JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

Communication

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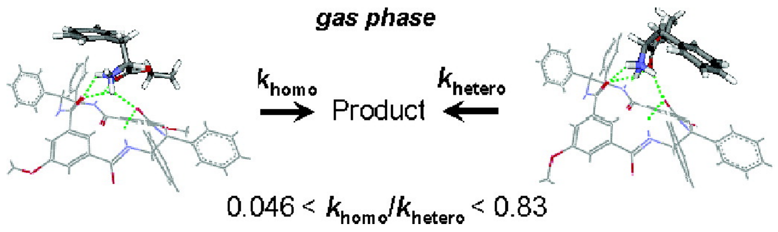
*J. Am. Chem. Soc.*, **2005**, 127 (34), 11912-11913• DOI: 10.1021/ja0533038 • Publication Date (Web): 05 August 2005



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# Exceptional Gas-Phase Enantioselectivity of Chiral Tetramide Macrocycles

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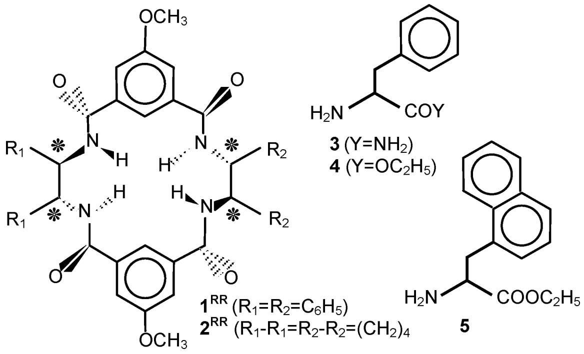
Although mass spectrometry (MS) has often been thought of as a "chirally blind" technique, it may represent a powerful tool for discriminating and even quantifying chiral species by interaction with chiral reference molecules.[1] The majority of MS-based chiral recognition experiments are based on (i) the measurement of the relative abundance of noncovalent diastereomeric adducts between a chiral reference compound and the enantiomers (one isotopically labeled) of the molecule of interest;[2,3] (ii) the determination of the relative stability of diastereomeric adducts by equilibrium measurements[4−7] or by collision-induced dissociation (CID) experiments (Cooks' kinetic method);[8−17] and (iii) the measurement of the rates of ion/molecule reactions between diastereomeric adducts and suitable chiral or achiral reactants.[4,18−27]



**1**$^{RR}$ ($R_1=R_2=C_6H_5$)
**2**$^{RR}$ ($R_1$-$R_1$=$R_2$-$R_2$=$(CH_2)_4$)
**3** (Y=NH$_2$)
**4** (Y=OC$_2$H$_5$)
**5**

This communication presents a case of exceptional enantioselectivity exhibited in the gas phase by the chiral macrocycles (M), that is, **1**$^{\mathbf{RR}}$, **1**$^{\mathbf{SS}}$, and **2**$^{\mathbf{RR}}$ (the superscripts refer to the configuration of the C* centers), toward several derivatives of phenyl- (**3** and **4**) and 1-naphthylalanine (**5**) (A). The factors determining such an exceptional enantioselectivity have been investigated by the combined application of the experimental approaches ii and iii described above, supported by molecular mechanics (MM2* force field) conformational search and docking simulations (see Supporting Information).[28]

Type ii experiments were carried out by generating in the ESI source of an ion trap MS the proton-bound three-body complexes $[M_2HA]^+$, containing two molecules of the macrocycle M and one enantiomer of A, either $A^R$ or $A^S$. The homochiral $[M^R{}_2HA^R]^+$ and the heterochiral $[M^R{}_2HA^S]^+$ complexes were then individually subjected to collision-induced dissociation (CID) using He ($10^{-5}$ Torr) as the target gas (Figure 1). According to Cooks' kinetic method, the different CID fragmentation patterns reflect the relative stability of the diastereomeric adducts $[M^RHA^R]^+$ or $[M^RHA^S]^+$ versus $[M^R{}_2H]^+$. The $[M^RHA^R]^+/[M^R{}_2H]^+$ ratio from $[M^R{}_2HA^R]^+$ is defined as $R_{homo}$, and the $[M^RHA^S]^+/[M^R{}_2H]^+$ ratio from $[M^R{}_2HA^S]^+$ is defined as $R_{hetero}$. The chiral resolution factor $R_{chiral}$ corresponds to the $R_{homo}/R_{hetero}$ ratio. The stability gap between the homochiral $[M^RHA^R]^+$ and the heterochiral $[M^RHA^S]^+$ cluster ($\Delta\Delta G_{CID} = \Delta G_{homo} - \Delta G_{hetero}$) can be expressed by $\Delta\Delta G_{CID} = -RT_{eff} \ln R_{chiral}$, where $T_{eff}$, defined as the "effective temperature", is an empirical parameter corresponding to the temperature of the canonical ensemble of clusters for which fragmentation would yield the same branching ratios as observed experimentally.

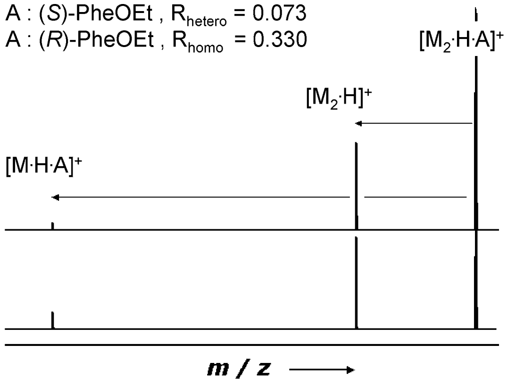


***Figure 1.*** CID spectra of diastereomeric $[M_2HA]^+$ (M = **1**$^{\mathbf{RR}}$; A = **4**$^{\mathbf{S}}$ (top); **4**$^{\mathbf{R}}$ (bottom)) complexes; $R_{chiral} = 4.52$.

Type iii experiments were carried out by introducing into a Fourier transform ion cyclotron resonance mass spectrometer (FT-ICR-MS), equipped with an electrospray ionization source (ESI), the proton-bonded two-body complexes $[MHA]^+$ and by measuring the rate of the displacement reaction 1, where B is either (*R*)-(−)- ($B^R$) or (*S*)-(+)-2-butylamine ($B^S$).

$$[MHA]^+ + B \rightarrow [MHB]^+ + A \qquad (1)$$

Rate constants $k'$ of reaction 1 were obtained from the slopes of the pseudo-first-order rate plots ($\ln(I/I_0)$ vs $t$), where $I$ is the intensity of complex $[MHA]^+$ at the delay time $t$, and $I_0$ is the sum of the intensities of $[MHA]^+$ and $[MHB]^+$. Irrespective of the configuration of B, linear rate plots are invariably observed with M/A = **1**$^{\mathbf{RR}}$/**3**$^{\mathbf{R}}$, **1**$^{\mathbf{RR}}$/**3**$^{\mathbf{S}}$, **1**$^{\mathbf{RR}}$/**4**$^{\mathbf{S}}$, **2**$^{\mathbf{RR}}$/**4**$^{\mathbf{R}}$, and **2**$^{\mathbf{RR}}$/**4**$^{\mathbf{S}}$, whereas reaction 1 follows a biexponential kinetics with M/A = **1**$^{\mathbf{RR}}$/**4**$^{\mathbf{R}}$, **1**$^{\mathbf{SS}}$/**5**$^{\mathbf{S}}$, and **1**$^{\mathbf{RR}}$/**5**$^{\mathbf{S}}$ (see Supporting Information). As pointed out in related studies,[18,21,25] biexponential reaction kinetics denote the occurrence of two noninterconverting isomeric $[MHA]^+$ structures, one less reactive ($[MHA]^+{}_{slow}$) and the other more reactive ($[MHA]^+{}_{fast}$).

Table 1 reports the relevant second-order rate constants, $k = k'/[B]$, measured in relation to the configuration of A and B, as well as the enantioselectivity factors $\rho$ and $\xi$. The $\rho$ term is defined as the ratio between the $k$ value for the reaction of a given base B with the homochiral $[M^RHA^R]^+$ complex and that for the same reaction with the heterochiral $[M^RHA^S]^+$ one. It should be noted that the $\rho$ factors, relative to the **1**$^{\mathbf{SS}}$/**5**$^{\mathbf{S}}$ and **1**$^{\mathbf{RR}}$/**5**$^{\mathbf{S}}$ pairs ($\rho$ = 0.05), represent the largest enantioselectivity ever measured in the gas phase. The $\xi$ term is defined as the ratio between the $k$ value for the reaction of a given $[M^RHA]^+$ complex with the homochiral base (i.e., (R)-(−)-2-butylamine) versus the heterochiral one (i.e.,

10.1021/ja0533038 CCC: $30.25

*Table 1.* Exchange Rate Constants ($\times 10^{-10}$ cm$^3$ molecule$^{-1}$ s$^{-1}$)

| complex $[MHA]^+$ | $(R)$-(−)-$C_4H_9NH_2$ $k^a$ | $(S)$-(+)-$C_4H_9NH_2$ $k^a$ | $\xi$ |
|---|---|---|---|
| $[\mathbf{1^{RR}}H\mathbf{3}^R]^+$ | 3.36 ± 0.07 (0.30) | 4.21 ± 0.05 (0.37) | 0.80 ± 0.02 |
| $[\mathbf{1^{RR}}H\mathbf{3^S}]^+$ | 4.04 ± 0.07 (0.36) | 4.81 ± 0.11 (0.42) | 0.84 ± 0.03 |
| | $\rho = 0.83 \pm 0.03$ | $\rho = 0.87 \pm 0.03$ | |
| $[\mathbf{1^{RR}}H\mathbf{4^R}]^+_{fast}$ | 2.63 ± 0.30 (0.24) | 2.52 ± 0.06 (0.22) | 1.04 ± 0.17 |
| $[\mathbf{1^{RR}}H\mathbf{4^R}]^+_{slow}$ | 0.40 ± 0.02 (0.04) | 0.36 ± 0.02 (0.03) | 1.11 ± 0.12 |
| $[\mathbf{1^{RR}}H\mathbf{4^S}]^+$ | 2.06 ± 0.03 (0.18) | 2.63 ± 0.03 (0.23) | 0.78 ± 0.02 |
| | $\rho_{fast} = 1.28 \pm 0.18$ | $\rho_{fast} = 0.96 \pm 0.02$ | |
| | $\rho_{slow} = 0.19 \pm 0.02$ | $\rho_{slow} = 0.14 \pm 0.01$ | |
| $[\mathbf{1^{SS}}H\mathbf{5^S}]^+_{fast}$ | 0.122 ± 0.004 (0.01) | 0.125 ± 0.007 (0.01) | 1.02 ± 0.10 |
| $[\mathbf{1^{SS}}H\mathbf{5^S}]^+_{slow}$ | 0.006 ± 0.001 (0.01) | 0.006 ± 0.001 (0.01) | 0.91 ± 0.16 |
| $[\mathbf{1^{RR}}H\mathbf{5^S}]^+_{fast}$ | 2.63 ± 0.13 (0.22) | 2.50 ± 0.25 (0.21) | 1.05 ± 0.18 |
| $[\mathbf{1^{RR}}H\mathbf{5^S}]^+_{slow}$ | 0.123 ± 0.009 (0.01) | 0.120 ± 0.006 (0.01) | 1.02 ± 0.04 |
| | $\rho_{fast} = 0.046 \pm 0.004$ | $\rho_{fast} = 0.050 \pm 0.009$ | |
| | $\rho_{slow} = 0.052 \pm 0.007$ | $\rho_{slow} = 0.048 \pm 0.009$ | |
| $[\mathbf{2^{RR}}H\mathbf{4^R}]^+$ | 1.91 ± 0.02 (0.17) | 1.93 ± 0.06 (0.17) | 0.99 ± 0.04 |
| $[\mathbf{2^{RR}}H\mathbf{4^S}]^+$ | 2.92 ± 0.03 (0.26) | 3.10 ± 0.12 (0.27) | 0.94 ± 0.05 |
| | $\rho = 0.65 \pm 0.02$ | 0.62 ± 0.05 | |

[a] The values in parentheses represent the reaction efficiency expressed as the ratio between the measured rate constants and the corresponding collision constant, $k_C$, calculated using the trajectory calculation method (Su, T.; Chesnavitch, W. J. *J. Chem. Phys.* **1982**, *76*, 5183).

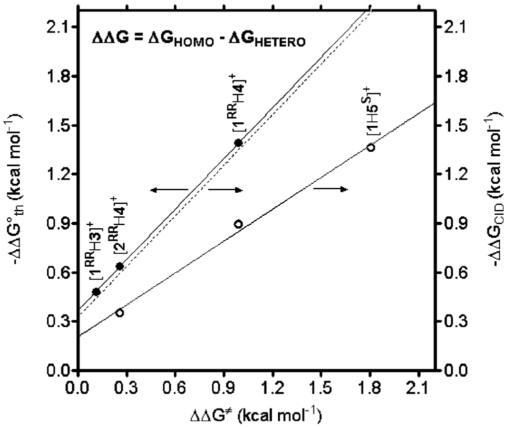


*Figure 2.* Comparative plots of $\Delta\Delta G^{\ddagger}$ versus $-\Delta\Delta G_{CID}$ and $-\Delta\Delta G°_{th}$.

(S)-(+)-2-butylamine). In all systems investigated, no significant effect of the B configuration was observed ($0.78 < \xi < 1.11$).

From the measured kinetic enantioselectivity terms $\rho$, it is possible to derive the $\Delta\Delta G^{\ddagger}$ difference of the activation barriers for the displacement reaction 1 involving the homochiral and the heterochiral clusters ($\Delta\Delta G^{\ddagger} = \Delta G^{\ddagger}_{homo} - \Delta G^{\ddagger}_{hetero} = RT\ln\rho$). The relevant values, calculated at the FT-ICR temperature of 300 K, are compared in Figure 2, with the corresponding $\Delta\Delta G_{CID}$ and with the standard Gibbs energy difference $-\Delta\Delta G°_{th} = \Delta G°_{hetero} - \Delta G°_{homo}$, computed at the MM level of theory for the global minima of the $[MHA]^+$ diastereomers (Figure 3).

The slope = 1.030 of the excellent linear correlation between $\Delta\Delta G^{\ddagger}$ and $-\Delta\Delta G°_{th}$ ($r^2 = 0.999$) points to the enantioselectivities of Table 1, as determined essentially by the different thermodynamic stability of the diastereomeric $[MHA]^+$ complexes. This conclusion is further supported by the linear correlation between $\Delta\Delta G^{\ddagger}$ and $-\Delta\Delta G_{CID}$ (slope = 0.651; $r^2 = 0.995$), which superimposes to the $\Delta\Delta G^{\ddagger}$ versus $-\Delta\Delta G°_{th}$ one if a $T_{eff} = 472$ K value is assumed for all of the CID experiments (broken line in Figure 2; slope = 1.031).

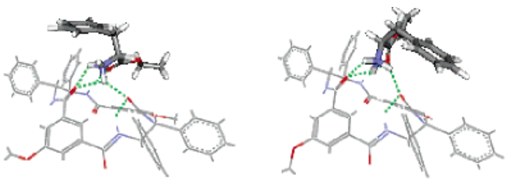


*Figure 3.* Structures corresponding to the global minima of the diastereomeric M/A = $\mathbf{1^{RR}}/\mathbf{4}$ complexes.

**Acknowledgment.** This work was supported by the Ministero dell'Istruzione dell'Università e della Ricerca (MIUR-COFIN) and the Consiglio Nazionale delle Ricerche (CNR). M.S. and A.F. express their gratitude to F. Angelelli for technical assistance.

**Supporting Information Available:** Kinetic plots. This material is available free of charge via the Internet at http://pubs.acs.org.

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JA0533038