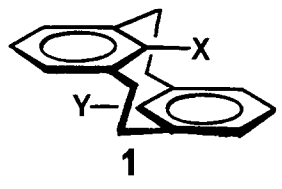
Tetrahedron Letters,Vol.25,No.9,pp 907-910,1984 0040-4039/84 $3.00 + .00
Printed in Great Britain

CYCLOPHANES WITH LARGE INTERNAL SUBSTITUENTS. THE SYNTHESIS AND CONFORMATIONAL BEHAVIOR OF 2,11-DITHIA[3,3]METACYCLOPHANES AND A [2,2]METACYLOPHANE WITH tert-BUTYL SUBSTITUENTS.[1]

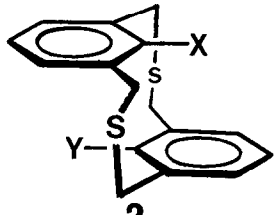
Reginald H. Mitchell,* Kumudini S. Weerawarna and Gordon W. Bushnell
Department of Chemistry, University of Victoria, Victoria, BC V8W 2Y2 Canada.

Summary: The preparation, ^{1}Hmr spectra and stereochemistry of **1E**, **3E**, **2F**, **3F** and **2G** are described. The stereochemistry of **3E** is supported by an X-ray structure determination.

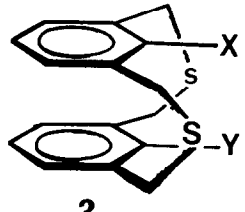
The synthesis and stereochemical aspects of cyclophanes have been of particular interest over the last two decades.[2,3] However, recently the size of the internal substituents, X,Y, in the [2,2]metacyclophane **1** and the 2,11-dithia[3,3]metacylophanes **2** and **3** has attracted attention from several points of view.[3c,4] Firstly the size of X,Y in **2** and **3** affects the relative stabilities of the two conformers. For example when X=Y=H, only the syn-compound **3A** is found.[5] When X=Y=Ø, i.e. a large substituent, both conformers exist, but the anti-conformer **2B** is formed in a 10:1 ratio to the syn-conformer **3B**.[4c] With substituents of less equal size, the pattern is less clear. For example, with X=Ø, Y=Me the **2C** : **3C** ratio was 4:1,[4c] but for X=Ø, Y=H only a single compound is formed,[4a,6] which we have shown to be syn-**3D** by an X-ray structure determination.[4d] Other examples have been discussed in a



1



2

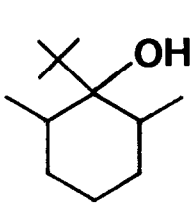


3

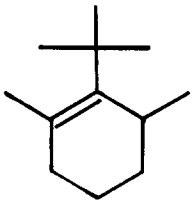
A: X=Y=H
B: X=Y=Ø
C: X=Ø, Y=Me
D: X=Ø, Y=H
E: X= t-Bu, Y=H
F: X= t-Bu, Y=Me
G: X=Y= t-Bu

review,[7] but the overall picture as to exactly how the nature of X,Y controls the stereochemistry of **2** and **3** is not yet clear. Secondly as the size of X,Y in **2**, **3** increases the chance of interesting interactions between either X and Y or the two rings in **3** or between X,Y and a ring in **1** or **2** increases. Vogtle has most elegantly suggested,[4a,b] that internal phenyl groups are attractive to study in this respect, and these have now been well studied.[4c,d,6,8] In the cases of **2B**, **3B** rotation about the substituent-ring bond was severely limited, owing to interactions between the substituent ortho-hydrogen atoms and the methylene bridge hydrogens.[4c]

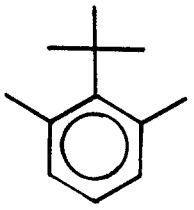
We thus became intensely interested in the outcome of having tert-butyl groups as substituents, to determine the effect of such a bulky substituent on the relative stabilities of **2** , **3** and as well to determine if restricted rotation about the tert-butyl-ring bond would occur in any of **1** , **2** or **3** . We now report the synthesis of the first cyclophanes with internal tert-butyl substituents, namely **1E** , **3E** ; **2F** , **3F** ; **2G**.



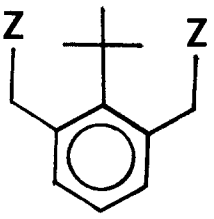
4



5



6



7: Z = Br

8: Z = SH

Reaction of 2,6-dimethylcyclohexanone with t-butyllithium at -70°C in hexane gave 92-95% yields of alcohol **4** .[9] Heating this at 70°C for 10 minutes in conc. H_3PO_4 yielded 65% of the alkene **5** . Other acidic catalysts, or basic routes, e.g. TsCl/py gave much rearranged material, and only low yields of **5** . Dehydrogenation of **5** to 2,6-dimethyl-t-butylbenzene,[10] **6** , proceeded poorly with chloranil but smoothly with DDQ (3 equiv) in 68% yield. Bromination of **6** with NBS/CCl_4 gave 65% of dibromide **7** , mp 111-112°C; ^{1}Hmr (90MHz) δ 7.4-6.9 (3H,AB_2,ArH), 4.80 (4H,s,-CH_2Br), 1.65 (9H,s,-$C(CH_3)_3$). This dibromide was extremely readily solvolysed by water, alcohol or on attempted chromatography. It was therefore converted to the dithiol **8** by refluxing in dry THF with thiourea, and then hydrolysing the resultant bis-isothiouronium salt with aq. KOH to give 85% of **8** , mp ~20°C; ^{1}Hmr (90MHz) δ 7.4-6.9 (3H,m,ArH), 4.00 (4H,d,J=7Hz, -CH_2SH), 1.77 (2H,t,J=7Hz,-CH_2SH), 1.60 (9H,s,-$C(CH_3)_3$).

Cyclisation[12] of **8** with m-xylylene bromide in refluxing ethanol-benzene yielded 50% of the thiacyclophane **3E** , mp 132-133°C; ^{1}Hmr (250MHz) δ 6.60,7.02 (AB_2,J=7.5Hz,Ar-$C(CH_3)_3$), 7.02,6.89,6.26 (AB_2X,J= ~7.2,~1Hz,Ar-H_1), 4.57,3.86 (AB,J=15.0Hz,-CH_2S-), 3.75,3.65 (AB,J=15.2Hz,-CH_2S-), 1.52 (s,-$C(CH_3)_3$). This compound was assigned[7] the syn-structure on the basis of its internal hydrogen signal, H_1, at δ 6.26, and its relatively normal t-butyl signal at δ 1.52, and this was confirmed by an X-ray crystallographic structure determination.[13] With 2,6-bis(bromomethyl)toluene, **8** yielded 30% of **2F**: **3F** in a 4:6 ratio at reflux temperature, 3:7 ratio at ~50°C. Chromatography yielded pure syn-**3F** , mp 141-142°C; ^{1}Hmr (250MHz) δ 6.50,7.01 (AB_2,J=7.4Hz,Ar-$C(CH_3)_3$), 6.83,6.91 (AB_2,J=7.8Hz,Ar-CH_3), 2.29 (s,Ar-CH_3), 1.45,(s,Ar-$C(CH_3)_3$). Also obtained was anti-**2F** , mp 156-157°C; ^{1}Hmr (250MHz) δ 7.04,7.15 (AB_2,J=7.4Hz,Ar-$C(CH_3)_3$), 7.06,7.36 (AB_2,J=7.4Hz,Ar-CH_3), 3.81 (s,-CH_2-), 3.73,3.68 (AB,-CH_2S-), 1.68 (s,Ar-CH_3), 1.04 (s,Ar-$C(CH_3)_3$).

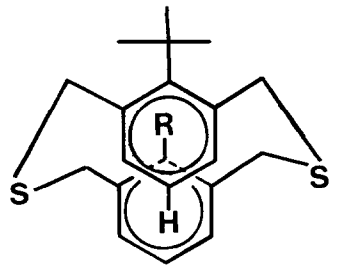
Finally **8** with **7** , in DMF using KH as base at 40°C, yielded about 7% of anti-**2G** , mp 223-225°C; ^{1}Hmr (250MHz) δ 6.95,7.06 (AB_2,J=7.3Hz,Ar-$C(CH_3)_3$), 3.89 (s,-CH_2-), 1.06 (s,Ar-$C(CH_3)_3$). This compound was assigned the anti-structure on the basis of its shielded t-butyl group at δ 1.06 (compare **2F** at δ 1.04). No syn-**3G** could be detected.

Several points of interest emerge: formation of only syn-**3** , analogous to the observed results for **3A** and **3D** , would suggest that the stereochemistry of other cyclophanes where H is one of the internal substituents, is probably also syn-, and thus some reinvestigation of such systems is merited. When two large internal substituents are present, clearly the anti-conformer **2** is preferred. With one large and one smaller substituent however, still no clear pattern emerges. Surprisingly in each of the above examples, the t-butyl signal is a singlet, and remains so down to at least -90°C. Evidently steric interactions in these cyclophanes are not so severe as to prevent rotation about the aryl-substituent bond. Changes do occur however to the bridge and arvl protons, and suggest that one conformer is frozen out at low temperatures, in which the bridge interactions are minimised.

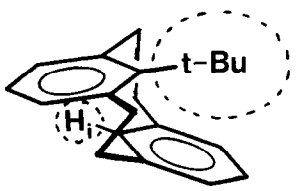
The shielding of the hydrogens para to the t-butyl group in **3E** and **3F** is of exceptional note, and may arise by a sliding of the opposite ring, as in **A** , in order to avoid the $R/C(CH_3)_3$ interactions. The para-hydrogen is then shielded by the opposite ring. An effect of this is that R (CH_3,H) should also be shielded, and indeed they are: δ 2.29 and 6.26 respectively for R=CH_3,H relative to the parent compounds **3** (X=Y=R; R=CH_3,H; δ 2.52 and 6.76 respectively). The strain in **3G** is not so readily apparent from its ^{1}Hmr spectrum, but probably is the most severe in any of the [3,3]cyclophanes, and perhaps this is reflected by its unusual ease of decomposition, e.g. on chromatography.

Thus far our attempts to obtain a [2,2]cyclophane with an internal t-butyl substituent have only yielded **1E** , mp 111-113°C, which was obtained in 50% yield by application of a Stevens rearrangement-Raney nickel desulphurisation[12] to **3E** . Its anti-structure was readily apparent from its ^{1}Hmr spectrum, which showed the internal hydrogen at δ 3.47, the highest field yet recorded[4a] for a [2,2]metacyclophane, and the t-butyl protons as a singlet also highly shielded to δ 0.73. The aromatic protons were a multiplet at δ 6.9-7.0 and the bridge protons were at δ 2.3-3.2. That the t-butyl group is still a singlet was surprising, and probably reflects the ability of the molecule to distort somewhat, e.g. into **B** , which pushes the other internal substituent, H_i, into the cavity of the opposite benzene ring, shielding it substantially. We intend to continue our researches into this area, and seek the even more strained **1F** and **1G**.

We thank the Natural Sciences and Engineering Research Council of Canada and the University of Victoria for financial support.



A



B

REFERENCES AND NOTES.

1. Presented at the 66th Chemical Institute of Canada Conference, Calgary, Alberta, OR7-3, June 6,1983.
2. New Book: "Cyclophanes", edited by P. Keehn and S. Rosenfeld, Academic Press, New York, 1983.
3. Reviews: (a) B. H. Smith in "Bridged Aromatic Compounds", Academic Press, New York, 1964; (b) F. Vogtle and P. Neumann, Angew. Chem. Int. Ed. Engl., **11** 73 (1972); Synthesis, 85 (1973); (c) H. Forster and F. Vogtle, Angew. Chem. Int. Ed. Engl., **16**, 429 (1977); (d) S. Misumi and T. Otsubo, Acc. Chem. Res., **11**, 251 (1978); (e) F. Vogtle and G. Hohner, Top. Curr. Chem., **74**, 1 (1978). (f) Y. H. Lai, Heterocycles, **16**, 1739 (1981).
4. (a) K. Bockmann and F. Vogtle, Chem. Ber., **114**, 1048 (1981). (b) K. Bockmann and F. Vogtle, Chem. Ber., **114**, 1065 (1981). (c) R. H. Mitchell and W. Anker, Tetrahedron Lett., **22**, 5135 (1981); (d) W.Anker, K. A. Beveridge, G. W. Bushnell and R. H. Mitchell, Can. J. Chem., in press, 1983; (e) G.R. Newkome, S. Pappalardo and F. R. Fronczek, J. Am. Chem. Soc., **105**, 5152 (1983).
5. W. Anker, G. W. Bushnell and R. H. Mitchell, Can. J. Chem., **57**, 3080 (1979).
6. F.Vogtle, J. Grutze, R. Natscher, W. Wieder, E. Weber and R. Grun, Chem. Ber., **108**, 1694 (1975)
7. R. H. Mitchell in reference 2, chapter 4.
8. W. Anker, Ph.D. Thesis, University of Victoria, March 1982.
9. All new compounds showed satisfactory spectroscopic properties and elemental analyses.
10. The literature synthesis[11] of **6** gave only a 2% yield!
11. A. W. Burgstahler, D. J. Malfer and M. O. A. Rahman, Tetrahedron Lett., **21**, 1625 (1965).
12. R. H. Mitchell, T. Otsubo and V. Boekelheide, Tetrahedron Lett., 219 (1975); R. H. Mitchell, Heterocycles, **11**, 563 (1978).
13. The crystal system was monoclinic with space group $P2_1/c$ (No14), with a=13.604(6), b=15.666(7), c=17.281(7)A°, and β=100.99(5)°. D_{meas}=1.24 g.cm^{-3}(flot). D_{calc}=1.26 g.cm^{-3}. Z= 8 molecules per cell, with 2 molecules per asymmetric unit. Measurements were made on a Picker 4-circle diffractometer. One of the molecules has a disordered bridging conformation. The structure was solved by direct methods, and refined by least squares to R=0.1058, R_w=13.15 for 3249 independant observations and 417 parameters. This will be reported in detail elsewhere.

(Received in USA 21 November 1983)