

5-ARYLIDENETETRONATE AS A VERSATILE ELECTROPHORE FOR PI-EXTENDED ELECTRON ACCEPTORS

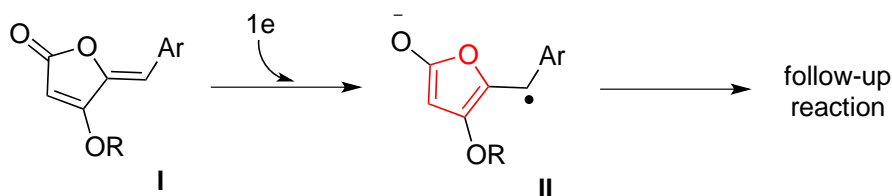
Yuki Hayashi,^{a,b} Yusuke Ishigaki,^c Jérémy Merad,^a Takanori Suzuki,^{c*} and
Maurice Médebielle^{a*}

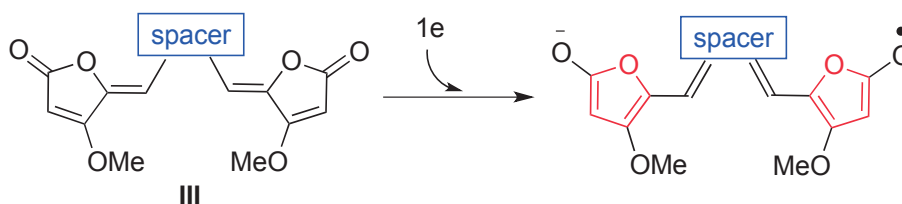
Dedicated to Prof. Dr. Yasuyuki Kita on the occasion of his 77th Birthday

^aUniv Lyon, Université Lyon 1, CNRS, INSA, CPE-Lyon, ICBMS, UMR 5246, 43 bd du 11 Novembre 1918, 69622 Villeurbanne cedex, France. ^bOn leave from Hokkaido University. ^cDepartment of Chemistry, Faculty of Science, Hokkaido University, Sapporo, Hokkaido 060-0810, Japan.

Abstract – Bis[4-methoxy-5-methylenefuran-2(5*H*)-one]-type electron acceptors with anthracene-9,10-diyl and thiophene-2,5-diyl spacer were prepared by one-pot condensation of methyl tetronate with the corresponding dialdehydes. They undergo reversible electrochemical reduction, thus showing the potential utility of 5-arylidenetetronate as an electrophore for developing novel electron acceptors.

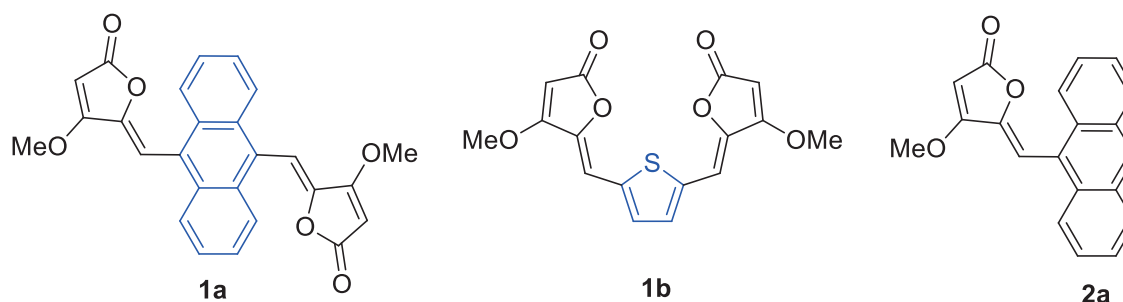
5-Ylidenetetronic acid [4-hydroxy-5-methylenefuran-2(5*H*)-one] derivatives are attracting considerable recent attention from the viewpoint of potential chemotherapeutic agents with displaying interesting biochemical activity.^{1,2} During our synthetic studies³ on a series of 5-arylidenetetronate compounds (**I**), we have got interested in the redox reaction of them since they would undergo one-electron reduction to the corresponding anion radicals (**II**), which is facilitated by formation of aromatic furan ring (Scheme 1).





Scheme 2

By combination with the molecular design that stabilizes the resulting anionic species, we envisaged that 5-arylidene-tetronate could be used as a versatile redox-active chromophore (electrophore) to develop novel electron acceptors undergoing reversible electrochemical reduction. Since the dimerization of **II** at the ylidene carbon would be the main decomposition path, we designed here the bis(tetronic) molecules (**III**), in which the charge and spin can be delocalized over the two electrophores. Pi-extended structure is also favored to stabilize the charged species, and thus a certain pi-spacer is inserted between them (Scheme 2). Here we report preparation and redox properties of bis[4-methoxy-5-methylenefuran-2(5*H*)-one]s (**1a** and **1b**), in which anthracene-9,10-diyl or thiophene-2,5-diyl is used as a spacer, respectively.



Acceptors **1a**⁴ and **1b**⁴ were prepared in respective yields of 43% and 23% through condensation of methyl tetronate with the corresponding dialdehyde by using DBU in MeCN.⁵ They were isolated as stable yellow-orange crystalline solids. As a reference, 9-anthrylmethylidene compound **2a**⁴ with only one tetronate unit was also prepared in 30% yield. Although the yields are not high, this one-pot procedure^{3b} is more convenient than the multistep protocol starting with 2-lithiated tetronate.⁶ In terms of the stereochemistry of the newly formed double bond, *Z*-configuration is assumed based on the results in the previous studies,³ in which the endocyclic oxygen atom of the furanone ring is facing to the aryl group. The configuration of the double bond in **1b** and **2a** was finally confirmed to be *Z,Z* and *Z* by the X-ray analyses (Figures 1, S1 and S2).^{7,8}

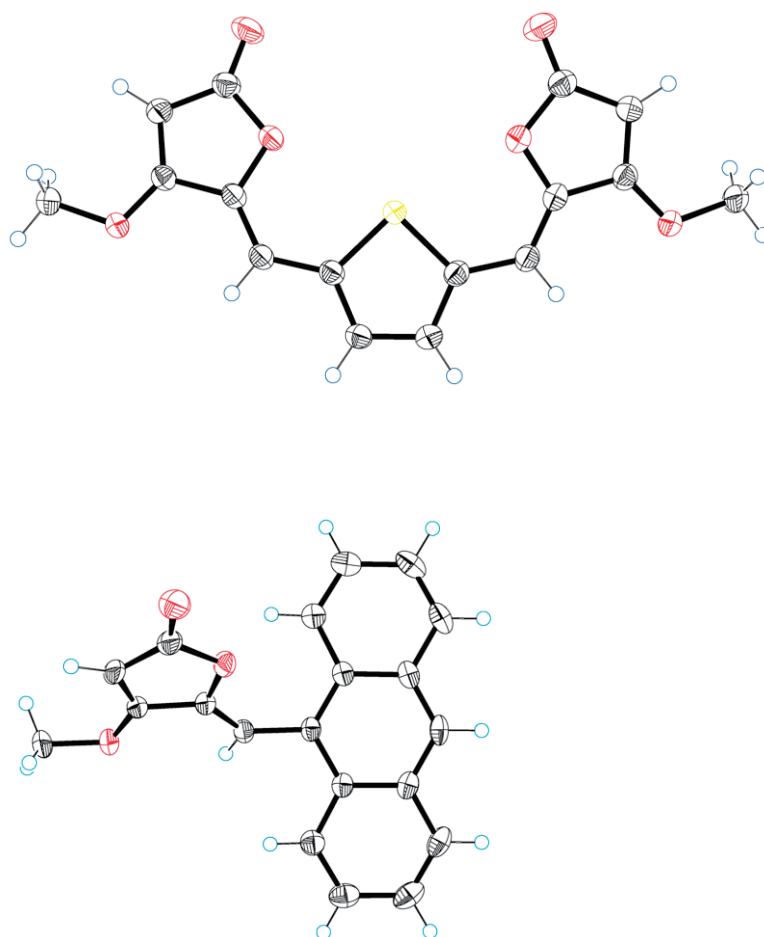


Figure 1. ORTEP drawings of **1b** (upper) and **2a** (lower) obtained by X-ray analyses at 150 K

According to the density functional theory (DFT) calculation [B3LYP/6-31G(d,p)] of the thiophenediyl derivative **1b**, *E,E*-isomer is higher in energy by about 10 kcal mol⁻¹ than *Z,Z*-isomer (Table S1).⁸ The *Z,Z*-isomer can adopt two conformations that can be interconverted by rotation of the thiophene ring. The more stable geometry is *Z,Z-anti*-form, exhibiting short C-H \cdots O contacts (2.41 Å) between H of the thiophene ring and the endocyclic O of the tetronate unit which can be assigned as weak hydrogen bonds.⁹ The *Z,Z-syn*-form was actually found in the crystal of **1b**, which is higher in energy only by 0.31 kcal mol⁻¹. Both forms would coexist in solution. The HOMO and LUMO for both of *Z,Z-anti*- and *Z,Z-syn-1b* are similar to each other (Figure S3),⁸ and coefficients are distributed over the thiophene ring as well as tetronate rings, as expected for the pi-extended acceptors. In contrast to the nearly planar geometry of **1b** in crystal, the tetronate unit and the anthracene unit cannot be located on the same plane in **2a** due to the steric repulsion. The dihedral angle of 53.3° can afford partial conjugation between the two units, which would hold true for bis(tetronate) **1a**.

By considering their low solubility in other solvents, the voltammetric studies on the newly prepared accepters were conducted in DMSO (Figure 2). The reference compound **2a** with only one tetronate unit undergoes electrochemical reduction at the peak potential of $-1.94\text{ V vs Ag/Ag}^+$. Irreversibility of this process suggests that the $\mathbf{2a}^{\bullet-}$ is unstable and undergoes some follow-up reaction(s) (Scheme 1). In contrast, bis(tetronate) **1a** undergoes reversible reduction at the peak potential of -1.73 V , and the less negative value by ca. 0.2 V comes from the interaction between two electrophores through the anthracene-9,10-diyl spacer. The peak current is twice as large as that for **2a**, showing that **1a** undergoes one-wave two-electron reduction. The similar two-electron process¹⁰ has been reported for the dichromophoric redox systems with the anthracene-9,10-diyl spacer.¹¹ The slight anodic shift of the reoxidation peak (-1.34 V) results from the non-planar twisted geometry of **1a** as well as butterfly-shaped geometry of $\mathbf{1a}^{2-}$. Such separation of redox peaks is often accompanied by the drastic geometrical change upon electron transfer in the anthracene-9,10-diyl/9,10-anthraquinodimethane skeleton¹² (Scheme 3).

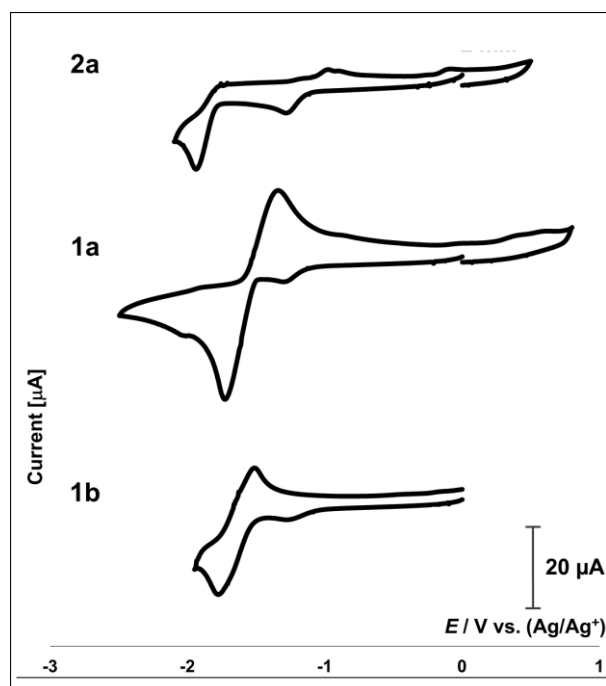
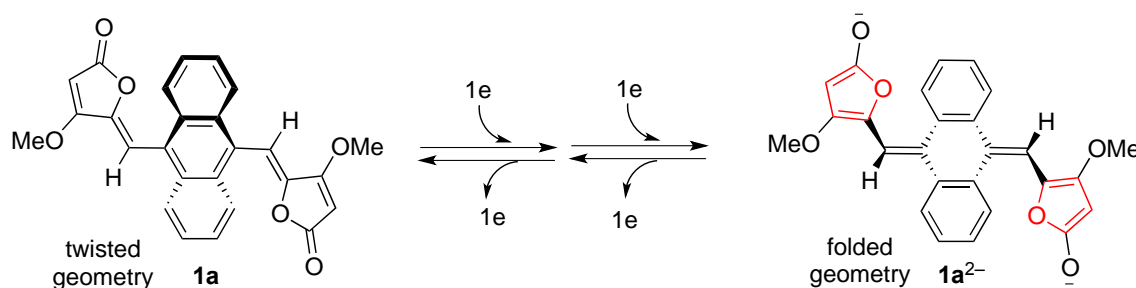
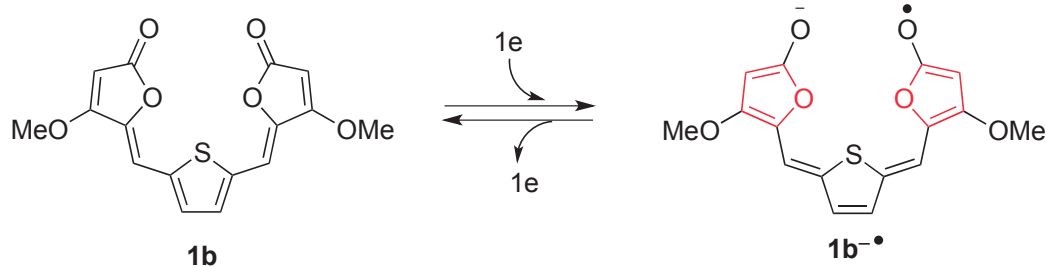


Figure 2. Cyclic voltammograms of **2a**, **1a**, and **1b** (2 mM) in DMSO containing 0.1 M Bu_4NPF_6 as a supporting electrolyte (scan rate 100 mV s^{-1} , glassy carbon electrode). The small cathodic peak around -1.3 V corresponds to the reduction process of O_2 .

On the other hand, **1b** with a thiophene spacer undergoes reversible one-electron reduction at -1.66 V . Thus, negative charge and spin can be delocalized over the two tetronate units for $\mathbf{1b}^{\bullet-}$ as shown in Scheme 4 thanks to coplanarity of the thiophene spacer and the tetronate units. Similar delocalization of charge and spin has been observed in other dichromophoric electron donors with the thiophene spacer.¹³



Scheme 3



Scheme 4

This work has revealed that methyl tetronate is a versatile electrophore to construct pi-extended electron acceptors. By connecting two units with a proper spacer such as anthracene-9,10-diyl or thiophene-2,5-diyl, the newly constructed acceptors undergo reversible electrochemical reduction. Further studies toward the molecular response systems based on bis(tetronate)s are now in progress.

ACKNOWLEDGEMENTS

Financial support by the “Programme Exploration Japon 2018” from the French Embassy in Tokyo, CNRS and Université Lyon 1 to MM is gratefully acknowledged. We thank Grant-in-Aid for Scientific Research on Innovative Areas: "Middle molecular strategy" (No. 2707) from MEXT and Grant-in-Aid from JSPS (Nos. 15H03790, 16K13968, JP19K15528) Japan. TS acknowledges The Orange Foundation for Hepatitis B Suit Hokkaido. YI acknowledges the Sasakawa Scientific Research Grant from The Japan Science Society. YH thanks MEXT through Program for Leading Graduate Schools (Hokkaido University "Ambitious Leader's Program"). This work was also supported by the Research Program of “Five-star Alliance” in “NJRC Mater. & Dev.” MEXT, and we are grateful for Prof. Takanori Fukushima at Laboratory for Chemistry and Life Science, Institute of Innovative Research, Tokyo Institute of Technology.

SUPPORTING INFORMATION

Supplementary data (X-ray, DFT calculation) associated with this article can be found, in the online version, at URL: <https://www.heterocycles.jp/newlibrary/downloads/PDFsi/26318/103/0>.

REFERENCES AND NOTES

1. R. A. Pilli and M. C. Ferreira de Oliveira, *Nat. Prod. Rep.*, 2000, **17**, 117.
2. (a) T. Sekine, F. Ikegami, N. Fukusawa, Y. Kashiwagi, T. Aizawa, Y. Fujii, N. Ruangrungsi, and I. Murakoshi, *J. Chem. Soc., Perkin Trans. 1*, 1995, 391; (b) S. Jiwajinda, N. Hirai, K. Watanabe, V. Santisopasri, N. Chuengsamarnyart, K. Koshimidzu, and H. Ohigashi, *Phytochemistry.*, 2001, **56**,

- 693; (c) F. Velázquez and H. F. Olivo, *Org. Lett.*, 2002, **4**, 3175; (d) E. Ideue, J. Shimokawa, and T. Fukuyama, *Org. Lett.*, 2015, **17**, 4964; (e) X. D. Dau, A. C. Willis, and S. G. Pyne, *Eur. J. Org. Chem.*, 2015, 7682.
3. (a) S. Iikawa, N. Chopin, G. Pilet, J.-P. Bouillon, and M. Médebielle, *Tetrahedron Lett.*, 2013, **54**, 4577; (b) N. Chopin, H. Yanai, S. Iikawa, G. Pilet, J.-P. Bouillon, and M. Médebielle, *Eur. J. Org. Chem.*, 2015, 6259.
4. Data of new compounds are as follows. **1a**: mp > 300 °C; ¹H NMR (DMSO-*d*₆): δ/ppm 8.08 (4H, dd, *J* = 6.8 Hz, 3.3 Hz), 7.60 (4H, dd, *J* = 6.8 Hz, 3.3 Hz), 7.27 (2H, s), 5.89 (2H, s), 4.15 (6H, s); ¹³C NMR (DMSO-*d*₆): δ/ppm 170.36 (2C), 168.19 (2C), 145.46 (2C), 129.21 (4C), 127.62 (2C), 126.75 (4C), 126.71 (4C), 103.91 (2C), 90.56 (2C), 60.71 (2C); HRMS (ESI⁺): Calcd for C₂₆H₁₉O₆ (M + H)⁺ 427.1176. Found 427.1175. **1b**: mp 153-160 °C (decomp.); ¹H NMR (CDCl₃): δ/ppm 7.41 (2H, s), 6.40 (2H, s), 5.29 (2H, s), 3.98 (6H, s); ¹³C NMR (CDCl₃): δ/ppm 170.36 (2C), 167.79 (2C), 141.55 (2C), 138.95 (2C), 131.58 (2C), 101.09 (2C), 88.78 (2C), 59.33 (2C); HRMS (ESI⁺): Calcd for C₁₆H₁₃O₆S (M + H)⁺ 333.0427. Found 333.0429. **2a**: mp 166-170 °C (decomp.); ¹H NMR (CDCl₃): δ/ppm 8.48 (1H, s), 8.03 (4H, m), 7.49 (4H, m), 7.16 (1H, s), 5.37 (1H, s), 4.11 (3H, s); ¹³C NMR (CDCl₃): δ/ppm 169.90 (1C), 168.12 (1C), 144.76 (1C), 131.30 (2C), 129.83 (2C), 128.84 (2C), 128.35 (1C), 126.17 (2C), 125.74 (2C), 125.32 (1C), 125.31 (2C), 104.65 (1C), 89.48 (1C), 59.45 (1C); MS (ESI⁺, relative intensity): 303 [BP, (M + H)⁺], 325 [85, (M + Na)⁺].
5. Experimental procedure: To a solution of methyl tetronate (322 mg, 2.80 mmol) and anthracene-9,10-dialdehyde (394 mg, 1.68 mmol) in MeCN (14 mL) was added DBU (0.84 mL, 5.6 mmol) under Ar atmosphere, and the mixture was heated at 65 °C for 18 h. After cooling, yellow precipitates were filtered and washed with MeCN and CHCl₃ to give pure **1a** (258 mg, y. 43%). By the similar procedure, **1b** and **2a** were also prepared, and the crude products were purified by SiO₂ column chromatography.
6. A. Pelter, R. I. H. Al-Bayati, M. T. Ayoub, W. Lewis, P. Pardasini, and R. Hansel, *J. Chem. Soc., Perkin Trans. 1*, 1987, 717.
7. Crystal data deposition numbers: **1b**, CCDC1982516; **2a**, CCDC1982517.
8. Supplementary Materials are available: Figures S1 and S2 showing details of X-ray analyses; Table S1 showing the energies and MO levels for various geometries and stereoisomers of **1b**; Figure S3 showing HOMOs and LUMOs of *Z,Z*-*anti*-**1b** and *Z,Z*-*syn*-**1b**.
9. (a) R. Taylor and O. Kennard, *Acc. Chem. Res.*, 1984, **17**, 320; (b) G. R. Desiraju and T. Steiner, In *The Weak Hydrogen Bond*, Oxford University Press, Oxford, 1999; (c) T. Steiner, *Crystallogr. Rev.*, 2003, **9**, 177; (d) C. H. Schwalbe, *Crystallogr. Rev.*, 2012, **18**, 191.

10. S. Ito, T. Iida, J. Kawakami, T. Okujima, and N. Morita, *Eur. J. Org. Chem.*, 2009, 5355.
11. (a) G. M. Chu, I. Fernández, and M. A. Sierra, *Chem. Eur. J.*, 2013, **19**, 5899; (b) Y.-P. Ou, J. Zhang, M. Xu, J. Xia, F. Hartl, J. Yin, G.-A. Yu, and S. H. Liu, *Chem. Asian J.*, 2014, **9**, 1152.
12. (a) Y. Sakano, R. Katoono, K. Fujiwara, and T. Suzuki, *Chem. Lett.*, 2014, **43**, 1143; (b) Y. Ishigaki, K. Sugawara, M. Yoshida, M. Kato, and T. Suzuki, *Bull. Chem. Soc. Jpn.*, 2019, **92**, 1211; (c) Y. Ishigaki, Y. Hayashi, and T. Suzuki, *J. Am. Chem. Soc.*, 2019, **141**, 18293; (d) Y. Ishigaki, T. Hashimoto, K. Sugawara, S. Suzuki, and T. Suzuki, *Angew. Chem. Int. Ed.*, 2020, ASAP (doi: 10.1002/anie.201916089).
13. (a) T. Suzuki, Y. Hoshiyama, K. Wada, Y. Ishigaki, Y. Miura, H. Kawai, R. Katoono, K. Fujiwara, and T. Fukushima, *Chem. Lett.*, 2013, **42**, 1004; (b) Y. Ishigaki, H. Kawai, R. Katoono, K. Fujiwara, and T. Suzuki, *Heterocycles*, 2015, **90**, 136; (c) Y. Ishigaki, H. Kawai, R. Katoono, K. Fujiwara, H. Higuchi, H. Kikuchi, and T. Suzuki, *Can. J. Chem.*, 2017, **95**, 243.