Cyclophanes, XLIV[+]

Synthesis of 4,5,12,13-Tetraformyl[2.2]paracyclophane and Its Bis-acetal

Sethuraman Sankararaman,[a] Henning Hopf,*[b] Ina Dix,[b] and Peter G. Jones[c]

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4,5,12,13-Tetraformyl[2.2]paracyclophane (**1f**) has been prepared for the first time by the cycloaddition of 4,4-diethoxy-2-butynal (**3**) to 1,2,4,5-hexatetraene (**2**) under various conditions and hydrolysis of the initially produced bis-acetals **5a** and **5b**. An X-ray crystal structural analysis of **5a** is reported.

Introduction

Tetrasubstituted [2.2]paracyclophane derivatives such as **1b−d** (Scheme 1) are easily accessible by simple functional group interconversion from the tetraester **1a**, which is itself readily obtained by cycloaddition of dimethyl acetylenedicarboxylate to 1,2,4,5-hexatetraene (**2**).[2] Derivatives **1a−d** are valuable starting materials for the synthesis of multibridged[3,4] and multilayered [2.2]paracyclophanes[5] and for the annelation of carbocyclic rings to the phane framework.[6] Other activated triple bond dienophiles such as dicyanoacetylene[7] and perfluoro-2-butyne[7] provide still more tetrasubstituted derivatives, and although 3-hexyne-2,5-dione could be added to **2** to provide **1e**,[8] one important derivative for further studies on [2.2]paracyclophanes, the tetraaldehyde **1f**, was until now still unavailable. Clearly, with the functional groups at an intermediate oxidation state this could be a most interesting and useful starting material for the annelation of carbo- and heterocyclic ring systems by Wittig and other carbonyl condensation reactions. Attempts to prepare **1f** either by the reduction of the tetraester **1a** or by the oxidation of the tetraalcohol **1b** yielded only an isomeric mixture of the corresponding bisphthalides, evidently via intermediately generated hemiacetals.[9] A retrosynthetic analysis of **1f** based on the methodology of the cycloaddition of **2** to prepare [2.2]paracyclophane derivatives gives acetylene dicarboxaldehyde as the dienophile. Although known in the literature,[10] this reactive dienophile is thermally unstable and undergoes explosive decomposition. A suitable and more stable synthetic equivalent is the corresponding monoacetal, 4,4-diethoxy-2-butynal (**3**), the synthesis[11] and several cycloaddition reactions[12] of which have been described in literature. Herein we finally report the synthesis of **1f** and the corresponding bis-acetal **5a**, which has been structurally characterized by X-ray structural analysis.

Results and Discussion

The cycloaddition of **2** and **3** was carried out under two different conditions: either by heating an equimolar mixture of the components in toluene at 70 °C for 24 h or by stirring the mixture in a 2.5 M lithium perchlorate/diethyl ether (LPDE) medium at room temperature for 4.5 days. In the former case the crude product consisted of a nearly 1:1 mixture of the bis-acetals **5a** and **5b** (as shown by the ^{1}H NMR spectrum), the two products to be expected from the dimerization of the intermediately produced *p*-xylylene **4**.[2−9] From this mixture the isomer **5a** could be readily isolated by recrystallization from an ether/pentane mixture at −30 °C leading to the analytically pure adduct as a pale yellow solid. When the crude product, after removal of most of the solvent, was left in the freezer at −30 °C overnight, single crystals suitable for X-ray crystallography could be obtained. The molecular structure of **5a** in Figure 1 shows the pseudo-*para* orientation of the equivalent groups, corresponding to the crystallographic inversion symmetry.

The crude product obtained from the reaction in LPDE consisted of a mixture of the bis-acetals **5a** and **5b**, the mono-acetal **3** and the tetraaldehyde **1f** as shown by GC- and GC/MS-analysis. Because the attempted crystallization of the bis-acetal from the crude mixture was unsuccessful in this case, the mixture was hydrolyzed with 3 N aqueous HCl in dioxane without further purification to yield **1f**, which was obtained as a pale tan-colored solid in 60% yield. Recrystallization from a CH_2Cl_2/pentane mixture then yielded the analytically pure tetraaldehyde **1f**, which was characterized by the usual analytical and spectroscopic

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[a] Department of Chemistry, Indian Institute of Technology, Madras 600 036, India
Fax: (internat.) + 91-44/235-0509
E-mail: sanka@acer.iitm.ernet.in
[b] Institut für Organische Chemie, Technische Universität Braunschweig, Hagenring 30, D-38106 Braunschweig, Germany
Fax: (internat.) + 49-(0)531/391-5388
E-mail: h.hopf@tu-bs.de
[c] Institut für Anorganische und Analytische Chemie, Technische Universität Braunschweig, Hagenring 30, D-38106 Braunschweig, Germany
Fax: (internat.) + 49-(0)531/391-5382
E-mail: p.jones@tu-bs.de

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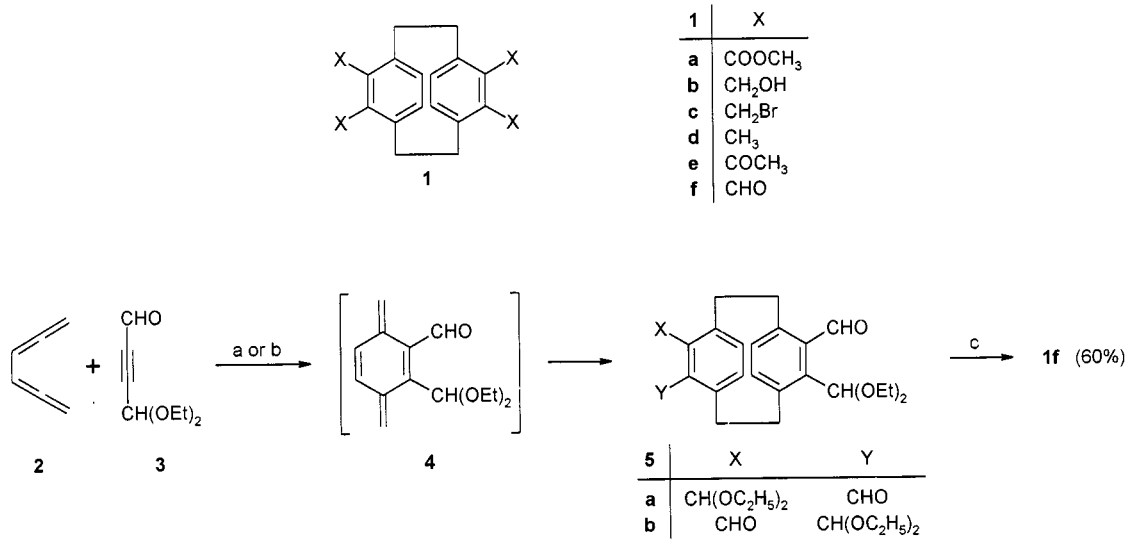

Scheme 1. The preparation of 4,5,12,13-tetraformyl[2.2]paracyclophane (**1f**)

methods (see below). The use of the tetraaldehyde for further transformations will be described in due course.

Experimental Section

Starting Materials: An ethereal solution of 1,2,4,5-hexatetraene (**2,** 54 mg/mL) was prepared from propargyl bromide according to the literature procedure.[2] 4,4-Diethoxy-2-butynal (**3**) was prepared by the partial hydrolysis of the corresponding bis-acetal using $HCOOH/CHCl_3$ according to a reported procedure.[12] The yield of the product varied between 70−76% in various runs. Preparation of 5 M lithium perchlorate in ether has been described earlier.[13]

5,13-Bis(diethoxymethyl)-4,12-bis(formyl)-[2.2]paracyclophane (5a): A mixture of 1,2,4,5-hexatetraene (**2**, 1.08 g, 0.0138 mol) in 20 mL of ether and 4,4-diethoxy-2-butynal (**3**, 2.00 g, 0.013 mol) in toluene (20 mL) was heated at 70−75 °C under nitrogen for 24 h. The reaction mixture was then cooled and the solvent was removed under reduced pressure to yield a red gummy substance. Upon trituration of the crude product (2.74 g, 85%) with pentane with vigorous stirring, a pale yellow solid was obtained, which was identified as a 1:1 mixture of the bis-acetals **5a** and **5b** from the ^1H NMR spectrum. The aromatic region showed a pair of AB-quadruplets at δ = 6.62, 6.52 (J = 7.8 Hz) and 6.73, 6.46 (J = 8.2 Hz) for **5a** and **5b**, respectively. Recrystallization from ether/pentane ca. 2:1, v/v at −30 °C yielded the analytically pure isomer **5a** as a pale yellow solid; m.p. 158−160 °C. − IR (KBr): $\tilde{\nu}$ = 2977 cm^{-1}, 2928, 1678 (C=O), 1103, 1059. − UV/Vis ($CHCl_3$): λ_{max} (log ε) = 262 nm (3.40), 310 (3.43). − ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.07 (t, J = 7.0 Hz, 6 H), 1.40 (t, J = 7.1 Hz, 6 H), 2.79 (m, 2 H), 3.21 (m, 4H), 3.41 (m, 4 H), 3.76 (m, 4 H), 4.08 (m, 2H), 5.57 (s, 2 H), 6.62 and 6.52 (AB-quadruplet, J = 7.8 Hz, 4 H), 10.52 (s, 2 H). − ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 15.1 (q), 15.2 (q), 32.8 (t), 34.1 (t), 62.5 (t), 64.4 (t), 101.1 (d), 135.0 (d), 135.1 (s), 135.6 (d), 138.5 (s), 138.9 (s), 140.5 (s), 195.6 (s). − MS (EI, 70 eV): m/z (%) = 469 (24) [M^+ + 1], 468 (78) [M^+], 423 (48), 422 (46), 393 (50), 319 (78), 291 (64), 275 (42), 161 (78), 103 (100). − HRMS ($C_{28}H_{36}O_6$): calcd. 468.25119; found 468.2500. − $C_{28}H_{36}O_6$ (468.6): calcd. C 71.75 H 7.75; found C 71.48 H 7.74.

X-ray Crystallography of 5a: The crystal data, data collection and refinement parameters measured for compound **5a** are summarized in Table 1. Structure determination: A cut needle was mounted in inert oil on a glass fiber and transferred to the cold gas stream of a Siemens P4 diffractometer. Data collection was performed with the ω-scan method using a graphite monochromator for Mo-K_α radiation (λ = 0.71073 Å). The structure was solved by direct methods and refined anisotropically on F^2 using all reflections.[14]

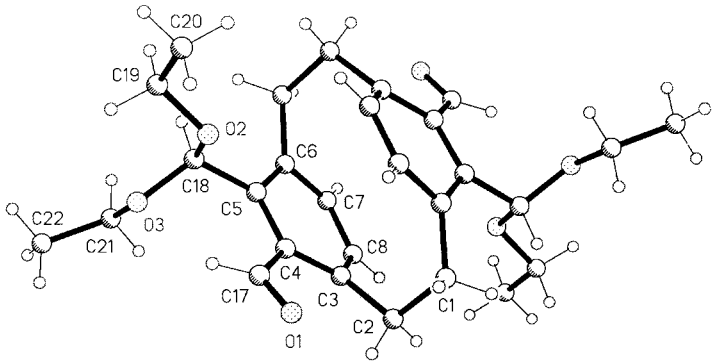

Figure 1. Single crystal X-ray structure of **5a**

Table 1. Summary of crystal data, data collection, and refinement parameters for **5a**

Compound	**5a**
Formula	$C_{28}H_{36}O_6$
M_r	468.57
Crystal habit	Colorless needle
Crystal size (mm)	0.62 × 0.24 × 0.18
Crystal system	Monoclinic
Space group	$P2_1/c$
Cell constants:	
a (Å)	7.3374(10)
b (Å)	11.588(2)
c (Å)	14.727(2)
α (°)	90
β (°)	91.367(10)
γ (°)	90
V (Å^3)	1251.8
Z	2
D_x (Mg m^{-3})	1.243
μ (mm^{-1})	0.086
Transmissions	
F(000)	504
T (°C)	−100
$2\theta_{max}$	50
No. of reflections:	
measured	3027
unique	2202
R_{int}	0.016
Parameters	185
Restraints	214
$wR(F^2$, all refl.)	0.123
R [$F > 4\sigma(F)$]	0.045
S	0.89
max. Δρ (e Å^{-3})	0.18

The small crystal diffracted weakly; an extensive system of restraints to components of displacement parameters was employed. One of the ethoxy groups (O3−C22) in the acetal is disordered over two positions with occupancies of 0.54(1) for O3 to C22 and 0.46(1) for O3′ to C22′. The hydrogen atoms (except rigid methyls) were refined with a riding model.

Crystallographic data (excluding structure factors) for the structure(s) included in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-135527 (**5a**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: (internat.) + 44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

4,5,12,13-Tetraformyl[2.2]paracyclophane (1f): A 5 M lithium perchlorate solution (150 mL) in diethyl ether was added slowly by syringe to a stirred ice-cold solution of 1,2,4,5-hexatetraene (**2**, 4.7 g, 0.06 mol) in 150 mL of diethyl ether under nitrogen. To the resulting mixture, which was pale yellow and homogeneous, was added 4,4-diethoxy-2-butynal (**3**, 9.36 g, 0.06 mol). The mixture was stirred at room temp. for 4.5 days during which time the solution turned dark brown. The reaction mixture was poured onto crushed ice, and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL) and the combined organic extracts were dried with anhydrous $MgSO_4$. Removal of solvents yielded a brown viscous oil (12.4 g), which consisted of a mixture of the bis-acetals **5a** and **5b** [MS: m/z = 468 (M^+)], the monoacetal [m/z = 394 (M^+)] and the tetraaldehyde [m/z = 320 (M^+)] as indicated by GC and GC/MS analysis. The crude product (5 g) was dissolved in 75 mL of dioxane and the solution cooled in an ice bath. An ice cold solution of 3 N HCl was added with stirring and the mixture was left at room temp. for 24 h. The reaction mixture was extracted with CH_2Cl_2, the organic layer was washed with aq. $NaHCO_3$ solution, and solvent was removed after drying with $MgSO_4$ to yield a brown oil. Trituration with ether led to the precipitation of the tetraaldehyde as a tan-colored solid, which was further purified by recrystallization from CH_2Cl_2/pentane to give a colorless solid (2.1 g, 60%), m.p. 118−120 °C. − IR (KBr): $\tilde{\nu}$ = 1683 cm^{-1} (C=O). − ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 3.13 (m, 4 H), 3.70 (m, 4 H), 6.76 (s, 4 H), 10.15 (s, 4 H). − ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 33.6 (t), 137.3 (d), 137.4 (s), 142.4 (s), 191.8 (s). − MS (EI, 70 eV): m/z = 321 (14) [M^+ + 1], 320 (56) [M^+], 292 (22), 291 (100), 161 (26), 160 (38), 132 (76), 131 (30), 103 (34). − HRMS ($C_{20}H_{16}O_4$): calcd. 320.10486; found 320.1048. − $C_{20}H_{16}O_4$ (320.33): calcd. C 74.99, H 5.03; found C 75.28, H 5.12.

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