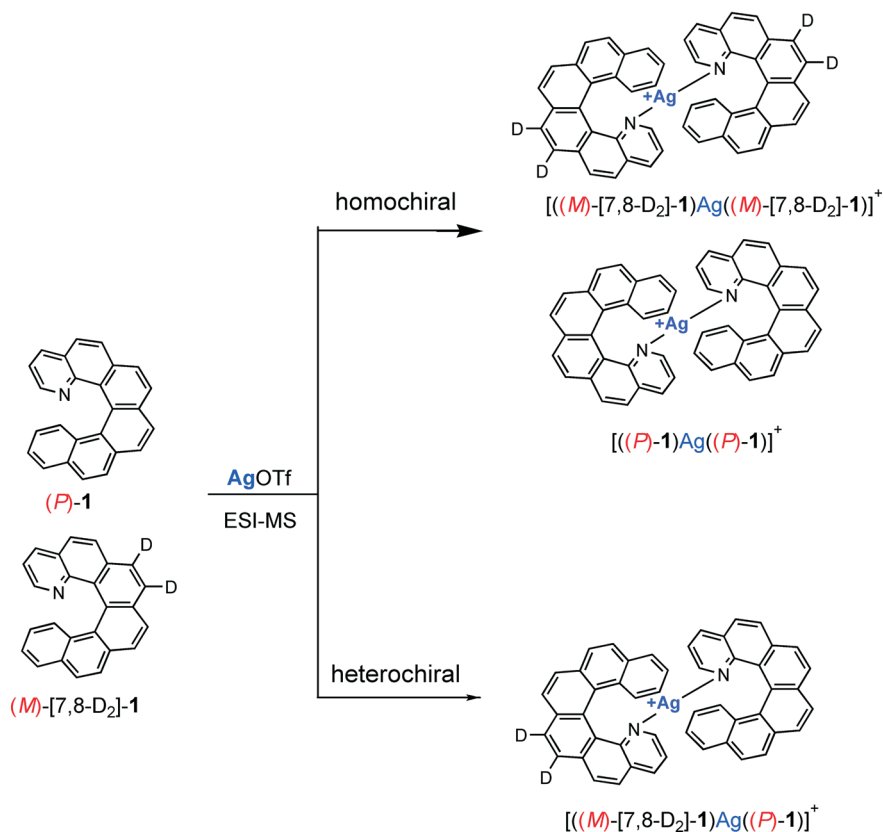
FIG. 1

Normalized ion abundances of the mass region of the silver(I)-bound dimers of 1-aza[6]helicenes in two typical ESI mass spectra: (a) ca. 1:1 mixture of a (*P*)-[D₀]-1 and (*M*)-[7,8-D₂]-1, (b) (*M*)-[D₀]-1 and (*M*)-[7,8-D₂]-1. Fitting of the experimental spectra of the prepared mixtures (blue bars) by linear combinations of the isotope patterns of the separate components (red bars) reveals the stereochemical effect (SE) as well as the equilibrium isotope effect (EIE) operative in the formation of the bisligated complexes. For comparison, also the statistical patterns, i.e. the intensities for SE = EIE = 1, are given (pink bars)

ditions rather than the true equilibrium values. However, the differences are likely to cancel in the comparison of (*P*)- and (*M*)-enantiomers performed here. Moreover, the EIE can be determined in an independent control experiment using the labeled and unlabeled samples of the same chirality (i.e. SE = 1), and the effect of the EIE can hence be unconvoluted from the SE.

Figure 1 shows the results obtained for two samples. For a mixture of (*P*)-[D₀]-**1** and (*M*)-[7,8-D₂]-**1**, the experimental isotope pattern (blue bars in Fig. 1a) fairly deviates from the ion abundances for a merely statistical distribution (pink bars in Fig. 1a). The latter predicts significantly lower abundances for the low- and high-mass ions, which correspond to the homochiral complexes [((*P*)-[D₀]-**1**)Ag((*P*)-[D₀]-**1**)⁺ (*m/z* 765 for the ¹⁰⁷Ag and *all*-¹²C isotope) and [((*M*)-[7,8-D₂]-**1**)Ag((*M*)-[7,8-D₂]-**1**)⁺ (*m/z* 769 for the ¹⁰⁷Ag and *all*-¹²C isotope). Instead, a satisfactory fit (red bars in Fig. 1a) is obtained with a stereochemical effect of SE = 5.4 and an equilibrium isotope effect of EIE = 0.90, of which the former indicates a large preference for the formation of the bisligated complexes with aza[6]helicene ligands of the same chirality. Figure 1b shows a control experiment with a mixture of (*M*)-[D₀]-**1** and (*M*)-[7,8-D₂]-**1**, i.e. the identical enantiomers for which no stereochemical discrimination is expected. The experimental pattern (blue bars in Fig. 1b) can indeed be modeled with the parameters SE = 1.0 and EIE = 1.03 (red bars in Fig. 1b), very close to the statistical expectation (pink bars in Fig. 1b).

From a series of independent experiments with five different mixtures of [D₀]-**1** and [7,8-D₂]-**1**, average values of SE = 6.6 ± 1.2 and EIE = 0.96 ± 0.07 are obtained. While the EIE does not significantly deviate from 1, a distinct preference for the formation of the homochiral dimers is observed (Scheme 2). In analogy, an even more pronounced effect of SE = 13 ± 2 has been found for the proton-bound dimers of 1-aza[6]helicene¹⁷. From a chemical point of view, the preferential formation of the homochiral complexes can be ascribed to the lowered steric repulsion when both ligands bear the same helicity. This conclusion drawn from the electrospray measurements is in perfect agreement with previous studies of aza[6]helicene complexes with silver(I) in the solid phase²². Thus, single-crystal X-ray analysis of the silver(I) complex of racemic **1** have confirmed that homochiral coordination dimers are formed exclusively. The previous and our present results together with studies of Murguly et al.²⁹ indicate that longing of helicene enantiomers for partners of the same chirality is an important and more general feature.



SCHEME 2

Preferential formation of homochiral Ag^+ -bound dimers upon electro spray of the "artificial racemate" of *(P)*-[D_0]-**1** and *(M)*-[7,8- D_2]-**1** in the presence of silver(I) triflate

Given the availability of [7,8- D_2]-**1**, we also probed the possible stereochemical discrimination in the mixed complexes of [7,8- D_2]-**1** with (unlabeled) **2**. Unlike the above mentioned, quasi-degenerate case of the isotopologues **1** and [7,8- D_2]-**1**, the usage of the isomeric compound **2** introduces the equilibrium constant K_{eq} as an additional parameter which describes the preference of Ag^+ to bind two molecules of either **1**- or **2**-aza[6]helicene rather than **1**- and **2**-aza[6]helicene at the same time. The experimental results (Fig. 2) indicate a preferential binding of Ag^+ to 1-aza[6]helicene, **1**, with $K_{eq} = 24 \pm 8$ (Scheme 3), which is consistent with the previously determined⁵ larger proton affinity of $PA(\mathbf{1}) = 1000 \pm 4 \text{ kJ mol}^{-1}$

versus $PA(\mathbf{2}) = 992 \pm 4 \text{ kJ mol}^{-1}$ and the fact that silver(I) affinities correlate well with differences in PAs ²⁵. Due to the large preference for coordination of **1**, the sensitivity of the modeling of the isotope profile with respect to the stereochemical effect is limited. However, the best fit in Fig. 2b is obtained for $SE = 3.2$, while the results for the mixture of the (*M*)-enantiomers in Fig. 2a give a satisfactory fit for $SE = 1$.

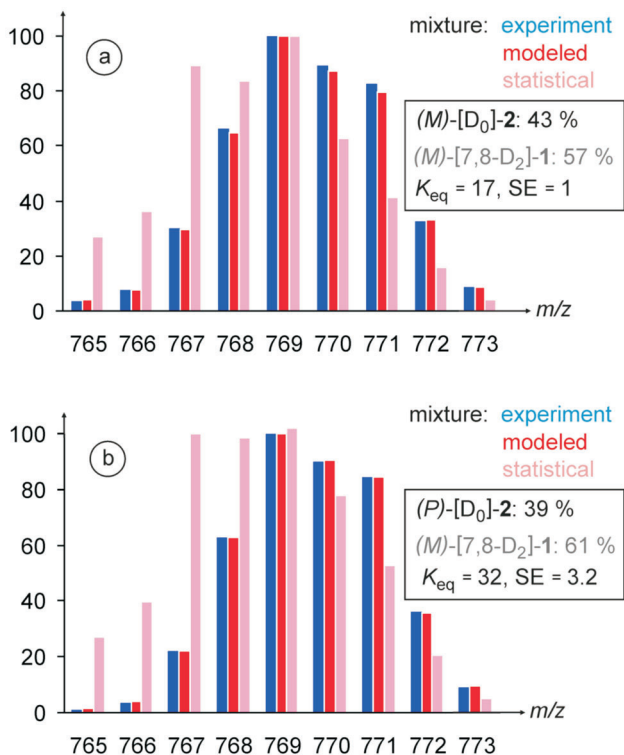
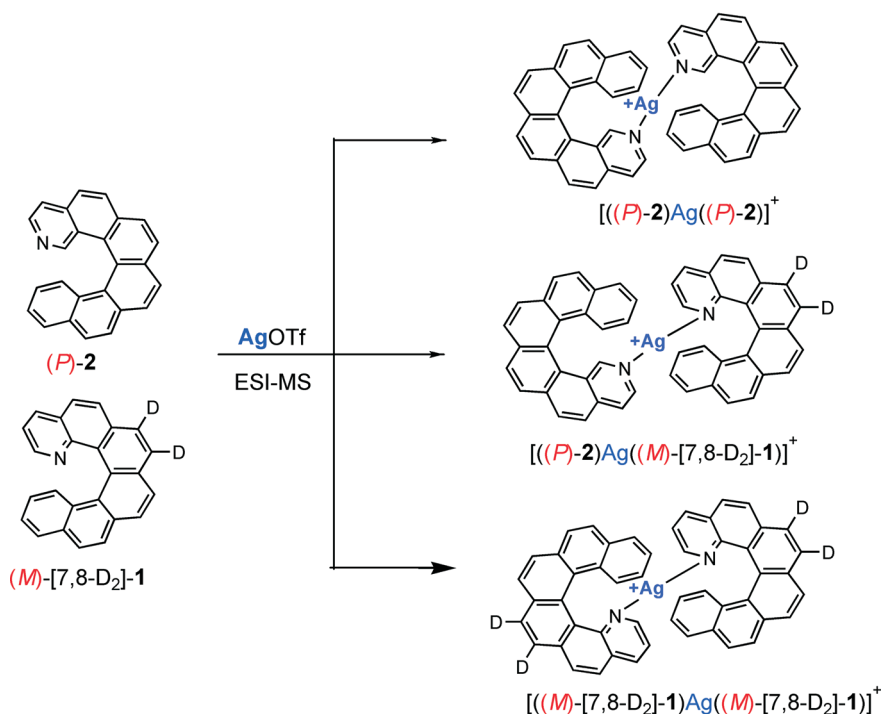


FIG. 2

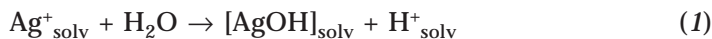
Normalized ion abundances of the mass region of the silver(I)-bound dimers of 1- and 2-aza[6]helicenes generated upon ESI of (a) ca. 1:1 mixture of a (*M*)-[D₀]-**2** and (*M*)-[7,8-D₂]-**1**, (b) (*P*)-[D₀]-**2** and (*M*)-[7,8-D₂]-**1**. Fitting of the experimental spectra of the prepared mixtures (blue bars) by linear combinations of the isotope patterns of the separate components (red bars) reveals the equilibrium constant (K_{eq}) and the stereochemical effect (SE); in order to avoid random fitting within the experimental uncertainties when using three independent parameters, the averaged value $EIE = 0.96$ is adopted from Fig. 1. For comparison, also the statistical patterns, i.e. the intensities for $K_{eq} = SE = 1$, are given (pink bars)



SCHEME 3

Preferential formation of homochiral Ag^+ -bound dimers upon electrospray of the "artificial racemate" of *(P)*-[D_0]-**2** and *(M)*-[7,8- D_2]-**1** in the presence of silver(I) triflate

However, the values derived for K_{eq} are only to be considered as lower limits, because, in contrast to the various mixtures of **1** and [7,8- D_2]-**1**, those of [7,8- D_2]-**1** and **2** show a significant change in the pattern of the protonated bases upon addition of silver(I) triflate. Specifically, the signal of $[[7,8\text{-}D_2]\text{-}1 + H]^+$ relative to $[2 + H]^+$ increases by about a factor of 2 upon addition of CF_3SO_3Ag to a solution of [7,8- D_2]-**1** and **2** in acetone. We attribute this drastic change of the relative abundance to the variation of the pH value of the solution. Thus, recombination of solvated silver(I) species, Ag^+_{solv} , with residual protons, most likely from traces of water (reaction (1)), liberates protons for which the aza[6]helicenes serve as acceptor bases **B** (reaction (2)).



As 1-aza[6]helicene, **1**, is significantly more basic than 2-azahelicene, **2** (see above), it is more likely to accept the protons liberated upon addition of silver(I) triflate to the feed solution admitted to the ESI source. Accordingly, an increase of the signal due to $[[7,8\text{-D}_2]\text{-}\mathbf{1})\text{H}]^+$ relative to that of $[(\mathbf{2})\text{H}]^+$ is observed. In the absence of $\text{CF}_3\text{SO}_3\text{Ag}$, we assume that the formation of the protonated aza[6]helicenes occurs during the electrospray process in separated droplets, such that the large dilution applied renders unlikely a competition between the basic compounds **1** and **2**. Nevertheless, discrimination of the signals for $[(\mathbf{2})\text{H}]^+$ via proton transfer (reaction (3)) may also occur in the absence of a metal salt (or any other acids added). Analysis of the isotope patterns of the protonated bases would thus lead to an underestimation of the fraction of **2** in its mixture with $[7,8\text{-D}_2]\text{-}\mathbf{1}$, and the preference for silver(I) binding 1-aza[6]helicene, **1**, as a ligand would thus even be larger.

In conclusion, this work demonstrates that aza[6]helicenes can serve as chiral nitrogen ligands for the complexation of metal ions with a clear preference for the formation of homochiral complexes upon ligation of silver(I) with two aza[6]helicene molecules. The observed stereochemical effect of $\text{SE} = 6.6 \pm 1.2$ for Ag^+ coordinating to 1-azahelicene is, however, significantly smaller than $\text{SE} = 13 \pm 2$ previously reported for the proton-bound dimers¹⁷ of 1-aza[6]helicene, **1**. This finding is consistent with the larger ionic radius of Ag^+ compared to H^+ , and thus decreased repulsion of the sterically demanding helical backbones. While 2-aza[6]helicene, **2**, can also serve as a ligand for Ag^+ , it is bound significantly more weakly than 1-aza[6]helicene, **1**, which correlates with the larger basicity of the latter compound⁵.

This work was supported by the Center for Biomolecules and Complex Molecular Systems (LC512), the Academy of Sciences of the Czech Republic (Z40550506), the European Commission (FP6-015847), and the Czech Science Foundation (203/07/1664 and 203/08/1487).

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