Unexpected Formation of Novel [4.3.3]Propellane-type Trilactone by Dehydration of Aliphatic Tetracarboxylic Acid

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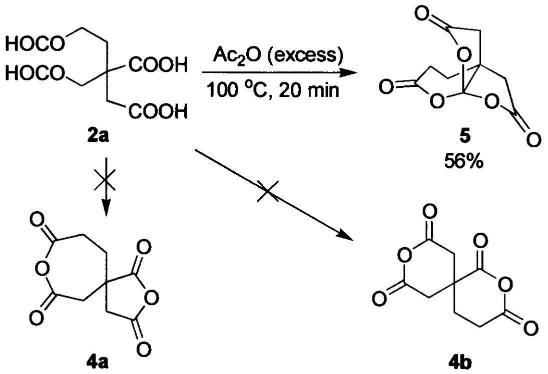
Dehydration of 3-carboxy-3-(carboxymethyl)hexanedioic acid with excess acetic anhydride resulted in the formation of a novel propellane-type trilactone (orthoester), 2,9,10-trioxa[4.3.3]propellane-3,8,11-trione. This is the first one-step synthesis of a propellane from an acyclic compound.

Itaconic anhydride (**1**) has a unique structure with the potential of utilization in various chemical conversions. Nevertheless, there were few reports on highly-sophisticated utilization because of the lability of **1** towards isomerization to citraconic anhydride.[1] On the other hand, polybasic carboxylic acids and their derivatives having a quaternary or a spiro carbon atom have attracted much attention as building blocks for chiral compounds[2] and for dendrimers.[3] Therefore, we have developed a practical synthesis of such compounds from the commercially available **1**[4,5] and have utilized them as building blocks for strictly alternating copolyimides.[6]

In previous papers, we have reported the syntheses of 3-carboxy-3-(carboxymethyl)hexanedioic acid (**2a**)[4] and 3-carboxy-3-(carboxymethyl)pentanedioic acid (**2b**).[5] The tetracarboxylic acid **2a** potentially gives five-, six-, and/or seven-membered anhydride(s) by dehydration. Nevertheless, the dehydration of **2a** using an equimolar amount of acetic anhydride gave only a five-membered anhydride-di(carboxylic acid) **3**.[4] On the other hand, the dehydration of tetracarboxylic acid **2b** using excess acetic anhydride gave only a spirocyclic dianhydride with five- and six-membered rings.[5] These results prompted us to examine the further dehydration of **2a** or **3**. Interestingly, the dehydration of **2a** or **3** with excess acetic anhydride did not afford any spirocyclic dianhydrides (with either five- and seven-membered rings, **4a**, or two different six-membered rings, **4b**) but resulted in the formation of [4.3.3]propellane-type trilactone **5** (Scheme 1). Here, we wish to present this unexpected outcome of the dehydration of tetracarboxylic acid **2a** and the reactivity of the resulting trilactone **5**.



Scheme 1.

The tetracarboxylic acid **2a** was treated in an excess amount of acetic anhydride at 100 °C for 20 min to give a white solid (94% as a crude product, 56% after purification) (Scheme 1).[7] The molecular formula of the resulting product was determined to be $C_9H_8O_6$ by mass spectroscopy and elemental analysis, indicating that this compound was a two molecular dehydration product of **2a**. From the spectral data (IR, ^{1}H NMR and 2D NMR) and the reactivity (*vide infra*) of this product, it was initially thought that one of the expected dianhydrides **4b** had formed. However, in the ^{13}C NMR spectrum of this product, one of the peaks appeared at 124.3 ppm. This peak was inexplicable as a carbon in the dianhydride **4b**. This situation prompted us to investigate further the structure of the product. X-Ray crystallography was performed on the product to establish it as the unexpected propellane-type trilactone, 2,9,10-trioxa[4.3.3]propellane-3,8,11-trione (**5**), which is also a tricyclic orthoester. The ORTEP drawing of **5** is shown in Figure 1.[8]

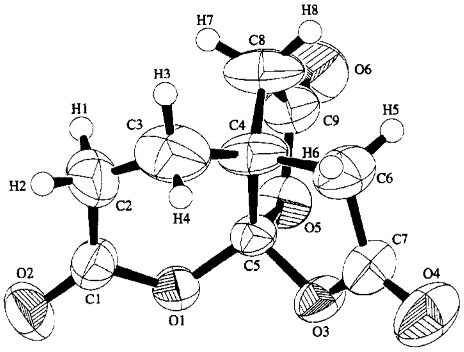
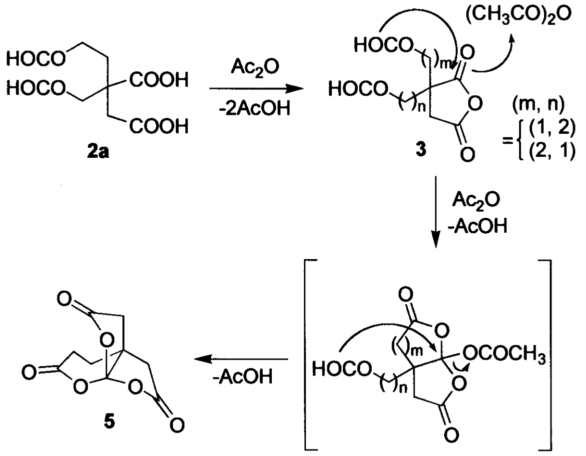


Figure 1. Molecular structure of **5**. Selected bond lengths (Å) and angles (°): C(4)-C(5) 1.536(7), O(1)-C(5) 1.383(6), O(3)-C(5) 1.413(6), O(5)-C(5) 1.414(6), O(1)-C(1) 1.353(7), O(3)-C(7) 1.377(7), O(5)-C(9) 1.366(7), O(2)-C(1) 1.196(7), O(4)-C(7) 1.175(8), O(6)-C(9) 1.177(8), O(1)-C(5)-O(3) 104.8(3), O(1)-C(5)-O(5) 106.9(4), O(3)-C(5)-O(5) 106.8(4), C(3)-C(4)-C(6) 108.7(6), C(3)-C(4)-C(8) 116.3(5), C(6)-C(4)-C(8) 112.2(6).

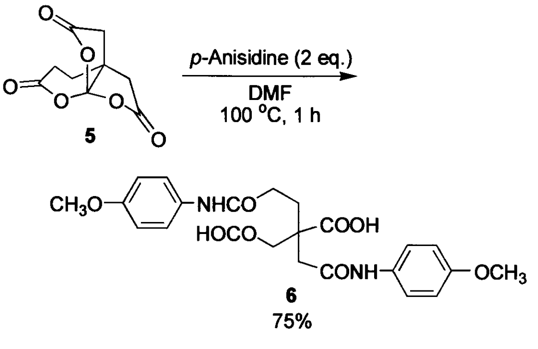
The trilactone **5** naturally fulfills all the above analytical results including the ^{13}C NMR spectrum.[7] In the IR spectrum, the two peaks at 1771 and 1805 cm^{-1} are assignable to the C=O stretching bands of δ- and γ-lactones, respectively. In the ^{13}C NMR spectrum, the peak at 124.3 ppm is interpreted due to the bridgehead carbon linked to three oxygen atoms.

Scheme 2 depicts a possible mechanism for the formation of the propellane-type trilactone **5**. The trilactone **5** is formed via the five-membered anhydride-di(carboxylic acid) **3** from tetracarboxylic acid **2a**. This was established by the experimental facts that the dehydration of **2a** in a short time (10 min) gave a mixture of **3** (67%) and **5** (21%), and that the heating of **3** in acetic anhydride at 100 °C for 20 min gave **5**. First, a five-membered anhydride ring is formed by the intramolecular dehydration of **2a** to give **3**. Then, the successive nucleophilic attacks of two remaining carboxyl groups in **3**, first to the carbonyl carbon adjacent to a quaternary carbon atom and then to the orthoester carbon, take place to give **5**. Although this mechanism (**3**→**5**) seems to be similar to that of spirodilactone from 4-oxopimelic acid,[9] it is noteworthy that the anhydride carbonyl carbon of **3** undergoes such an intramolecular dehydration.



Scheme 2.

The reactivity of the propellane-type trilactone **5** was investigated. Hydrolysis of **5** in water under reflux for 1 h gave the original tetracarboxylic acid **2a**. The reaction with two-fold molar amounts of *p*-anisidine in DMF at 100 °C for 1 h gave a single diamide-di(carboxylic acid), 2-(*N*-(*p*-methoxyphenyl)-carbamoylethyl)-2-(*N*-(*p*-methoxyphenyl)carbamoylmethyl)-butanedioic acid (**6**) (Scheme 3).[10] It is worth mentioning that this propellane-type trilactone **5** underwent regioselective ring opening upon this reaction.



Scheme 3.

The trilactone **5** is unique from the viewpoint of both functional group and structure. There are very few reports on preparing tris(acyloxy)methane[11] and thus far one-step syntheses of propellanes from acyclic compounds have not been reported at all.[12] Further investigations on the reactions of this propellane-type trilactone **5** using other reagents are currently in progress.

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7 Selected data for **5**: a white powder (56%): mp 202-203 °C (acetone/hexane); MS (CI) *m/z* 213 (MH$^+$); IR (KBr) 2950, 1805, 1771, 1302, 1241, 1118, 1050, 1012, 985, 954, 873, 735 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6, TMS) δ 3.26 (d, J = 19 Hz, 2H, -CH$_2$CO-), 3.16 (d, J = 19 Hz, 2H, -CH$_2$CO-), 2.72 (t, J = 6.4 Hz, 2H, -CH$_2$CO-), 2.16 (t, J = 6.4 Hz, 2H, -CH$_2$-); ^{13}C NMR (125 MHz, DMSO-d_6, TMS) δ 170.25, 165.97, 124.30, 41.51, 40.76, 27.75, 25.92. Anal. Calcd for $C_9H_8O_6$: C, 50.95; H, 3.80%. Found: C, 50.76; H, 3.66%.

8 Crystal data for **5**: $C_9H_8O_6$, M = 212.16, monoclinic, a = 10.966(3), b = 7.300(3), c = 11.018(2) Å, β = 90.35(2)°, U = 882.0(5) Å^3, T = 296 K, space group Pc (no. 7), Z = 4, D_c = 1.598 g cm^{-3}, μ(MoKα) = 0.137 mm^{-1}, R = 0.057 [$I > 2\sigma(I)$], R_w = 0.193 (all data) for 2695 unique data and 299 parameters. Goodness of fit S = 1.02. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.40 and -0.25 e Å^{-3}, respectively.

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10 Selected data for **6**: a white powder (75%): mp 150-153 °C (acetone/hexane); MS (ESI) *m/z* 459 (MH$^+$); IR (KBr) 3348, 3300-2500 (br), 1712, 1689, 1627, 1609, 1554, 1536, 1512, 1414, 1249, 1175, 1032, 828 cm^{-1}; ^{1}H NMR (500 MHz, DMF-d_7, TMS) δ 12.77 (br, 2H, -COOH), 9.93 (s, 1H, -CONH-), 9.89 (s, 1H, -CONH-), 7.61 (d, J = 9 Hz, 4H, ArH), 6.90 (d, J = 9 Hz, 2H, ArH), 6.89 (d, J = 9 Hz, 2H, ArH), 3.770 (s, 3H, -OCH$_3$), 3.767 (s, 3H, -OCH$_3$), 3.06-2.95 (m, 4H, -CH$_2$CO-), 2.50-2.41 (m, 2H, -CH$_2$CO-), 2.21-2.10 (m, 2H, -CH$_2$-); ^{13}C NMR (125 MHz, DMF-d_7, TMS) δ 176.73, 173.56, 170.94, 169.72, 156.29, 156.16, 133.75, 133.53, 121.38, 121.17, 114.38, 55.60, 45.93, 40.87, 38.60, 32.88, 32.41. Anal. Calcd for $C_{23}H_{26}N_2O_8$: C, 60.26; H, 5.72; N, 6.11%. Found: C, 60.01; H, 5.63; N, 6.11%.

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