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J. Am. Chem. Soc., **2008**, 130 (9), 2732-2733 • DOI: 10.1021/ja710687e

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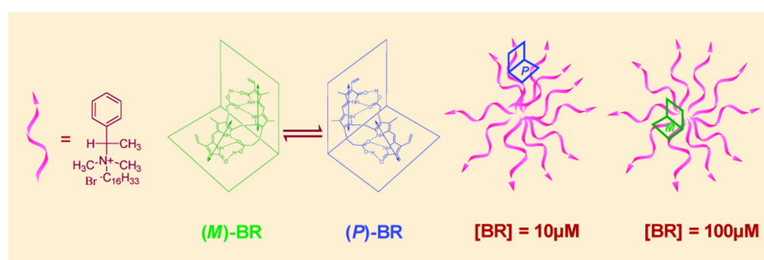

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Published on Web 02/08/2008

Concentration as the Switch for Chiral Recognition in Biomembrane Models

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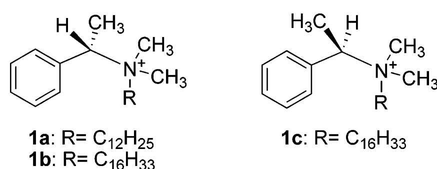
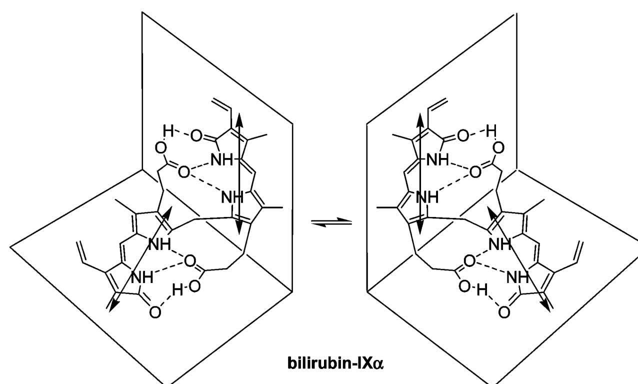
Chirality and enantiopurity of biomembrane components have a fundamental role in their organization and in their biological functions.[1] Most of the investigations on this facet of biomembranes, that are formed by hundreds of different components, have relied on models such as micelles and liposomes where chemical composition and complexity are kept under control. Some aspects of the function of chirality on self-assemblies have been evidenced and elucidated, at a certain extent.[2] It was found that the stereochemical information of chirality may influence the morphology and the stability of the aggregates[2a,b] and may govern enantiodiscrimination in the interaction of chiral self-assemblies with chiral solutes;[2c−g] however, the mechanisms of translation of the chiral information into a chiral function and its site of expression in the assembly have not been clarified yet. We have largely investigated chiral recognition in biomembrane models by using as probes of chiral recognition, the deracemization of chiral biphenylic derivatives,[2d,g−i] or the recognition of chiral dipeptides.[2f] In some cases, experimental evidence suggested a site of enantiodiscrimination in the assembly far from the stereogenic centers of the assembly components.[2f,h,i] Here we report on the investigation of the expression of chirality in micellar aggregates formed by enantiopure *N*-alkyl-*N*,*N*-dimethyl-*N*-(1-phenyl)ethyammonium bromides, **1**, that had already been used as media for diastereoselective reactions[3] and as models for investigating chirality in biomembranes.[2d]



As a probe for detecting the chirality of the aggregates, we used bilirubin-IXα, a bile pigment that assumes a dissymmetric ridge−tile structure stabilized by intramolecular hydrogen bonds and is, therefore, a racemic mixture of equilibrating enantiomers.[4] Preferential complexation of one of the enantiomers was observed by circular dichroism, CD, in the presence of chiral selectors such as albumins, chiral amines, and cyclodextrins;[5] analogously, we have found that the transfer of the stereochemical information from the chiral aggregates to the probe induces an overall imbalance in the 1:1 equilibrium ratio of bilirubin enantiomers. The extent and the direction of the observed deracemization is shown to strongly depend on the hydrophobic alkyl chain length and on concentration conditions.



The CD spectra of samples relative to bilirubin-IXa in aggregates of either 100 mM *N*-dodecyl-*N*,*N*-dimethyl-*N*-(*S*)-(1-phenyl)-ethyammonium bromide **1a** or 10 mM *N*-hexadecyl-*N*,*N*-dimethyl-*N*-(*S*)-(1-phenyl)ethyammonium bromide **1b** (cmc of **1a** and **1b** are 7.7 mM and 0.24 mM, respectively)[2d] reported in Figure 1 show a bisignate band whose intensity and sign depend on the length of alkyl chain and on bilirubin concentration.

The presence of a bisignate band in such a system, that is, in the absence, in the surfactant mojety, of a chromophore adsorbing in the same region of the spectrum as bilirubin, can be reasonably ascribed to deracemization of bilirubin.[5c,d] The spectra relative to samples of bilirubin in **1a** aggregates (Figure 1a) show bands of modest intensity independently from the concentration conditions, whereas in aggregates of **1b** (Figure 1b) the band intensity increases at certain concentrations of bilirubin and, interestingly, their sign inverts at 100 μM bilirubin.

It was reported that inversion of Cotton effect signs of bilirubin can be observed without an inversion of molecular chirality, at values of the dihedral angle between the dipyrrinone planes of bilirubin $\theta \sim 140°$, and that such a conformation features an adsorbance spectrum in which the higher energy transition of exciton splitting is more intense.[4d] Actually the adsorbance spectrum of 100 μM bilirubin in 10 mM **1b** (Figure 1b) shows transitions of exciton splitting of similar intensity. Another issue that contrasts the ascription of the inversion of Cotton effect signs to a dihedral angle of $\sim 140°$, is that those conformers of bilirubin-IXα with inverted CD curves are computed to lie much higher in energy than the global minimum.[4d]

Therefore, this last consideration and the analysis of UV−vis and CD spectra suggest an inversion of molecular chirality rather than a conformational change. The different concentration conditions, by inducing either a different organization of the aggregate or a different site of binding of bilirubin, would yield an opposite enantioselection. The process is, as expected, enantiomeric in the presence of aggregates formed by **1c** (Figure 2); furthermore, it is

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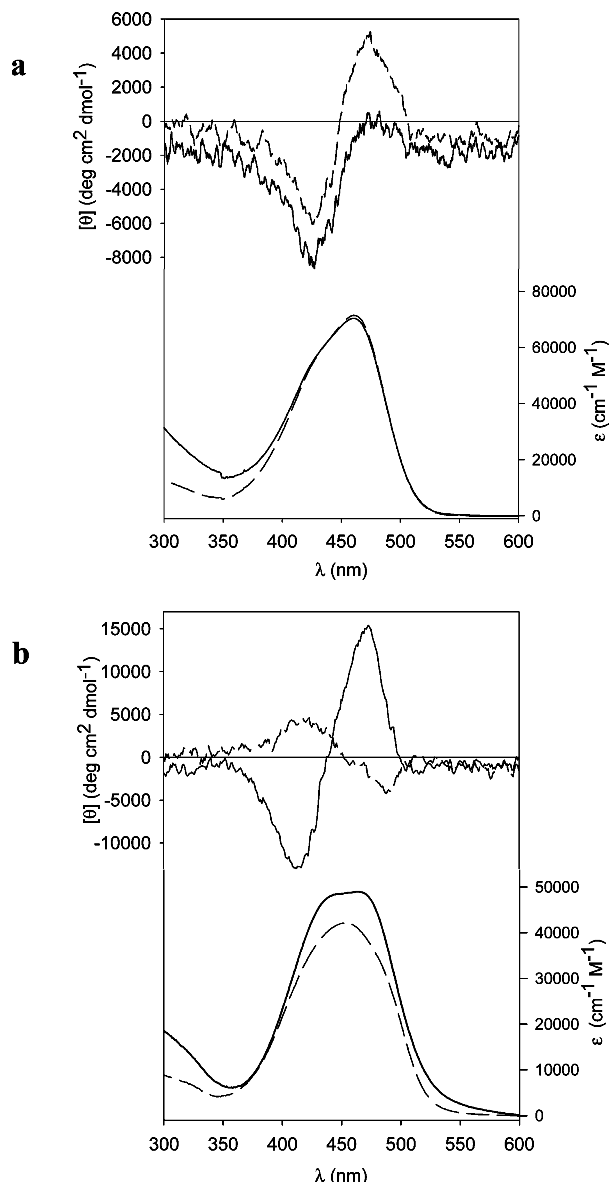

Figure 1. CD and UV spectra of bilirubin 10 μM (solid), 100 μM (dashed) in aqueous (a) 100 mM **1a**, and (b) 10 mM **1b**.

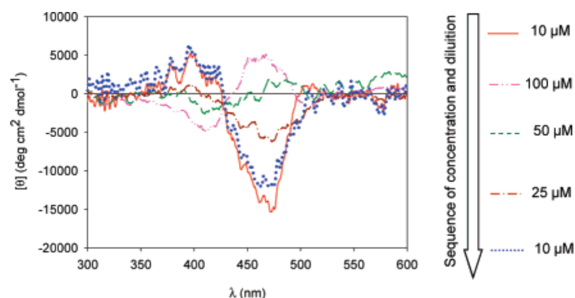

Figure 2. CD spectra of bilirubin at different concentrations in aqueous 10 mM **1c**.

reversible, because dilution of 100 μM bilirubin with aqueous 10 mM **1b** switches again the positive bisignate band into a negative one passing through a CD silent concentration.

The switch of the enantioselecting capabilities of the aggregates by modulation of the concentration conditions was not obtained in aggregates of **1a**, thus demonstrating a role of the hydrophobic portion in the enantiodiscriminating process. The aqueous solution of 10 μM bilirubin-IXα in 0.050 mM **1b**, (below the cmc and therefore in the absence of aggregates) is CD silent. This last result rules out the possibility that inversion of CD curves might be ascribed to an opposite enantioselectivity of aggregate and monomer, respectively, evidenced by the different concentration conditions. Both the role of alkyl chain length and the switch of enantiodiscrimination based on concentration conditions demonstrate that the chiral information is translated from the monomer to the aggregate through the complex sequence of recognition processes that control aggregation and organization, and that chiral recognition in self-assemblies cannot be simply ascribed to an interaction with the functional groups close to stereogenic centers as it occurs at the molecular level.

The finding of deracemization of bilirubin in biomembrane models together with the finding of modulation of recognition by concentration conditions also raises new perspectives in the study of the mechanism of bilirubin neurotoxicity, that has been ascribed to the perturbation of membrane dynamics;[6] in fact, at the best of our knowledge, the possibility that chiral recognition might play a role in bilirubin neurotoxicity has not been considered up to now.

Acknowledgment. We acknowledge financial support from CNR, Dipartimento di Progettazione Molecolare and PRIN Contract No. 2006034372.

References

(1) (a) Fadok, V. A.; de Cathelineau, A.; Daleke, D. L.; Henson, P. M.; Bratton, D. L. *J. Biol. Chem.* **2001**, *276* 1071−1077. (b) Cohen, M.; Joester, D.; Geiger, B.; Addadi, L. *Chem. Biochem.* **2004**, *5*, 1393−1399.

(2) (a) Fuhrop, J. H.; Schnieder, P.; Rosenberg, J.; Boekema, E. *J. Am. Chem. Soc.* **1987**, *109*, 3387−3390. (b) Uragami, M.; Miyake, Y.; Regen, S. L. *Langmuir* **2000**, *16*, 3491−3496. (c) Pathirana S.; Neely, W. C.; Myers, L. J.; Vodyanoy, V. *J. Am. Chem. Soc*. **1992**, *114*, 1404−1405. (d) Andreani, R.; Bombelli, C.; Borocci, S.; Lah, J.; Mancini, G.; Mencarelli, P.; Vesnaver, G.; Villani, C. *Tetrahedron: Asymmetry* **2004**, *15*, 987−994. (e) Nakagawa, H.; Onoda, M.; Masuoka, Y.; Yamada, K.-I. *Chirality* **2006**, *18*, 212−216 and references therein. (f) Bombelli, C.; Borocci, S.; Lupi, F.; Mancini, G.; Mannina, L.; Segre, A. L.; Viel, S. *J. Am. Chem. Soc.* **2004**, *126*, 13354−13362 and references therein. (g) Ceccacci, F.; Mancini, G.; Sferrazza, A.; Villani, C. *J. Am. Chem. Soc.* **2005**, *127*, 13762−13763 and references therein. (h) Ceccacci, F.; Giansanti, L.; Mancini, G; Mencarelli, P.; Sorrenti, A. *New J. Chem*. **2007**, *31*, 86−92. (i) Alzalamira, A.; Ceccacci, F.; Monti, D.; Levi Mortera, S.; Mancini, G.; Sorrenti, A.; Venanzi, M.; Villani, C. *Tetrahedron: Asymmetry* **2007**, *18*, 1868−1876.

(3) (a) Moss, R. A.; Sunshine, W. L. *J. Org. Chem.* **1974**, *39*, 1083−1088. (b) Cleij, M.; Drenth, W.; Nolte, R. J. M. *J. Org. Chem.* **1991**, *56*, 3833−3891.

(4) (a) Bonnett, R.; Davies, J. E.; Hrsthouse, M. B.; Sheldrick, G. M. *Proc. R. Soc. London, Ser. B* **1978**, *B202*, 249. (b) Trull, F. R.; Ma, J.-S.; Landen, G. L.; Lightner, D. A. *Isr. J. Chem.* **1983**, *23*, 211−218. (c) Navon, G.; Frank, S.; Kaplan, D. *J. Chem. Soc., Perkin Trans 2* **1984**, 1145−1149. (d) Pearson, R. V.; Peterson B. R.; Lightner, D. A. *J. Am. Chem. Soc.* **1994**, *116*, 42−49.

(5) (a) Blauer, G. *Isr. J. Chem*. **1983**, *23*, 201−209. (b) Lightner, D. A.; Wijekoon, W. M. D.; Zhang, M. H. *J. Biol. Chem.* **1988**, *263*, 16669−16676. (c) Lightner, D. A.; Gawromski, J. K.; Gawromska, K. *J. Am. Chem. Soc*. **1985**, *107*, 2456−24. (d) Lightner, D. A.; Gawromski, J. K.; Wijekoon, W. M. D. *J. Am. Chem. Soc.* **1987**, *109*, 6354−6362.

(6) (a) Vásquez, J.; Garcia-Calvo, M.; Valdivieso, F.; Mayor, F. F.; Mayor, F., Jr. *J. Biol. Chem.* **1988**, *263*, 1255−1264. (b) Rodrigues, C. M. P.; Solá, S.; Castro, R. E.; Laires, P.; Brites, D.; Moura, J. J. G. *J. Lipid Res.* **2002**, *43*, 885−894.

JA710687E