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Chiral Aggregates Formed from Methylated Tetraenoic Fatty Acids: Formation of Both Antipodes of Chiral Aggregates from a Single Enantiomer and Time-Dependent Stereomutation

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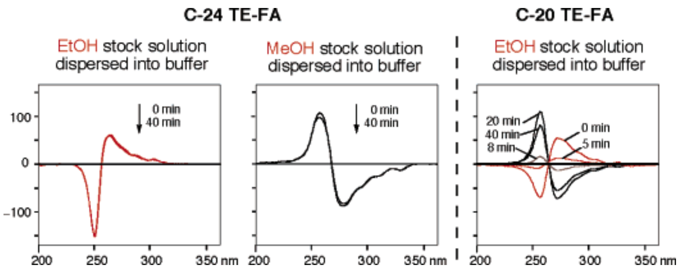
ABSTRACT



Formation and behaviors of chiral aggregates of methylated tetraenoic fatty acids (TE-FAs) were reported. In the C-24 TE-FA series, the aggregate prepared by dispersing an *ethanol* stock solution of C-24 TE-FA 1b into sodium phosphate buffer gave a strong *positive* Cotton effect, whereas the aggregate prepared from a *methanol* stock solution gave a *negative* Cotton effect. In the C-20 TE-FA series, the aggregate prepared from an ethanol stock solution of C-20 TE-FA 2b exhibited time-dependent chirality inversion.

We recently reported the aggregate-forming process of tetraenoic fatty acids (TE-FAs) and the properties of resultant aggregates.[1] The aggregate formation of C-24 TE-FA **1a** proceeds through the states of dynamic *K*-aggregate, static T^1-aggregate, and static T^2-aggregate. The step of dynamic *K*-aggregate formation is reversible, whereas the following steps, i.e., dynamic *K*-aggregate→static T^1-aggregate and static T^1-aggregate→static T^2-aggregate, are (almost) irreversible (Figure 1).[2] We suggested that these steps may be universally involved in aggregation of TE-FAs. On the balance of enthalpy and entropy, TE-FAs exhibit a unique property, depending on the FA backbone length. Among a number of TE-FAs studied, C-24 TE-FA **1a** was found to be an ideal substrate to study the static T^1-aggregate, whereas

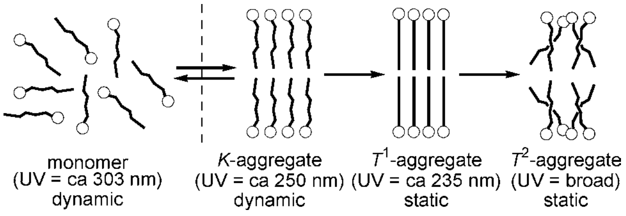


Figure 1. Schematic representation of the aggregate-forming process and the characteristics of resultant aggregates.[1,2]

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(1) Wang, Y.; Ma, J.; Cheon, H.-S.; Kishi, Y. *Angew. Chem., Int. Ed*. In press.

(2) On the basis of the doping experiment of C-24 TE-FA **1a** with saturated FAs, we suggested that the process of *K*- to T^1-aggregates was virtually irreversible. However, on the basis of the titration experiment with sMMPs/sMGPs, we noticed a tendency for the T^1-aggregate to slowly deaggregate. Interestingly, in the C-26 TE-FA series, both experiments demonstrated that the T^1-aggregate is irreversible.[1]

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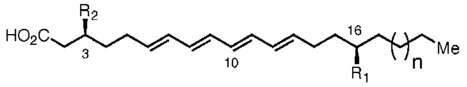
C-20 TE-FA **2a** was found to be an ideal substrate to study the dynamic *K*-aggregate. With this insight, we have noticed the possibility that TE-FAs with a chiral center incorporated in the FA backbone might form chiral aggregates. Chiral supramolecular assemblies are known for certain classes of compounds, most notably π-conjugated compounds.[3] To the best of our knowledge, however, *monomeric* fatty acids (FAs) have not been studied for chiral aggregation.[4] In this communication, we report our observations on the chiral aggregates formed from methylated TE-FAs **1b**,**c** and **2b**,**c** (Figure 2).



TE-FA C-24 Series (n=5)

1a : R_1=R_2=H; **1b** : R_1=Me, R_2=H; **1c** : R_1=H, R_2=Me

TE-FA C-20 Series (n=1)

2a : R_1=R_2=H; **2b** : R_1=Me, R_2=H; **2c** : R_1=H, R_2=Me

Figure 2. Structure of TE-FAs.

Our previous study demonstrated that TE-FA **1a** in the C-24 series forms a "static" aggregate with the stability of at least 1 day at room temperature, and therefore, we felt that a methylated TE-FA is a suitable substrate to test the possibility of forming a chiral aggregate and arbitrarily chose two TE-FAs, **1b**,**c**.[5] Thus, we synthesized TE-FAs **1b**,**c** and their antipodes. The optical purity of these substrates was confirmed to be better than 95%. The UV spectrum (Figure 3, panel **A-1**) clearly demonstrated that **1b** in aqueous solution (sodium phosphate buffer, pH = 7.0) exists as an aggregate with stability comparable to that observed for TE-FA **1a**. However, unlike TE-FA **1a**, the shape of the UV spectrum is not symmetrical, thereby suggesting that an H-aggregate is indeed formed, but it is twisted.

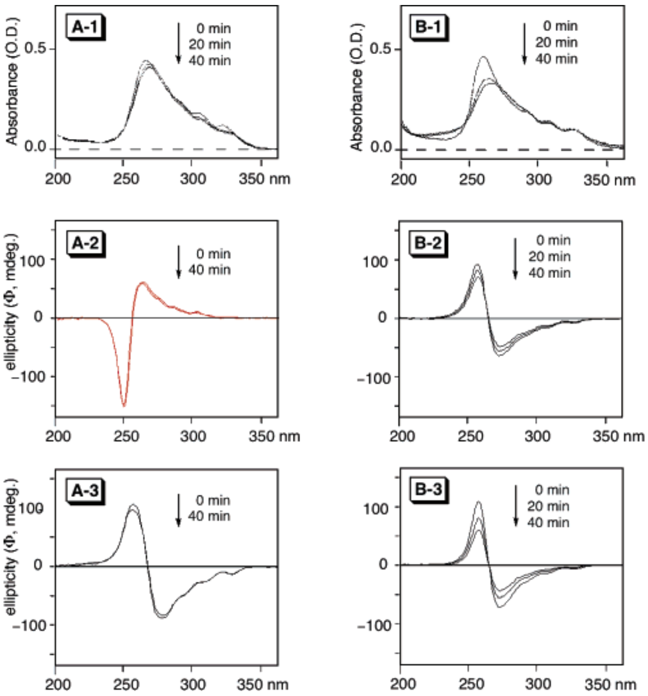


Figure 3. UV and CD spectra of the aggregates formed from **1b**,**c** in sodium phosphate buffer (pH = 7.0, 1 × 10^{-5} M) at room temperature (23 ± 2 °C). Panels **A-1** and **B-1**: UV spectra of **1b** and **1c**, respectively. Panels **A-2** and **B-2**: CD spectra of the aggregate prepared by dispersing an ethanol stock solution of **1b** and **1c** into buffer, respectively. Panels **A-3** and **B-3**: CD spectra of the aggregate prepared by dispersing a methanol stock solution of **1b** and **1c** into buffer, respectively.

Encouraged by this UV experiment, we then recorded the CD spectrum of the aggregate prepared by dispersing an *ethanol* stock solution of TE-FA **1b** into sodium phosphate buffer (pH = 7.0). To our delight, we detected a strong *positive* Cotton effect (panel **A-2**, Figure 3). The stability of the Cotton curve was found to be consistent with the aggregate stability estimated from the UV experiment. The antipode of TE-FA **1b** exhibited the mirror image of the CD spectrum shown in panel **A-2** in Figure 3.

We then observed the surprising CD behavior of the aggregate derived from TE-FA **1b**. Namely, the CD spectrum (panel **A-3**, Figure 3) of the aggregate prepared by dispersing a *methanol* stock solution of TE-FA **1b** into sodium phosphate buffer gave a *negative* Cotton effect, which has the opposite sign of the Cotton effect shown in panel **A-2**.[6] The CD behaviors of the aggregates prepared from ethanol and methanol stock solutions were found to be highly reproducible. In addition, the antipode of TE-FA **1b** exhibited the mirror images of behaviors.

Knowing that TE-FA **1a** forms a static aggregate, we assume that, once formed, the resultant aggregates remain as formed. Then why did dispersing an ethanol or methanol stock solution into sodium phosphate buffer result in the left- or right-handed chiral aggregates? We speculate that it might

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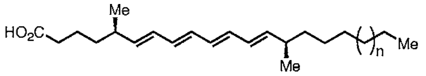
(3) For recent reviews, see: (a) Hoeben, F. J. M.; Jonkheijin, P.; Meijer, E. W.; Schenning, A. P. H. J. *Chem. Rev.* **2005**, *105*, 1491. (b) Brunsveld, L.; Folmer, B. J. B.; Meijer, E. W.; Sijbesma, R. P. *Chem. Rev.* **2001**, *101*, 4071. (c) Hill, D. J.; Mio, M. J.; Prince, R. B.; Hughes, T. S.; Moore, J. S. *Chem. Rev.* **2001**, *101*, 3893. (d) Stone, M. T.; Heemstra, J. M.; Morre, J. S. *Acc. Chem. Res.* **2006**, *39*, 11. (e) Pu, L. *Acta Polym.* **1997**, *48*, 116.

(4) Supramolecular aggregates of azobenzene phospholipids and related compounds were studied by Whitten and co-workers: Song, X.; Perlstein, J.; Whitten, D. G. *J. Am. Chem. Soc.* **1997**, *119*, 9144.

(5) In preliminary experiments, we observed that **i** and **ii** and their *anti*-diastereomers exhibited the monomer-like UV absorption, thereby suggesting that a methyl group at the adjacent carbon to the tetraene chromophore interferes with the intermolecular electronic interaction of the chromophore within a H-aggregate.



i: n=1
ii: n=3

(6) Formation of both left- and right-handed aggregates from a single enantiomer is known. See: (a) Boiadjiev, S. E.; Lightner, D. A. *J. Am. Chem. Soc.* **2000**, *122*, 378. (b) See ref 4. (c) Langeveld-Voss, B. M. W.; Christiaans, M. P. T.; Janseen, R. A. J.; Meijer, E. W. *Macromolecules* **1998**, *31*, 6702. (d) Sinkeldam, R. W.; van Houtem, M. H. C. J.; Pieterse, K.; Vekemans, J. A. J. M.; Meijer, E. W. *Chem.−Eur. J.* **2006**, *12*, 6129. (e) Bouman, M. M.; Meijer, E. W. *Adv. Mater.* **1995**, *7*, 385. (f) Satrijo, A.; Meskers, S. C. J.; Swager, T. M. *J. Am. Chem. Soc.* **2006**, *128*, 9030.

be attributed to the difference in solvent polarity between ethanol and methanol; the solution structure of **1b** in methanol and ethanol might be different, and these structural characteristics might be conserved on dispersion into sodium phosphate buffer.[7] Clearly, further work is required to shed light on the intriguing behaviors.

The UV spectrum of TE-FA **1c** was found to resemble that of TE-FA **1b**, except for one aspect: the time-course study of UV behaviors showed that the aggregate formed from TE-FA **1c** is less stable than the corresponding aggregate formed from TE-FA **1b** (panel **B-1**, Figure 3). The observed difference in stability may be attributed to the fact that the packing near the head of the TE-FA is tighter than the packing near the tail, and therefore the chiral methyl group at C-3 causes more severe disruption on aggregate formation/stability than that at C-16. The CD spectrum of TE-FA **1c** was found to resemble that of TE-FA **1b**, except for two aspects (panel **B-2**, Figure 3). First, consistent with the time-course study of the UV spectrum, the chiral aggregate in the **1c** series was found to be less stable than the chiral aggregate in the **1b** series. Second, both aggregates prepared from ethanol and methanol stock solutions gave Cotton curves with the same sign (panel **B-2** vs panel **B-3**, Figure 3).

Our previous study showed that TE-FA **2a** in the C-20 series forms a kinetic aggregate, which is stable for several hours up to overnight at room temperature. Through the doping experiment with a saturated FA and a complexation experiment with *s*MMP and *s*MGP,[1,8] we demonstrated that the aggregate in the C-20 series exhibits a vastly different property from the aggregate in the C-24 series. For example, upon addition of *s*MMP or *s*MGP, the former aggregate was deaggregated, whereas the latter aggregate was not. We refer to these properties as “dynamic” and “static”.[1,2] Thus, we anticipated that TE-FAs **2b**,**c** (methylated analogues of **2a**) exhibit properties different from those of TE-FAs **1b**,**c** (methylated analogues of **1a**). With this anticipation, we synthesized both antipodes of TE-FAs **2b**,**c** and tested their UV behaviors, thereby demonstrating: (1) that TE-FA **2b** exists as an aggregate in sodium phosphate buffer and (2) that this aggregate exhibits the stability anticipated from the aggregate behavior observed for TE-FA **2a** (panel **A-1**, Figure 4).

The aggregate prepared by dispersing a methanol stock solution of TE-FA **2b** into sodium phosphate buffer exhibited the anticipated CD behavior (panel **A-3**, Figure 4).[9] This CD behavior compares well with that observed for TE-FA **1b**, including the handedness of the resultant chiral aggregate. However, as anticipated from the UV experiment, the chiral aggregate in the **2b** series had a shorter lifetime than that in the **1b** series.

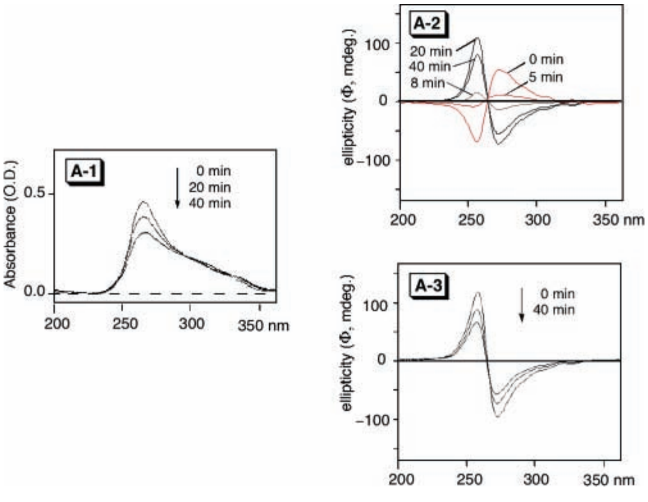


Figure 4. UV and CD spectra of the aggregates formed from **2b** in sodium phosphate buffer (pH = 7.0, 1 × 10^{-5} M) at room temperature (23 ± 2 °C). Panel **A-1**: UV spectrum of **2b**. Panel **A-2**: CD spectrum of the aggregate prepared by dispersing an ethanol stock solution of **2b** into buffer. Panel **A-3**: CD spectrum of the aggregate prepared by dispersing a methanol stock solution into buffer.

The aggregate prepared by dispersing an ethanol stock solution of TE-FA **2b** into phosphate buffer exhibited a surprising CD behavior (panel **A-2**, Figure 4). Extrapolating from the TE-FA **1b** case, we anticipated that the chiral aggregate thus prepared should give a positive Cotton effect. Indeed, the CD spectrum recorded immediately after the sample preparation did give a positive Cotton curve. However, within 10 min, the positive Cotton curve inverted to the negative Cotton curve, and its intensity reached a maximum at around 20 min and then gradually decreased.[10] The observed phenomenon is an example of so-called stereomutation. Stereomutation is known for a number of biomacromolecules[11,12] but is rarely recognized for small organic molecules.[13] It is worth noting that most of the reported examples for stereomutation are due to a change of the surrounding environments such as solvents[14−17] and temperature[16] or due to a method of sample preparation.[18,19] Perhaps, the case of helical merocyanine dye nanorods

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(7) An *i*-PrOH stock solution gave a result similar to an EtOH stock solution.

(8) *s*MMP and *s*MGP are abbreviations of synthetic 3-*O*-methylmannose- and 6-*O*-methylglucose-containing polysaccharides, respectively. Design and synthesis of *s*MMP and *s*MGP. (a) *s*MMP: Hsu, M. C.; Lee, J.; Kishi, Y. *J. Org. Chem*., submitted for publication. (b) *s*MGP: Meppen, M.; Wang, Y.; Cheon, H.-S.; Kishi, Y. *J. Org. Chem*., submitted for publication.

(9) The antipode of **2b** gave the identical CD results, but in the mirror image.

(10) The aggregate prepared from TE-FA **2c** exhibited UV and CD behaviors parallel with those observed for the aggregate prepared from TE-FA **1c**, except aggregate stability. For details, see Supporting Information.

(11) Stereomutation was observed for polypeptides. For example, see: (a) Steinberg, I. Z.; Harrington, W. F.; Berger, A.; Sela, M.; Katchalski, E. *J. Am. Chem. Soc*. **1960**, *82*, 5263. (b) Gratzer, W. B.; Rhodes, W.; Fasman, G. D.; *Biopolymers* **1963**, *1*, 319. (c) Bidan, G.; Guilerez, S.; Sorokin, V. *Adv. Mater.* **1996**, *8*, 157.

(12) Stereomutation was observed for nucleotides. For example, see: (a) Pohl, F. M.; Jovin, T. M. *J. Mol. Biol.* **1972**, *67*, 375. (b) McIntosh, L. P.; Zielinski, W. S.; Kalisch, B. W.; Pfeifer, G. P.; Sprinzl, M.; Drahovsky, D.; van de Sande, J. H.; Jovin, T. M. *Biochemistry* **1985**, *24*, 4806.

(13) For stereomutation of small organic compounds, see, for example: (a) ref 6e and (b) ref 4.

(14) Boiadjiev and Lightner observed a solvent-dependent chirality inversion for an optically active dimethylmesobilirubin-XIIIα: see ref 6a.

(15) Meijer and co-workers reported at least two cases: (a) solvent dependency of optical activity of chiral polythiophene aggregates (see ref 6c); (b) solvent dependency of chiral poly(ureidophthalimide) foldamers (see ref 6d).

reported by Würthner and co-workers[20] is closest to the current case. We should specifically note that time-dependent stereomutation, i.e., stereomutation via a metastable state, is a very rare phenomenon and that, in this context alone, the example reported here should warrant further studies.

As suggested, the aggregate formed from TE-FA **2b** is dynamic, and therefore an aggregate reorganization within the H-aggregate should be feasible in the C-20 TE-FA series. In contrary, the aggregate formed from TE-FA **1b** is static, and therefore an aggregate reorganization within the aggregate is not feasible in the C-24 TE-FA series. It is worth pointing out again that the handedness of the chiral aggregate formed from an ethanol stock solution of **1b** matches the handedness of the chiral aggregate initially observed in the **2b** series.

Structurally, we have suggested that both K- and T^1-aggregates are lamellar types in a local sense but are different in the packing mode of the FA backbone; the K-aggregate is a melted type, whereas the T^1-aggregate is a crystalline type (Figure 1).[1] A chiral methyl group introduced on the FA backbone would enforce the aggregate formation in a twisted manner, to furnish the chiral lamellar-type aggregates (Figure 5). In this context, it is worthwhile adding that bismethylated TE-FAs, i.e., $R_1 = R_2 = \mathrm{Me}$ in **1** and **2** and their *anti*-diastereomers, showed only very weak or no Cotton effect,[21] thereby suggesting that the two methyl groups are counteracting the enforcement of aggregate formation in one twisted direction.

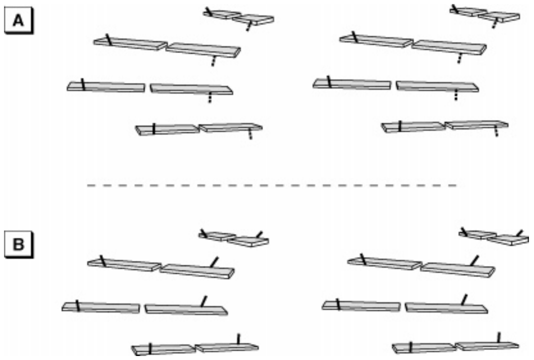

Figure 5. Stereostructure for two possible modes, **A** and **B**, of chiral lamellar-type aggregates. A shadowed plate and a solid or broken line attached to it represent a TE-FA and a chiral methyl group, respectively.

In summary, we reported the formation and properties of chiral aggregates from monomeric methylated TE-FAs for the first time. In a broad sense, these aggregates may be relevant to the supramolecular assemblies of π-conjugated and other systems.[3] Interestingly, the chiral aggregates formed from methylated TE-FAs appear to share the unique properties/behaviors with some of these supramolecular assemblies.

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

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(16) Fujiki and co-workers reported solvent and temperature effects on the chiral aggregates of poly(alkylarylsilane)s bearing remote chiral groups: Nakashima, H.; Fujiki, M.; Koe, J. R.; Motonaga, M. *J. Am. Chem. Soc.* **2001**, *123*, 1963.

(17) Swager and co-workers reported solvent dependency for transformation of a chiral poly(*p*-phenylenevinylene) derivative from solutions to films: see ref 6f.

(18) Whitten and co-workers showed the cooling rate dependency for chiral aggregate formation of azobenzene phospholipids: see ref 4.

(19) Bouman and Meijer reported the sample preparation dependency, i.e., the fast- and slow-cooled polymer films prepared from optically active regioregular polythiophenes (see ref 6e).

(20) Lohr, A.; Lysetska, M.; Würthner, F. *Angew. Chem., Int. Ed.* **2005**, *44*, 5071.

(21) For details, see Supporting Information.