

Induction and reversal of chirality of heterohelicene by charge transfer interaction in aqueous SDS micelles

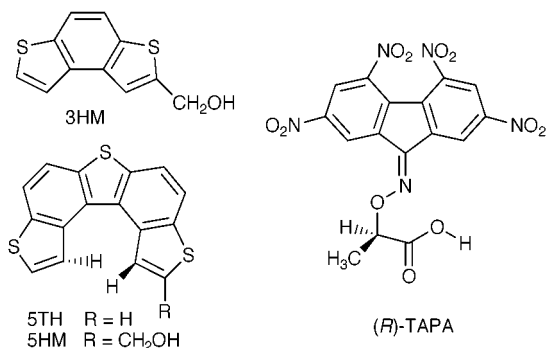
Koh-ichi Yamada,* Yuuki Kobori and Hiroko Nakagawa

Faculty of Pharmaceutical Sciences, Josai University, Sakado, Saitama 350-0295, Japan. E-mail: kyama@josai.ac.jp

Received (in Cambridge, UK) 1st November 1999, Accepted 30th November 1999

2-Hydroxymethylthieno[3,2-*e*:4,5-*e'*]di[1]benzothiophene and 2-(2,4,5,7-tetranitrofluoren-9-ylideneaminoxy)propionic acid in SDS micelles initially formed a 1:2 complex with a negative Cotton effect around 360 nm, which with time or sonication gradually changed to a 1:1 complex giving a reversed Cotton effect.

Chiral recognition occurs in artificial chiral environments such as membranes¹ and micelles² despite their intrinsically high fluidity. This is of interest because it mimics chiral recognition in biological receptors. Differences in diastereomeric interactions between each enantiomer of an incorporated racemic guest and the chiral host molecules have effected such recognition and have been sustained, so far, mainly by hydrogen bonding. Since charge-transfer (CT) interaction is one of the fundamental forces in molecular recognition by biological macromolecules,³ we investigated whether CT bonding exerts effective chiral discrimination between enantiomers in aqueous sodium dodecyl sulfate (SDS) micelles. We used 2-hydroxymethylthieno[3,2-*e*:4,5-*e'*]di[1]benzothiophene (5HM) as a



donor and 2-(2,4,5,7-tetranitrofluoren-9-ylideneaminoxy)propionic acid (TAPA) as a chiral acceptor. Although the helical shape of 5HM arises from steric repulsion between the terminal hydrogen atoms in the molecule,⁴ inversion of the helix readily occurs in solution, causing a rapid racemization at room temperature.⁵ However, the racemic 5HM is totally converted into the (*P*) enantiomer⁶ on uptake by the serum albumin of several species,⁷ and exhibits a slight (*M*) enantiomeric excess on incorporation into alkyl β-D-pyranoside micelles.⁸ Furthermore, X-ray crystallographic analysis determined that racemic 5TH was entirely converted into the (*P*) enantiomer upon crystallization to give the deep-red 1:1 CT complex with (*S*)-TAPA.⁹

Both 5HM and TAPA are practically insoluble in water. A dioxane solution of (*R*)-TAPA (120 μl, 1.0 × 10⁻² mol dm⁻³) was added to an aqueous SDS solution (2 ml, 2 × 10⁻² mol dm⁻³), which resulted in a pale yellow transparent solution. Then, a dioxane solution of 5HM (27 μl, 1.0 × 10⁻² mol dm⁻³) was dissolved in this, and a pale red colour developed due to the CT interaction between the two components. The total volume of the solution was adjusted to 3 ml by adding SDS solution, which yielded concentrations of (*R*)-TAPA (4.0 × 10⁻⁴ mol dm⁻³) and 5HM (9.0 × 10⁻⁵ mol dm⁻³) in the SDS micellar

solution (2 × 10⁻² mol dm⁻³) containing *ca.* 5% dioxane. CD measurements of this micellar solution at 20 °C gave intense absorptions in the range of 250–400 nm [Fig. 1(b), state (b)]. The wavelengths of these CD absorptions almost corresponded to those of the UV absorptions⁸ of 5HM in CHCl₃ and in SDS micelles. A CHCl₃ solution of a mixture of (*R*)-TAPA and 5HM with the same concentrations as above, despite the development of a reddish colour, demonstrated small CD absorptions which were quite similar to those of (*R*)-TAPA alone in the micelles [Fig. 1(a)]. Moreover, a lower planar homologue of 5HM, 2-hydroxymethylbenzo[1,2-*b*:4,3-*b'*]dithiophene (3HM), showed no special CD absorptions in the presence of (*R*)-TAPA in the micelles, though the colour did change to yellow. These facts lead to the following reasoning: (1) the appearance of the CD absorptions [Fig. 1(b)] is attributable to chiral 5HM being fixed to one enantiomer by the CT bonding of 5HM with chiral TAPA, and (2) the configuration of that enantiomer is determined as (*M*) by comparing the negative Cotton effect around 360 nm with the Cotton effects of 5HM incorporated in several albumins⁷ or in chiral micelles,⁸ and the CD spectrum of the 5TH-(*S*)-TAPA complex crystals in a KBr disk.⁹

On standing the micellar solution of 5HM and (*R*)-TAPA, the CD absorptions changed slowly with time. The intensity of Fig. 1(b) decreased to one fifth after 15 h at 20 °C. The decrease became faster with a rise in temperature. After *ca.* 10 h at 30 °C, the absorptions almost disappeared; instead, new absorptions began to appear in the opposite direction. Subsequently, the intensity increased very slowly over time, and finally the micellar solution became turbid after *ca.* 3 days, presumably because of the slow formation of the precipitate of the CT complex. This spontaneous alteration in the CD absorptions was accelerated by ultrasonic irradiation [Fig. 1(b)–(f)].¹⁰ Only 1 min of sonication converted the sign of the Cotton effect around 360 nm to the opposite sign [Fig. 1(c)]. By subsequent sonication, the absorption intensities were gradually enhanced so as to reach the maximum in *ca.* 15 min [Fig. 1(f), state (f)]. These changes with time imply the reversal of handedness of 5HM in the micelles, that is, an (*M*) enantiomer to a (*P*). It is noteworthy that the shape of curve (f) is not strictly symmetrical

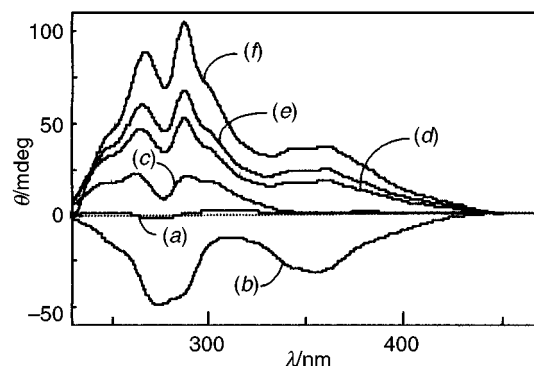


Fig. 1 Alterations in CD absorptions of 5HM-(*R*)-TAPA complex in SDS micelles: (a) (*R*)-TAPA alone, (b) immediately after the sample preparation, (c) sonication for 1, (d) 2, (e) 5 and (f) 15 min. [5HM] = 9.0 × 10⁻⁵ mol dm⁻³, [(*R*)-TAPA] = 4.0 × 10⁻⁴ mol dm⁻³, [SDS] = 2.0 × 10⁻² mol dm⁻³.

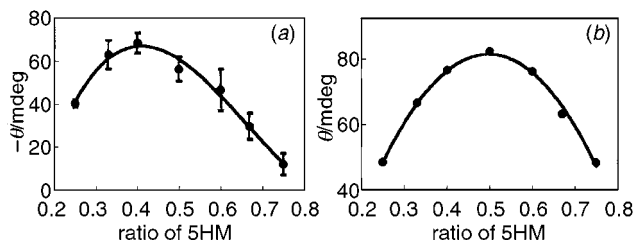


Fig. 2 Continuous variations experiments on the CD intensities at 359.2 nm: (a) for state (b) in Fig.1, (b) for state (f) in Fig.1, (the standard deviations are within the circles). $[5HM] + [(R)\text{-TAPA}] = 5.0 \times 10^{-4} \text{ mol dm}^{-3}$, $[\text{SDS}] = 2.0 \times 10^{-2} \text{ mol dm}^{-3}$.

with that of the initial curve (b), though they are similar to each other.

In order to account for this phenomenon, binding stoichiometries between 5HM and TAPA were determined for both states (b) and (f) by the methods of continuous variations¹¹ and HPLC. Fig. 2 illustrates how the CD intensities at the trough [state (b)] or the peak [state (f)] around 360 nm vary with the mole ratio of 5HM to TAPA. For state (b), the plots reveal a maximum in the vicinity of the ratio = 0.35, indicating the presence of a 1:2 complex. On the other hand, a 1:1 complex can be estimated for state (f) because the maximum is observed in the vicinity of the ratio = 0.5. These stoichiometries were substantiated by HPLC experiments. On preparing a micellar solution containing (R)-TAPA ($9 \times 10^{-4} \text{ mol dm}^{-3}$) and 5HM ($9 \times 10^{-5} \text{ mol dm}^{-3}$), the precipitation occurred immediately. The precipitate collected was extracted with CHCl_3 , the CHCl_3 solution being washed with water. The content of 5HM and TAPA in the CHCl_3 solution was determined by HPLC (silica gel column, CHCl_3 -hexane-EtOH = 15:4:1), revealing a ratio of 5HM/TAPA = 0.47. Furthermore, the micellar solution containing (R)-TAPA ($6 \times 10^{-4} \text{ mol dm}^{-3}$) and 5HM ($9 \times 10^{-5} \text{ mol dm}^{-3}$) was sonicated for ca. 15 min, giving CD absorptions similar to Fig. 1(f). After the solution was left for 3 days, the resulting precipitate was collected and treated in the same way as above. The 5HM/TAPA ratio was estimated by HPLC to be 1.02. The results provided by the HPLC experiments were in excellent agreement with those of the continuous variations method.

TAPA is a carboxylic acid that has a tendency to dimer formation. Therefore, TAPA incorporated by way of a dimeric form in the micelles can be expected to encounter 5HM and produce the 1:2 CT complex. The 1:2 complex thus formed would be gradually converted into a more stable 1:1 complex as observed in the 1:1 complex crystals of (S)-TAPA and 5TH. Accompanying such change in the composition of the complex, configurational alteration is evoked in the 5HM molecules, causing the reversal of chirality of 5HM. These phenomena can be said to result from micellar effects. With an increase of ethanol content in the solution of state (f), the CD absorptions were rapidly decreased and completely missing (Fig. 3) owing to destruction of the micellar structure. When the same experiments concerning the alternative combination, 5HM and

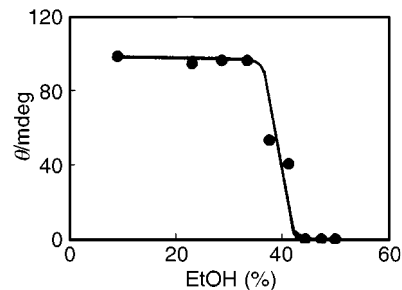


Fig. 3 Effect of an increase of EtOH content on the CD intensities at 287.0 nm for state (f) in Fig.1.

(S)-TAPA, were carried out, the same results were obtained except for the difference in the handedness of the 5HM molecules. In summary, the CT interactions have been proved to achieve effective recognition of chirality of heterohelicene in the SDS micelles. In particular, it is of interest that the initially fixed handedness of heterohelicene came to be spontaneously reversed with the composition change of the complex, although the structure of the 1:2 complex remains uncertain.

Notes and references

- 1 D. Dieudonne, A. Gericke, C. R. Flash, X. Jiang, R. S. Farid and R. Mendelsohn, *J. Am. Chem. Soc.*, 1998, **120**, 792; J. Partyka and K. Hiltrop, *Liq. Cryst.*, 1996, **20**, 611; N. Usol'tseva, K. Praefcke, D. Singer and B. Gundogan, *Liq. Cryst.*, 1994, **16**, 617; Y. Matsumoto and R. Ueoka, *Bull. Chem. Soc. Jpn.*, 1983, **56**, 3370.
- 2 P. Walde, E. Blochigner and K. Morigaki, *Langmuir*, 1999, **15**, 2346; S. Borocci, M. Erba, G. Mancini and A. Scipioni, *Langmuir*, 1998, **14**, 1960; D. Tickle, A. George, K. Jennings, P. Camilleri and A. J. Kirby, *J. Chem. Soc., Perkin Trans. 2*, 1998, 467; M. Lecouvey, C. Frochot, L. Miclo, P. Orlewski, M. Marraud, J. L. Gaillard, M. T. Cung and R. Vanderesse, *Lett. Pept. Sci.*, 1997, **4**, 359; K. Kano and T. Ishimura, *J. Chem. Soc., Perkin Trans. 2*, 1995, 1655; B. S. Jursic, *Tetrahedron Lett.*, 1993, **34**, 963.
- 3 H. Dugas, *Bioorganic Chemistry: A Chemical Approach to Enzyme Action*, 3rd edn., Springer-Verlag, New York, 1996.
- 4 H. Nakagawa, K. Yamada, H. Kawazura and H. Miyamae, *Acta Crystallogr.*, 1984, **C40**, 1039.
- 5 K. Yamada, H. Nakagawa and H. Kawazura, *Bull. Chem. Soc. Jpn.*, 1986, **59**, 2429.
- 6 The symbols (P) and (M) represent 'right-handed' and 'left-handed', respectively.
- 7 K. Yamada, R. Ishii, H. Nakagawa and H. Kawazura, *Tetrahedron: Asymmetry*, 1996, **7**, 737; K. Yamada, R. Ishii, H. Nakagawa and H. Kawazura, *Chem. Pharm. Bull.*, 1997, **45**, 936.
- 8 H. Nakagawa, K. Gomi and K. Yamada, *Enantiomer*, 1998, **3**, 175.
- 9 H. Nakagawa, K. Yamada and H. Kawazura, *J. Chem. Soc., Chem. Commun.*, 1989, 1378.
- 10 A titanium probe (Dr Hielscher GmbH, UP 50H, diameter 3 mm) sonication was carried out on samples in an ice bath at 270 W cm^{-2} .
- 11 In the continuous variations, individual components are mixed in variable ratios, but with constant total concentration. P. Job, *Ann. Chim.*, 1928, **9**, 113; J. O. Smith, D. A. Olson and A. Armitage, *J. Am. Chem. Soc.*, 1999, **121**, 2686.

Communication a908681a