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Photochromic difurylethene bisaldehyde as potential building block for [AA] and $[AB]_2$ macrocyclization

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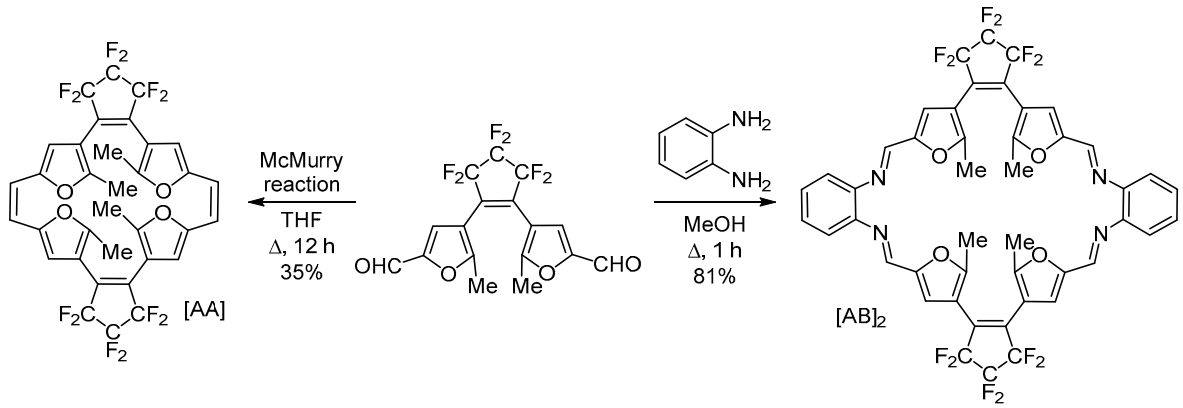


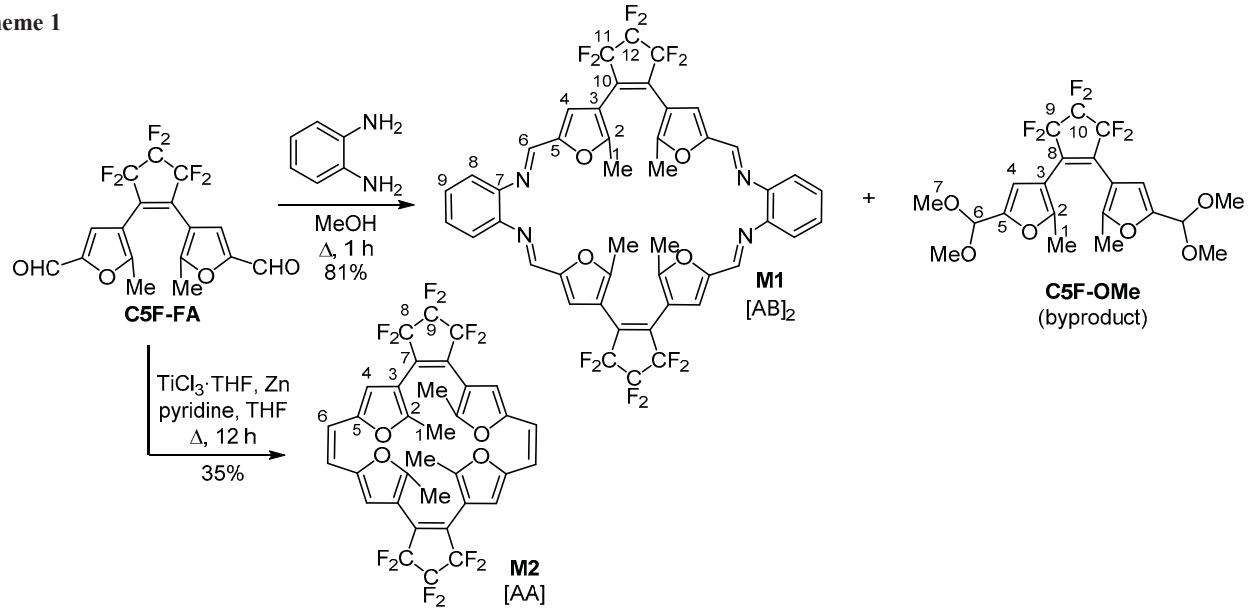
Catalyst- and template-free condensation of photochromic difurylethene bisaldehyde with *o*-phenylenediamine led to selective formation of macrocyclic Schiff base $[AB]_2$ product. Application of the same difurylethene bisaldehyde in the McMurry reaction resulted in cyclic dimer formation in moderate yield. No linear oligomers were observed in both approaches.

Keywords: difurylethene bisaldehyde, Schiff base macrocycle, McMurry reaction.

Incorporation of a stimuli-responsive unit in supramolecular structures is a promising way to address the macroscopic properties of functional materials by inducing geometrical changes on the molecular level.[1,2] Macrocycles containing photochromic azobenzenes[3] or diarylethenes[4] (DAE) established themselves to be attractive and simultaneously different scaffolds: azobenzene-based fragments exhibit remarkable length alternation (>3 Å) upon irradiation,[5] whereas DAE can be switched between planar and twisted states without significant change in linear dimension. Recent applications of DAE-based macrocycles include switchable molecular cages,[6] single molecule logic gates,[7] and dynamic reversible control of bioactive compound concentration profile in solution.[4] A straightforward one-pot synthetic approach toward DAE-based macrocycles often gives mixtures of open-chain and cyclic oligomers[8] and therefore remains a challenging task. Recently, selective high-yielding procedures for $[AB]_2$ and $[AB]_3$ cyclic organosilicon terephthalates[9] and azacrown ethers[10] were reported. Condensation reactions of aromatic dicarbonyl compounds bearing *o*-hydroxy or *o*-alkoxy group with various diamines, diamides, and carbohydrazides lead to controlled macrocyclization under metal template-free conditions if reaction conditions are carefully controlled.[11] Acid template synthesis of Schiff base macrocycles was reported to proceed selectively with moderate to high yields.[12] We were, however, interested in template-free one-pot synthesis of functional $[AB]_2$ DAE macrocycles for further application in bioimaging and ion sensing.

Previously, we investigated the influence of internal geometry in open-chain DAE molecules on their photoswitching properties.[13] Jung et al. demonstrated already the influence of the macrocycle geometry on switching efficiency of incorporated DAE units after a stepwise synthesis of formal tetrameric DAE ring.[14] Rare examples of one-step preparations of $[AB]_2$-type DAE macrocycles are represented by the guest-induced self-assembly of a bis(benzothienyl)ethylene boronic ester macrocycle[15] and by incorporation of ethene bridging units between bisthienylethene fragments.[16] Interestingly, the photoinduced

Scheme 1



switching of all DAE subunits in such macrocycles was achieved only in the flexible boronic ester,[15] whereas the rigidly connected DAE macrocycles were either nonphotochromic at all (ethene-bridged cycle[16]), or only certain DAE subunits were switchable.[14,16]

We were pleased to notice that our key photochromic scaffold, difurylethene bisaldehyde **C5F-FA**, unexpectedly exhibited a tendency to form the smallest possible $[AB]_2$ cyclic product **M1** in two-component condensation-driven macrocyclization. Catalyst- and template-free reaction of bisaldehyde **C5F-FA** with *o*-phenylenediamine in 1:1 molar ratio in refluxing MeOH resulted in the formation of Schiff base macrocycle **M1** in 67% yield together with diacetal byproduct **C5F-OMe**. Extension of the reaction time did not improve the outcome (yields remained below 70%), whereas increasing the DAE:diamine ratio to 1:1.4 improved the yield to 81%. Desired product **M1** precipitated directly upon reflux as a yellow solid and was isolated by filtration from the reaction mixture. Addition of catalytic amounts of acid (HCl or *p*-TsOH) shifted the reaction toward formation of diacetal **C5F-OMe** (up to 30% yield based on starting bisaldehyde). The structure of macrocycle **M1** was confirmed by NMR spectroscopy, mass spectrometry, and elemental analysis.

Next, we attempted to synthesize an ethylene-bridged difurylethene analog of thiophene-based[16] macrocycle. As long as synthetic route toward α,α'-dihalofuryl starting material was not available, bisaldehyde **C5F-FA** was used directly in McMurry reaction with $TiCl_3$·THF as low valent titanium source. The outcome was ethene-bridged macrocycle **M2** in 35% yield accompanied by unreacted starting material. As no other linear or cyclic oligomers were detected, we found this result as promising for further optimization of reaction conditions toward selective high-yielding synthesis of furan-based symmetric DAE macrocycles. The structure of compound **M2** was confirmed by NMR and IR spectroscopy and mass spectrometry.

In conclusion, we discovered the potential of photochromic difurylethene bisaldehyde scaffold to selectively form small macrocycles in condensation and dimerization reactions. The products derived thereof are subjects for further investigations toward photoswitching ability and solubility enhancing.

Experimental

IR spectra (ATR) were recorded on a PerkinElmer 100 Series FT-IR spectrometer. ^{1}H, ^{13}C, and ^{19}F NMR spectra (400, 100, and 376 MHz respectively) were recorded on a Bruker Avance III 400 instrument (compounds **M1**, **M2** and **C5F-OMe** (except for ^{13}C NMR spectra)). ^{13}C NMR spectra of compound **C5F-OMe** was recorded on a Bruker Avance 600 instrument (150 MHz). ^{1}H–^{13}C HSQC and ^{1}H–^{13}C HMBC experiments were performed on a Bruker Avance 400 instrument. ^{1}H NMR chemical shifts were referenced to residual protons of $CDCl_3$ (7.26 ppm for ^{1}H nuclei and 77.2 ppm for ^{13}C nuclei) or DMSO-d_6 (2.50 ppm). Assignments in ^{13}C NMR spectra were made on the basis of ^{1}H–^{13}C HSQC and ^{1}H–^{13}C HMBC experiments. Mass spectra were recorded on Agilent GCMS 7890A/5975C (EI, 70 eV) and Bruker Microflex (MALDI-TOF) instruments. High-resolution mass spectra were recorded on LTQ-Orbitrap XL (APCI, macrocycle **M2**) and Q-TOF micro (ESI, macrocycle **M1**) instruments. Elemental analysis was performed on a CHN-analyzer LECO. The fluoride content was determined by oxidative combustion ion chromatography using a Mitsubishi Chemical a1-envirotech instrument with Dionex ICS-1000 ion chromatograph. Chromatography was performed on MN Kieselgel 60 M silica gel (Macherey-Nagel, Germany).

All operations with air- and moisture-sensitive compounds were performed under N_2 atmosphere using standard Schlenk techniques. The solvents for column chromatography were purified according to standard procedures. Commercially available compounds were used without further purification. Phenylenediamine was purchased from Sigma-Aldrich. $TiCl_3$·THF was provided by MCAT GmbH.

Compound **C5F-FA** was prepared according to the literature procedure.[17] The structure confirmation of com-

pound **M1** as a Schiff base was carefully supported by spectroscopy data to avoid the misinterpretations described for similar products.[18]

Synthesis of macrocycle M1. Bisaldehyde **C5F-FA** (50 mg, 0.13 mmol) and *o*-phenylenediamine (20 mg, 0.18 mmol) were dissolved in MeOH (20 ml), and the reaction mixture was refluxed for 1 h. Yellow precipitate started to form after 15 min and was filtered off. The product was washed with Me_2CO and dried in air. Yield 48 mg (81%), yellow solid, mp >300°C (decomp., MeOH). IR spectrum, ν, cm^{-1}: 981, 1121, 1197, 1272, 1303, 1473, 1630 (C=N), 2910. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.02 (12H, s, CH_3); 7.15–7.18 (4H, m, H Ph); 7.26–7.29 (4H, m, H Ph); 7.35 (4H, s, H-4); 8.30 (4H, s, 6-CH). ^{13}C NMR spectrum (solid state, referenced to adamantane) δ, ppm: 12.9 (CH_3); 109.7; 114.6 (2C); 125.4 (2C); 133.5; 142.1; 149.1; 155.2. Signals of fluorinated carbon atoms mix with background noise. ^{19}F NMR spectrum (DMSO-d_6), δ, ppm: –109.94 ÷ –109.99 (4F, m, $C\underline{F}_2CF_2C\underline{F}_2$); –130.20 ÷ –130.25 (2F, m, $CF_2C\underline{F}_2CF_2$). Mass spectrum (EI), *m*/*z* (I_{rel}, %): 928 $[M]^+$ (100). Mass spectrum (MALDI-TOF), *m*/*z* (I_{rel}, %): 929 $[M+H]^+$ (100). Found, *m*/*z*: 929.1993 $[M+H]^+$. $C_{46}H_{29}F_{12}N_4O_4$. Calculated, *m*/*z*: 929.1991. Found, %: C 59.03; H 2.87; N 5.94; F 24.18. $C_{46}H_{28}F_{12}N_4O_4$. Calculated, %: C 59.49; H 3.04; N 6.03; F 24.55.

Synthesis of macrocycle M2. $TiCl_3$·THF (300 mg, 1.32 mmol, dissolved in 10 ml of dry THF) was added to a stirred suspension of Zn powder (130 mg, 2.00 mmol) in dry THF (30 ml), and the mixture was refluxed for 1 h. A solution of bisaldehyde **C5F-FA** (50 mg, 0.13 mmol) and pyridine (0.15 ml) in dry THF (40 ml) was added dropwise to the boiling mixture, and stirring under reflux was continued overnight. After cooling to room temperature, the reaction mixture was filtered through Celite. The volatiles were removed under reduced pressure, and the oily residue was washed with hexane–EtOAc, 10:1 mixture under ultrasonication. White precipitate of unreacted bisaldehyde was filtered off (recovering 12 mg, 0.03 mmol of starting material). The collected filtrate was concentrated under reduced pressure and quickly passed through a column filled with silica (eluent hexane–EtOAc, 20:1, then 8:1). Violet-colored fraction was collected, and the eluent was evaporated under reduced pressure providing macrocyclic product. Yield 16 mg (35%), dark-violet amorphous product. IR spectrum, ν, cm^{-1}: 821, 1007, 1138, 1275, 2922. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.35 (12H, s, CH_3); 5.66 (4H, s, 6-CH); 6.39 (4H, s, H-4). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 13.4 (CH_3); 110.7 (C-3); 111.4 (C-4); 115.1 (C-6); 133.7 (C-7, from HMBC); 151.9 (C-5); 153.26 (C-2). Signals of fluorinated carbons mix with background noise. ^{19}F NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): –109.31 (4F, t, *J* = 5.6, $C\underline{F}_2CF_2C\underline{F}_2$); –131.70 (2F, quint, *J* = 5.6, $CF_2C\underline{F}_2CF_2$). Found, *m*/*z*: 721.1234 $[M+H]^+$. $C_{34}H_{21}F_{12}O_4$. Calculated, *m*/*z*: 721.1242.

3,3'-(Perfluorocyclopent-1-ene-1,2-diyl)bis[5-(dimethoxymethyl)-2-methylfuran] (C5F-OMe) was isolated as byproduct of the above reaction as white solid. IR spectrum, ν, cm^{-1}: 944, 1100, 1278, 1290, 2901. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.94 (6H, s, $2CH_3$); 3.33 (12H, s, $4OCH_3$); 5.36 (2H, s, 6-CH); 6.45 (2H, s, H-4). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 13.5 (CH_3); 53.0 (OCH_3); 97.6 (C-6); 109.2 (C-4); 109.7 (C-3); 110.8–111.0 (m, C-10); 116.2 (tt, $^1J_{CF}$ = 259.0, $^2J_{CF}$ = 22.0, C-9); 132.4 (t, $^2J_{CF}$ = 24.0, C-8); 150.4 (C-5); 153.1 (C-2). ^{19}F NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): –110.14 (4F, t, *J* = 5.3, $C\underline{F}_2CF_2C\underline{F}_2$); –131.56 (2F, quint, *J* = 5.3, $CF_2C\underline{F}_2CF_2$). Mass spectrum (EI), *m*/*z* (I_{rel}, %): 484 $[M]^+$ (100).

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References

1. Qi, Z.; Schalley, C. A. *Acc. Chem. Res.* **2014**, *47*, 2222.
2. Merian, E. *Text. Res. J.* **1966**, *36*, 612.
3. Schweighauser, L.; Häussinger, D.; Neuburger, M.; Wegner, H. A. *Org. Biomol. Chem.* **2014**, *12*, 3371.
4. Nilsson, J. R.; O'Sullivan, M. C.; Li, S.; Anderson, H. L.; Andréasson, J. *Chem. Commun.* **2015**, *51*, 847.
5. Irie, M. *Bull. Chem. Soc. Jpn.* **2008**, *81*, 917.
6. Li, R.-J.; Holstein, J. J.; Hiller, W.; Andréasson, J.; Clever, G. H. *J. Am. Chem. Soc.* **2019**, *141*, 2097.
7. Jin, P.; Liu, M.; Cao, F.; Luo, Q. *Dyes Pigm.* **2016**, *132*, 151.
8. Alekseyev, V. V.; Saminskaya, A. G.; Yakimovich, S. I. *Chem. Heterocycl. Compd.* **2012**, *48*, 476. [*Khim. Geterotsikl. Soedin.* **2012**, 506.]
9. Basenko, S. V.; Soldatenko, A. S.; Vashchenko, O. V.; Smirnov, V. I. *Chem. Heterocycl. Compd.* **2018**, *54*, 826. [*Khim. Geterotsikl. Soedin.* **2018**, *54*, 826.]
10. Hieu, T. H.; Anh, L. T.; Soldatenkov, A. T.; Golovtsov, N. I.; Soldatova, S. A. *Chem. Heterocycl. Compd.* **2012**, *47*, 1317. [*Khim. Geterotsikl. Soedin.* **2011**, 1586.]
11. Borisova, N. E.; Reshetova, M. D.; Ustynyuk, Y. A. *Chem. Rev.* **2007**, *107*, 46.
12. Givaja, G.; Blake, A. J.; Wilson, C.; Schröder, M.; Love, J. B. *Chem. Commun.* **2003**, 2508.
13. Sysoiev, D.; Yushchenko, T.; Scheer, E.; Groth, U.; Steiner, U. E., Exner, T. E.; Huhn, T. *Chem. Commun.* **2012**, *48*, 11355.
14. Jung, I.; Choi, H.; Kim, E.; Lee, C.-H.; Kang, S. O.; Ko, J. *Tetrahedron* **2005**, *61*, 12256.
15. Iwasawa, N.; Takahagi, H.; Ono, K.; Fujii, K.; Uekusa, H. *Chem. Commun.* **2012**, *48*, 7477.
16. Yin, J.; Lin, Y.; Cao, X.; Yu, G.-A.; Liu, S. H. *Tetrahedron Lett.* **2008**, *49*, 1582.
17. Sysoiev, D.; Fedoseev, A.; Kim, Y.; Exner, T.; Boneberg, J.; Huhn, T.; Leiderer, P.; Scheer, E.; Groth, U.; Steiner, U. E. *Chem.–Eur. J.* **2011**, *17*, 6663.
18. Reyes-Gutiérrez, P. E.; Kapal, T.; Klepetářová, B.; Šaman, D.; Pohl, R.; Zawada, Z.; Kužmová, E.; Hájek, M.; Teplý, F. *Sci. Rep.* **2016**, *6*, 23499.