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Tetrahedron Letters 44 (2003) 2665–2667

TETRAHEDRON LETTERS

Synthesis of a biphenyl-based cyclophane via benzidine rearrangement of a constrained *m*-nitrophenol derivative

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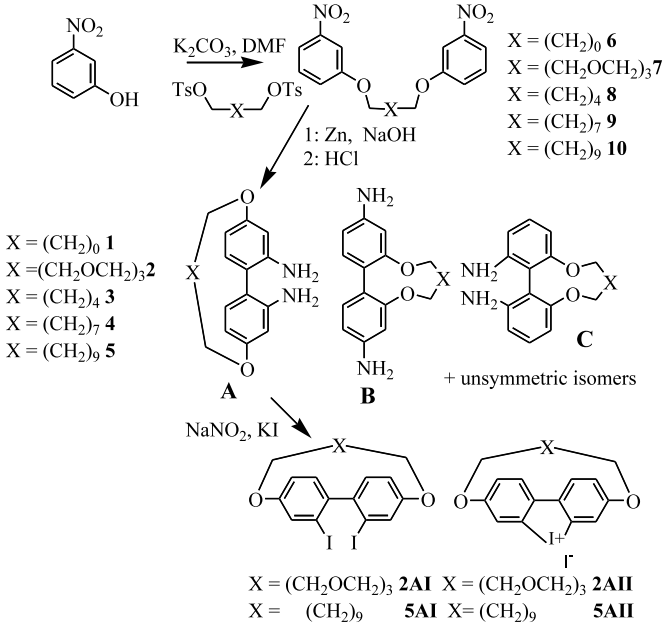
Received 11 December 2002; revised 24 January 2003; accepted 7 February 2003

Abstract—The benzidine rearrangement of a constrained *m*-nitrophenol derivative results in production of a cyclophane comprising a biphenyl group and a polyether tether connected at the 4,4′ positions. © 2003 Elsevier Science Ltd. All rights reserved.

First discovered over 100 years ago, the acid-catalysed rearrangement of hydrazobenzene affords a facile synthetic method for production of biphenyl-4,4′-diamine (benzidine).[1] Despite the fact that the [5.5] sigmatropic rearrangement product is not the sole material produced, and competing mechanisms operate to create unsymmetric isomers, the method is versatile enough to be used for the synthesis of benzidine derivatives.[2] Additionally, the benzidine rearrangement can be used in the manufacture of mixed organic species, and hence has found applications in the synthesis of 5,5′-bis(2-aminothiazole) derivatives,[3] and *p*-semidine from phenylhydrazinopyridine.[4]

During our own efforts to synthesise strapped biphenyl derivatives it became necessary to utilise the benzidine rearrangement reaction on bis-*m*-nitrophenol derivatives linked by alkyl and alkoxy chains (Scheme 1). In these compounds, unlike previous cases, the intramolecular benzidine rearrangement occurs within a constrained hydrazo precursor. For this reason it was expected that product formation would be seriously influenced by chain length, and that, in particular, isomer **A** would be highly disfavoured when the connector was short. Conversely, isomers **B** or **C** were expected to be favoured under these conditions as well as the unsymmetric isomers. As it turned out, in most of the reactions the benzidine rearrangement produced a number of products which could not be properly separated by column chromatography, or adequately identified by ^{1}H NMR spectroscopy. However, in the case where a polyether linker or long alkyl chain was used, a product was isolated that was confirmed to be a cyclophane in which the linker group is connected at



Scheme 1.

Keywords: cyclophane; benzidine rearrangement; supramolecular chemistry.

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doi:10.1016/S0040-4039(03)00343-5

the 4,4′ positions of the biphenyl group. Recently, there has been interest in the manufacture of cyclophanes containing biphenyl groups and incorporating polyether and polyaza linkages attached at the 2,2′-positions.[5] Interestingly, to date there have not been many reported examples of similar cyclophanes in which the anchor points are the 4,4′ sites.[6]

Linked derivatives **6**–**10** were prepared in excellent yield (80–90%) by reaction of deprotonated *m*-nitrophenol with an appropriate dibromoalkane or ditosylated tetraethyleneglycol.[7] The reduction and subsequent benzidine rearrangement reaction was performed on each derivative under identical conditions. Detailed computational molecular modelling calculations[8] were also carried out on the three symmetric products **A**, **B** and **C**, as well as key azo intermediates, and their enthalpies of formation are collected in Table 1. The reaction pathway (Scheme 2) serves to emphasise the intermediate products, and carbon atoms where new bond formation takes place in the creation of symmetric isomers **A**, **B** and **C**. It is evident that production of the strained azo intermediate is crucial if the reaction is to proceed to completion. As illustrated in Table 1, the azo derivative of precursor **6** is highly strained and its formation is unlikely, whereas the others are thermodynamically feasible. Indeed, compounds **7**–**10** were reduced, as monitored by TLC (silica gel, EtOAc/hexane), without difficulty to the azo and eventually hydrazo precursors, whereas **6** remained unaltered, even under prolonged heating in the presence of excess Zn powder. This later observation is likely to be a result of the poor solubility of the starting material. The benzidine rearrangement was carried out in situ, following reduction and acidification at 0°C using conc. HCl. Following work-up the crude reaction mixture was analysed by TLC to establish the number of products formed. The reactions using linkers **8**–**9** showed at least six products present in the crude mixture, which could not be adequately separated by column chromatography.[9] In contrast, the rearrangement reaction on the derivative containing either linker **7** or **10** afforded a less complex crude reaction mixture, from which a pure product could be isolated in an unoptimised overall yield of ca. 16%.[10] The splitting patterns and coupling constants of the ^{1}H NMR aromatic signals of the material immediately discounted its identification as isomer **C**. Unequivocal compound identification of the rearrangement products **2** or **5** was performed by single-crystal X-ray structure analysis of the diiodide derivative produced via a standard Sandmeyer reaction.[11] The molecular structure corresponding to **2** (Fig. 1) clearly identifies the polyether chain spanning across the two phenyl groups to create a cyclophane structure based on isomer **A**.[12] It is evident that the biphenyl unit is strained since the two aromatic rings are clearly twisted and bowed; the torsion angle C8–C7–C1–C6 within the biphenyl group being 135.6°. Also the C1–C7 bond lies 15.5 and 12.2° out of the mean plane of the two aromatic rings, and the C6–C1–C7 and C1–C7–C8 angles are widened to 125.0 and 125.7°, respectively. Further strain in the cyclophane is evident in the spanning polyether chain linking O1 and O5 in which three of the four segments are disordered over two sites. The two iodine atoms are

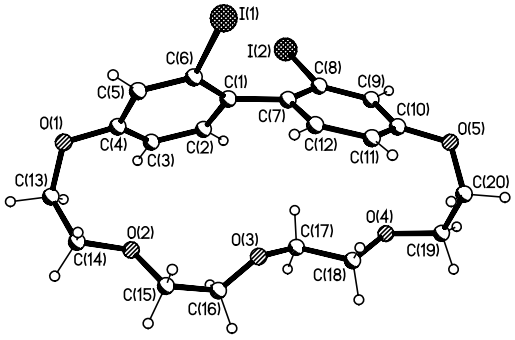
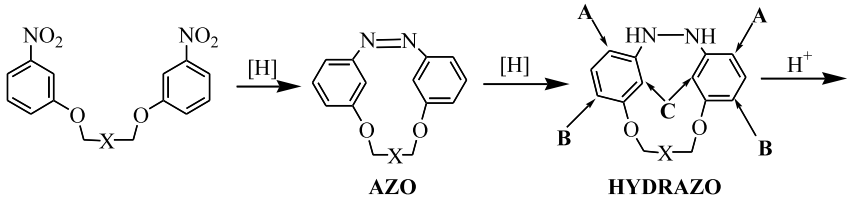


Figure 1. Ball and stick representation of the molecular structure of the diiodide derivative **2AI**. Minor disorder components are omitted.

Table 1.

No.	Atom span	ΔH_f **Azo**[a]	ΔH_f **A**[a]	ΔH_f **B**[a]	ΔH_f **C**[a]
6	2	+39.8	[b]	−15.6	−16.5
7	11	−112.1	−153.4	−158.5	−158.1
8	6	−3.0	[b]	−41.3	−39.8
9	9	−16.5	−58.5	−61.7	−62.4
10	11	−30.5	−73.6	−74.6	−74.9

[a] Enthalpy of formation kcal mol^{-1}.
[b] Product is not feasible.



Scheme 2. Sites for C–C bond formation in the linked hydrazo intermediate.

well separated (>5 Å), and each is disordered over two sites. On the whole it appears that the cyclophane in the solid state (and presumably in solution phase) is quite mobile at the polyether chain and biphenyl group. The overall cavity size of **2AI** is ca. 10 Å×3.5 Å, which is too small to accommodate a guest such as Na^+ ($r=0.95$ Å)[13] or even Zn^{2+} ($r=0.74$ Å)[13] generated during the synthetic procedure.

That the reaction of **10** affords a product similar to **2A** suggests that the Na^+ or Zn^{2+} ions do not, to any significant extent, act as a template during molecular rearrangement. It will be interesting to further test the scope of the benzidine rearrangement by using other extended polyether, alkyl and polyaza derivatives, as this may lead to an alternative strategy for producing new cyclophane hosts.

Supplementary material

Crystallographic data (excluding structure factors) for the structure in this paper, have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 199526. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 (0)-1223-336033 or email: deposit@ccdc.cam.ac.uk).

Acknowledgements

This work was supported by the Engineering and Physical Sciences Research Council (GR/23305/01). We would also like to thank Mr. Sven Bornemann for carrying out some preliminary work, and the EPSRC Mass Spectrometry Facility at Swansea.

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7. Selected analytical data: 1,13-di-(3-nitrophenyl)-1,4,7,10,13-pentaoxatridecane (**7**): ^{1}H NMR ($CDCl_3$) $\delta=$ 3.72 (m, 8H, CH_2-CH_2), 3.89 (m, 4H, CH_2-CH_2), 4.20 (m, 4H, CH_2-CH_2), 7.24 (ddd, 2H, $J=8.3$ Hz, $J'=2.5$ Hz, $J''=0.9$ Hz, Ar-H_6), 7.41 (t, 2H, $J=8.2$ Hz, Ar-H_5), 7.75 (t, 2H, $J=2.3$ Hz, Ar-H_2), 7.82 (ddd, 2H, $J=8.1$ Hz, $J'=2.1$ Hz, $J''=0.9$ Hz, Ar-H_4). EI-MS $m/z=436$ (M^+).
8. Computational studies on products and intermediates were carried out using the commercial package Titan at the semi-empirical AM1 level. Typically, a structure was allowed to energy-minimise and converge, and a single-point calculation carried out to determine the enthalpy of formation.
9. Preliminary HPLC separations carried out on the mixtures suggest that products could be isolated on a preparative scale and fully identified.
10. Analytical data:
6,9,12,15,18-Pentaoxa-tricylo[17.2.2.2^{2,5}]pentacosa-1(22),2(25),3,5(24),19(23),20-hexaene-3,21-diamine (**2A**): ^{1}H NMR ($CDCl_3$) $\delta=3.00$ (m, 8H, CH_2-CH_2), 3.63 (m, 4H, CH_2-CH_2), 4.26 (m, 4H, CH_2-CH_2), 6.53 (d, 2H, $J=2.3$ Hz, Ar-H_3), 6.64 (dd, 2H, $J=8.4$ Hz, $J'=2.3$ Hz, Ar-H_5), 7.14 (d, 2H, $J=8.4$ Hz, Ar-H_6). EI-MS $m/z=374$ (M^+).
22,25-Diiodo-6,9,12,15,18-pentaoxatricylo[17.2.2.2.^{2,5}]-pentacosa-1(22),2(25),3,5(24),19(23),20-hexaene (**2AI**): Yield 17%. ^{1}H NMR ($CDCl_3$) $\delta=2.88$ (m, 4H, CH_2-CH_2), 3.18 (m, 4H, CH_2-CH_2), 3.61 (m, 4H, CH_2-CH_2), 4.17 (m, 2H, CH_2-CH_2), 4.47 (m, 2H, CH_2-CH_2), 7.09 (d, 2H, $J=8.6$ Hz, Ar-H_6), 7.21 (dd, 2H, $J=8.6$ Hz, $J'=2.4$ Hz, Ar-H_5), 7.58 (d, 2H, $J=2.4$ Hz, Ar-H_3). EI-MS $m/z=596$ (M^+).
22,25-Iodonium-6,9,12,15,18-pentaoxatricyclo[17.2.2.2.^{2,5}]-pentacosa-1(22),2(25),3,5(24),19(23),20-hexaene iodide (**2AII**): Yield 24%. ^{1}H NMR (d_6-DMSO) $\delta=2.27$ (m, 2H, CH_2-CH_2), 2.68 (m, 6H, CH_2-CH_2), 3.54 (m, 4H, CH_2-CH_2), 4.33 (m, 4H, CH_2-CH_2), 7.53 (dd, 2H, $J=8.6$ Hz, $J'=2.2$ Hz, Ar-H_5), 8.06 (d, 2H, $J=2.2$ Hz, Ar-H_3), 8.22 (d, 2H, $J=8.6$ Hz, Ar-H_6) EI-MS $m/z=596$ (M^+).
11. The product from the Sandmeyer reaction using **5A** was identified as the iodonium salt **5AII** (yield = 31%). The overall molecular structure however was similar in appearance to that of the diiodide **2AI**.
12. Orange single crystals of the diiodide of **2AI** were grown by layering a saturated solution of the compound in CH_2Cl_2 with hexane. Selected X-ray crystallographic data: $C_{20}H_{22}I_2O_5$, M = 596.2, triclinic, $P\bar{1}$, $a=9.5481(7)$, $b=9.8179(7)$, $c=12.4608(9)$ Å, $\alpha=111.987(2)$, $\beta=93.074(2)$, $\gamma=102.740(2)°$, $V=1044.43(13)$ Å^3, $Z=2$, $T=160$ K; $R(F, F^2>2\sigma)=0.0362$, $Rw(F^2$, all data$)=0.0907$, goodness of fit on $F^2=1.031$, 337 parameters and 4904 unique data, final difference map within ±0.9 e Å^{-3}.
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