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ONE-POT SYNTHESIS OF MACROCYCLIC DIOXATETRALACTONES FROM THE SEQUENTIAL INTER- AND INTRAMOLECULAR [2+2] PHOTOCYCLOADDITION REACTIONS

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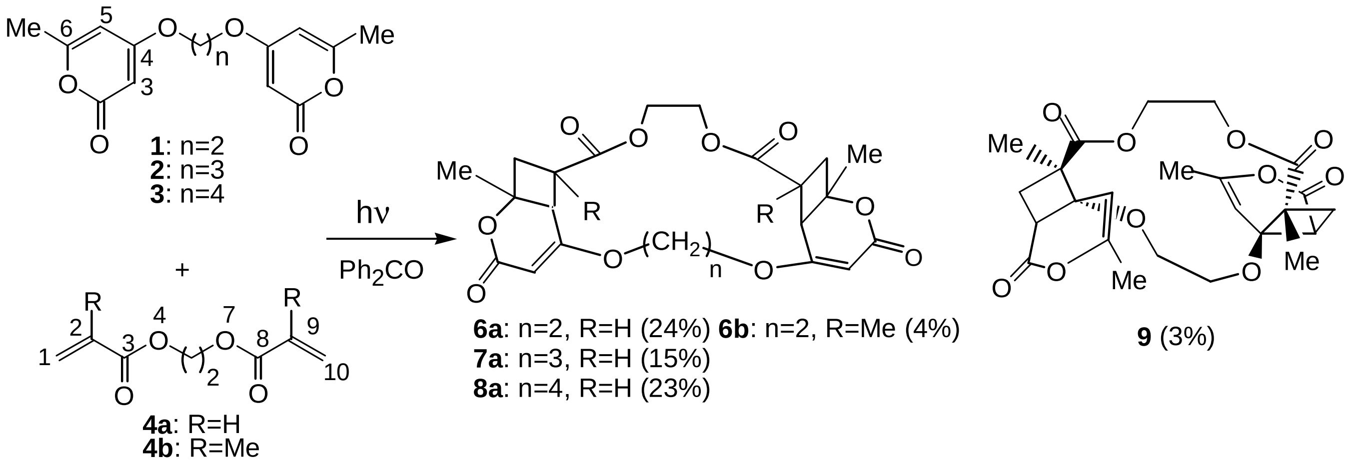
Abstract – Sensitized photocycloaddition reactions of polymethylenedioxy-di-2-pyrones (**1** - **3**) with ethylene diacrylate (**4a**) afforded macrocyclic dioxatetralactones (**6a** - **8a**) having sixteen- to eighteen-membered rings. Similar reaction of **1** with ethylene dimethacrylate (**4b**) afforded similar lactones (**6b**) and (**9**). The stereochemical features of **6a** and **7a** depending on the chain length elucidated by the X-Ray crystal analysis are figured by MOPAC conformational analysis of the reactants (**1**, **2** and **4a**).

It is well-known that the photochemical [2+2] cycloaddition reactions of conjugated enones with olefins are useful method to make cyclobutane ring system and utilized to synthesize many kinds of important compounds.[1] The intramolecular [2+2] photocycloadditions of α, ω-dienes have been known as a fruitful tool in the synthesis of a variety of macrocycles possessing one or two cyclobutane rings.[2, 3] On the other hand, the sequential inter- and intramolecular [2+2] photocycloaddition methodology has not been explored to one-pot synthesis of the macrocycles yet. The continuous double [2+2] cycloaddition reactions of bis-conjugated dienones tethered by methylene chains with α, ω-dienes can be applied to prepare a new type of macrocyclic compounds possessing two cyclobutane rings by one-pot reactions. We have already reported that the intermolecular photocycloadditions of 2-pyrones, which are composed of cyclic dienoate ring structures, with electron-poor and electron-rich olefins afforded [2+2] cycloadducts, site- and regioselectively,[4] in addition to the intramolecular [2+2] photocycloadditions of polymethylenedioxy-di-2-pyrones.[5] We report here the first example of the sequential inter- and intramolecular photocycloaddition reactions of polymethylenedioxy-di-2-pyrones (**1** - **3**) (methylene chain n=2 - 4) with α, ω-dienes to give a new type of macrocycles.

A solution of **1** (n=2) with two equivalents of ethylene diacrylate (**4a**) in dichloromethane (10 mM) was irradiated in the presence of benzophenone with a 300 W high-pressure mercury lamp using a UV cut filter under 350 nm under nitrogen atmosphere. The reaction was followed by TLC and three hours irradiation was required to fully convert all of the starting compound (**1**). After removal of the solvent, the oily residue was chromatographed by silica gel (eluent: ethyl acetate:hexane = 1:1) to give **6a** in 24% yield, which was the major product from the ^{1}H NMR spectrum of the reaction mixture, together with a complex mixture unable to isolate (Scheme 1). The amount of two equivalents of **4a** was required because of the polymerization of **4a** by irradiation. Similar photoreactions of **2** (n=3) and **3** (n=4) with **4a** afforded **7a** and **8a**[6] in 15 and 23% yields, respectively, together with intramolecular [2+2] photocycloadducts[5] of **2** and **3** (12 and 10% yields, respectively). The crystals of **6a** and **7a** suitable for the X-Ray structural analysis[7] were obtained by the recrystallization from ethyl acetate and acetonitrile, respectively. The ORTEP drawings of **6a** and **7a** (Figure 1) show sixteen- and seventeen-membered ring structures possessing two cyclobutane rings fused at the C5-C6 double bonds of the 2-pyrone rings. Compounds (**6a**) and (**7a**) having C_2 symmetry and C_s symmetry, respectively, were assigned as 2, 15-dimethyl-3, 7, 10, 19, 22-hexaoxapentacyclo[$22.1^{2,24}.\ 1^{15,7}.0.\ 0^{1,6}.\ 0^{11,16}$]hexacosa-5, 11-diene-4, 13, 18, 23-tetraone and 2, 16-dimethyl-3, 7, 11, 15, 20, 23-hexaoxapentacyclo[$23.\ 1^{2,26}.\ 1^{16,18}.0.\ 0^{1,6}.\ 0^{12,17}$]pentacosa-5, 12-diene-4, 14, 19,



Scheme 1

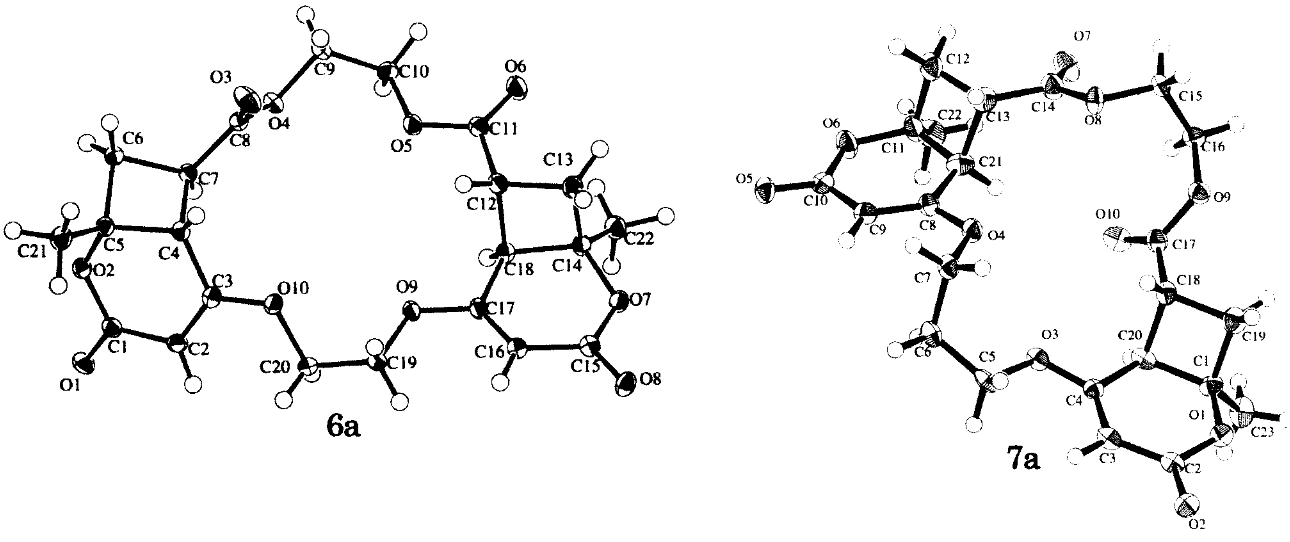
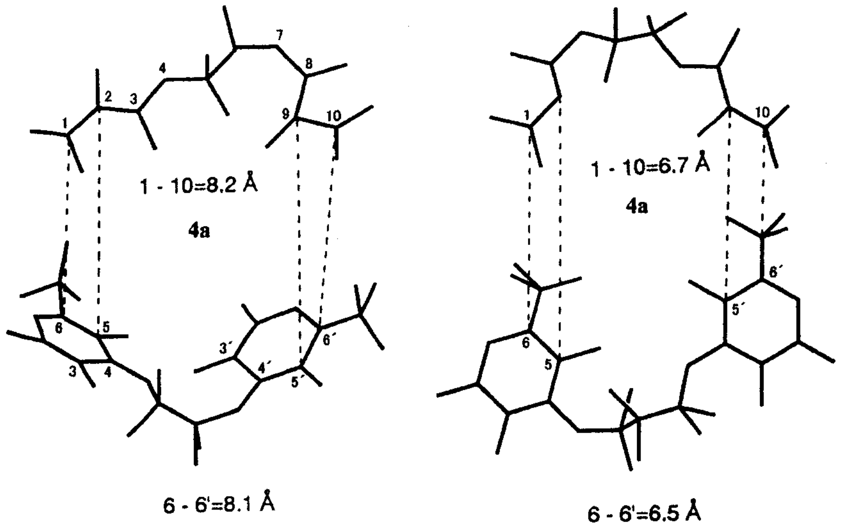


Figure 1. ORTEP drawings of **6a** and **7a**

24-tetraone, respectively. Similar photoreactions of **1** with ethylene dimethacrylate (**4b**) gave **6b** (4% yield) and **9**[8] (3% yield). The structure of **9** was determined by X-Ray structure analysis[9] as being another type of cycloadduct at the C3-C4 double bonds of the 2-pyrone rings.

The formation of **6a** - **8a** is considered *via* excited triplet states of di-2-pyrones similar to the case of 2-pyrones with electron-poor olefins,[4] through the stepwise two different [2+2] cycloadditions. Since the photoreaction of **1** with **4b** gave **9** (3,4-adduct) in addition to **6b** (5, 6-adduct) in poor yields, the lower yield of **6b** and the formation of **9** are inferred to be caused by the decrease of the electron-poor nature of the olefin parts compared to **4a**. The stereochemical difference of the cyclobutane rings of the products (**6a**) and (**7a**) was estimated from the conformational analysis of **1**, **2** and **4a** using MOPAC AM1 method.[10] The most stable conformational structure of **1** was calculated to have perpendicular relation between the 2-pyrone rings (Figure 2). The distances of the two reaction points, C6-C6' and C1-C10, were also calculated as almost the same values (*ca.* 8 Å). From these results it is reasonable to consider that the cycloaddition reaction of **1** with **4a** occurred predominantly at each different plane of the 2-pyrone rings to give a C_2-symmetry macrocycle (**6a**). On the other hand, the reaction of **2** having coplanar 2-pyrone rings calculated by the same method with **4a** occurred at the same planes of the 2-pyrone rings with almost the same distances of the two reaction points (*ca.* 6.5 Å) to give a C_s-symmetry macrocycle (**7a**).

The sequential inter- and intramolecular [2+2] cycloaddition reactions of di-2-pyrones with α, ω-dienes are found to be useful for the synthesis of macrocyclic compounds possessing two cyclobutane rings which make the macrocycles moderately rigid. These molecules may be expected as host compounds in metal cation or ammonium cation recognition.



1 **2**

Figure 2 The most stable conformational structures of 1 and 2, and metastable conformational structures of 4a

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6. All the new compounds gave the correct analytical and MS data. Selected spectral data are given below. **6a**: mp 251-253 °C (ethyl acetate: hexane=1:1); ^{1}H NMR ($CDCl_3$) δ 1.58 (6H, s), 2.45 (2H, ddd, J=12.8, 6.8, 1.6 Hz), 2.71 (2H, dd, J=12.8, 9.6 Hz), 3.20 (4H, m), 4.10 (2H, dd, J=17.3, 6.9 Hz), 4.17 (4H, m), 4.20 (2H, dd, J=17.3, 6.9 Hz), 5.21 (2H, s); ^{13}C NMR ($CDCl_3$) δ 26.3, 38.1, 39.2, 42.7, 62.6, 65.9, 78.7, 90.5, 164.8, 169.4, 172.6. IR (KBr) 1710, 1740 cm^{-1}. **7a**: mp 134-136 °C (ethyl acetate: hexane=1:1); ^{1}H NMR ($CDCl_3$) δ 1.61 (6H, s), 2.17 (2H, m), 2.48 (2H, m), 2.70 (2H, m), 3.1-3.2 (4H, m), 4.0-4.2 (6H, m), 4.81 (2H, dd, J=12.4, 6.0 Hz), 5.19 (2H, s). IR (KBr) 1735 (broad) cm^{-1}. **8a**: mp 187-190 °C (ethyl acetate: hexane=1:1); ^{1}H NMR ($CDCl_3$) δ 1.63 (6H, s), 1.86 (4H, m), 2.52 (2H, m), 2.70 (2H, m), 3.13 (4H, m), 3.95 (4H, s), 4.31

(2H, m), 4.45 (2H, m), 5.20 (2H, s). IR (KBr) 1710, 1740 cm^{-1}.

7. X-Ray crystal data for **6a** ($C_{22}H_{24}O_{10}$); T=93 K, Mo-Kα (Rigaku RAXSIS-RAPID imaging plate diffractometer, λ=0.71069 Å), crystal dimensions 0.40 x 0.15 x 0.40 mm^3 (colorless plate), a=14.2227 (7), b=15.1686 (8), c=10.4154 (4) Å, β= 110.716 (2)°, monoclinic, space group P2_1/n (#14), Z=4, $\mu_{MoK\alpha}$=1.13 cm^{-1}, Mr=448.43, V=2101.7 (2) Å^3, anode power 50 KV x 32 mA, ρ_{calc}=1.417 g/cm^3, 2θ_{max}=55.0°, F (000)=944.00. 19545 reflections measured, 3983 observed (I > 2σ (I)), number of parameters 386. The structure was solved by direct method and was refined on SIR.[11] Data were corrected for Lorentz polarizations. The data/parameter ratio was 10.32. R=0.070, R_w=0.219, GOF=1.12, max/min residual density +0.56/- 0.39 eÅ^{-3}. **7a** ($C_{23}H_{24}O_{10}$: CH_3CN); T=93 K, crystal dimensions 0.20 x 0.10 x 0.10 mm^3 (colorless plate), a=16.545 (2), b=6.3672 (6), c=23.307 (3) Å, β=92.613 (3) °, monoclinic, space group P2_1/n (#14), Z=4, $\mu_{MoK\alpha}$=1.06 cm^{-1}, Mr=503.50, V=2452.7 (4) Å^3, ρ_{calc}=1.363 g/cm^3, F (000)=1064.00. 14730 reflections measured, 1500 observed (I > 2σ (I)), number of parameters 325. The data/parameter ratio was 4.62. R=0.078, R_w=0.257, GOF=0.76, max/min residual density +0.60/- 0.58 eÅ^{-3}. All calculations were performed using the teXsan crystallographic software package of Molecular Structure Corporation.

8. **6b**: mp 210-212 ℃ (ethyl acetate: hexane=10:1); ^{1}H NMR ($CDCl_3$) δ 1.32, 1.54 (each 6H, s), 2.33 (2H, d, J=12.0 Hz), 2.59 (2H, d, J=12.0 Hz), 3.57 (2H, s), 4.07 (2H, m), 4.09 (2H, m), 4.20 (2H, d, J=7.6 Hz), 4.82 (2H, d, J=10.4 Hz), 5.32 (2H, s). IR (KBr) 1700, 1720 cm^{-1}. **9**: mp 245-247 ℃; ^{1}H NMR ($CDCl_3$) δ 1.50, 2.00 (each 6H, s), 2.04 (2H, dd, J=12.0, 9.6 Hz), 2.38 (2H, dd, J=12.0, 9.6 Hz), 3.18 (2H, t, J=9.6 Hz), 3.41 (2H, m), 4.15 (2H, d, J=9.2 Hz), 4.55 (2H, d, J=9.2 Hz), 5.02 (2H, s). IR (KBr) 1730, 1760 cm^{-1}.

9. X-Ray crystal data for **9** ($C_{24}H_{28}O_{10}$); T=123 K, crystal dimensions 0.10 x 0.10 x 0.10 mm^3 (colorless block), a=26.164 (3), b=9.598 (1), c=18.839 (2) Å, β=98.742 (4)°, monoclinic, space group C2/c (#15), Z=8, $\mu_{MoK\alpha}$=1.06 cm^{-1}, Mr=476.48, V=4675 (1) Å^3, ρ_{calc}=1.354 g/cm^3, F (000) =2016.00. 15752 reflections measured, 2541 observed (2σ < 54.97°), number of parameters 326. The data/parameter ratio was 7.79. R=0.087, R_w=0.275, GOF=0.98, max/min residual density +0.57/- 0.37 eÅ^{-3}.

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