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# A molecular ‘hamburger’: bonded benzene in a bun

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**The scaffold bis-succinimide 4 is shown to react twice with 1,2,4,5-tetrakis(bromomethyl)benzene 5 specifically at the *para*-related bromomethyl groups to form a multi-ring alicyclophane system 3 in which the benzene ring is sandwiched between the alicyclic frames to form a molecular ‘hamburger’.**

In earlier work on proximity effects and structure–activity, one of us (DNB) demonstrated that the chemistry of an alkene π-bond could be completely negated by screening access to the π-system by suitably positioned benzene rings,[1] as in **1** where the alkene π-bond was situated in the valley between the two benzene rings. In this paper, we report another aspect of reactivity modification by proximity screening in which a benzene ring is positioned in the centre of a pair of extended alicyclic frames in a molecular equivalent of a hamburger, where the benzene ring corresponds to the ‘meat’ and the framework as the protective ‘bun’ (Fig. 1)†.

The synthesis of the molecular ‘hamburger’ **3** represents the second generation of our alicyclophanes[3] and draws on ideas expressed by Vögtle (aliphanes)[4] and the concept of stacked [2.2]cyclophanes (chochins) reported by Misumi[5] and Nakazaki[6]. By building a benzene ring into the alicyclophane and then attaching a second alicyclic spacer component onto the opposite face, it is possible to screen both sides of the benzene ring from reagent approach.‡

Reaction of the bis-succinimide **4**[3] with 1,2,4,5-tetrakis-(bromomethyl)benzene **5** in dimethylformamide containing solid potassium carbonate afforded a bromine free product having *m/z* = 1157.2590 (M + $Na^+$, calcd. 1157.2607) and thus confirming the 2:1-molecularity of the reaction. Comparisons of the N–N separation in **4** (AM1 6.30 Å) with the different bromomethyl C–C distances in **5** (AM1 C–C distances[8] are annotated on **5** in Scheme 1 and range from 2.91–5.77 Å) support preferential formation of the dual *para*-substituted product **3**§ since less deformation of the molecular frame is required to achieve cyclisation.¶ In order to gain evidence upon which to secure the ‘hamburger’ structure **3**, reactions were conducted between **4** and *o*-, *m*- and *p*-xylylene dibromides **6**–**8** as these subunits are each present in **5**. In all cases, reference to the N–N distances of starting scaffold **4** and product alicyclophanes **3**, **9**, **10** (see Table, Scheme 2) shows that significant frame deformation is required for cyclisation to occur, a feature

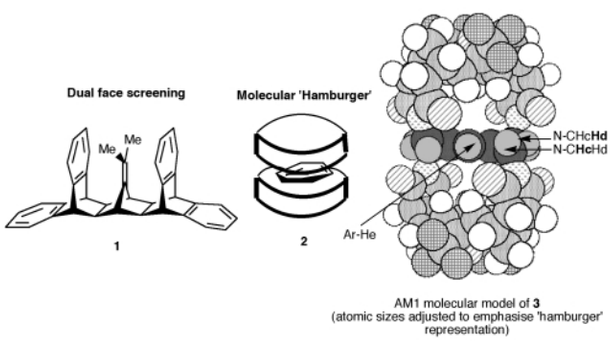
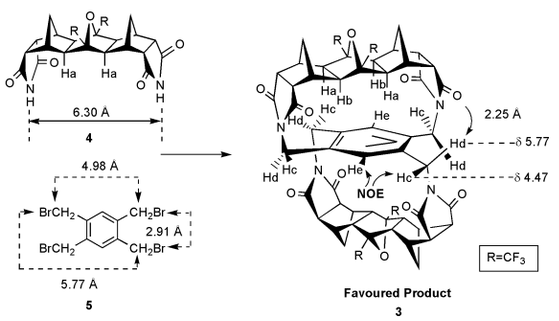



**Fig. 1**

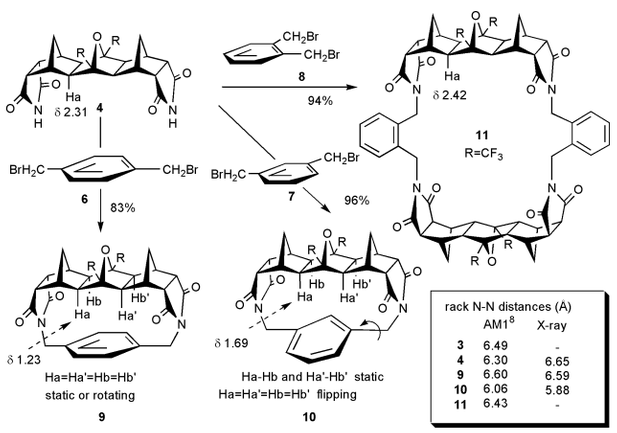



**Scheme 1**

somewhat surprising considering the expected rigidity in [*n*]polynorbornane frames comprised of fused norbornanes.‖

The product from bis-succinimide **4**** and *p*-xylylene dibromide **6** was assigned the alicyclophane structure **9**** on the basis of mass spectrometry (*m/z* 606.1591, calcd. 606.1589). Product **9**§ displayed $^1H$ and $^{13}C$ NMR spectra that reflected its *C*2*v*-symmetry. Similar reaction between *m*-xylylene dibromide **7** and spacer **4** produced an isomeric alicyclophane assigned structure **10**** (*m/z* = 606.1586). The $^1H$ NMR spectrum of **10** was also indicative of a compound with *C*2*v*-symmetry and was unchanged down to −70 °C supporting a facile ‘flipping’ motion of the *m*-phenylene bridge. By extrapolation, any *meta*,*meta*-linked structure for **3** is considered untenable since the N–$CH_2$ protons would not be diastereiotropic (as seen in **3**) owing to ring ‘flipping’. The reaction of *o*-xylylene dibromide **8** with **4** takes a different pathway and leads to production of a 2:2 product **11**§ (*m/z* 1212.3197, calcd. 1212.3179) resulting from dual intermolecular alkylation. Significantly, the *endo*-protons in **9** were more shielded than those in **10** and this offers further structural support for the *para*,*para*-structure of molecular ‘hamburger’ **3** in which the *endo*-protons occur at even higher field ($\delta$ 1.11, 1.21).

Conclusive chemical support for the structure of **3** was provided by the interrelation between alicyclophane **13**,§ prepared by the reaction of the dichlorodurene†† **12** with




**Scheme 2**

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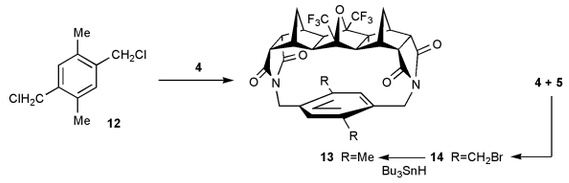


**Scheme 3**

scaffold **4**, with the alicyclophane **14**§ which has been isolated as an intermediate in the preparation of 'hamburger' **3** (Scheme 3). This was achieved by debromination of **14** by treatment with tributyltin hydride. As the alicyclophane **13** must be *para*-linked (single aryl proton resonance at $\delta$ 7.51 is definitive), this shows that **13** has the same motif and the derived 'hamburger' **3** must be *para*,*para*-linked.

In order to assess the steric protection offered by the scaffold structures to reagent approach to the benzene ring in the 'hamburger' **3**, it was treated with hot nitric–sulfuric acid (1:1 v/v). No reaction occurred even at elevated temperatures however blank reactions, conducted on the alicyclophane **9**, produced a mono nitro derivative, while the related alicyclophane **10** produced a mixture of dinitro derivatives similar to that observed for *m*-xylene. This demonstrates that nitration will proceed on the benzene ring when only one face is screened by the scaffold, but that reaction is precluded by incorporation of the second scaffold-containing ring.

In conclusion, we have demonstrated that macrocycles can be produced by reaction of xylylene dibromides with the bis-succinimide **4** and that intramolecular cyclisation occurs to form alicyclophanes with *p*-xylylene dibromide **6** and *m*-xylylene dibromide **7**, whereas intermolecular reaction occurs linking two scaffold units when the shorter *o*-xylylene dibromide is employed. The double cyclisation of the bis-imide **4** with 1,2,4,5-tetrakis(bromomethyl)benzene produced the *para*,*para* substitution 'hamburger' product **3** in which the benzene ring is sandwiched between the alicyclic scaffolds, so much so that it resisted electrophilic substitution even under forcing conditions.

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## Notes and references

† Stoddart *et al*. have described[2] a catenated system in which the benzene ring is positioned centrally in a three-dimensional array. Their structure contains other aromatic rings which would make it difficult to conduct reactivity studies of the central aryl ring; further, it does not have the 'hamburger' appearance.

‡ We have recently shown that alicyclophanes containing an isobenzofuran subunit already display increased stability owing to the scaffold frame offering reagent approach control from one face.[7]

§ All new compounds gave appropriate high resolution mass spectra and consistent $^1$H and $^{13}$C NMR spectra.

¶ While there is literature precedent[2,9] for intramolecular cyclisation involving successive nucleophilic reactions at the benzylic bromide positions of 1,2,4,5-tetrakis(bromomethyl)benzene **5** occurring exclusively at the *para*-related sites, literature examples reveal that for more flexible bis-alkylating linkers, such as those forming bis-(crowns ethers), *ortho*- and *meta*-linked products are the preferred mode of cyclisation.[9] Indeed, our finding is one of the few examples in which *para*-linkage occurs and is a direct consequence of the compatibility of the N–N separation of the scaffold (6.30 Å) and the fixed positions of the benzylic carbons (5.77 Å), as mentioned in the text.

‖ The IUPAC name for norbornane is bicyclo[2.2.1]heptane.

** *Crystal data* for **4** $C_{22}H_{18}O_5F_6N_2$, $M$ = 504.38, monoclinic, space group $P2_1/c$ (No. 14), $T$ = 150(1) K, $a$ = 13.7369(6), $b$ = 7.7697(4), $c$ = 20.4778(6) Å, $\beta$ = 108.483(2)°, $U$ = 2072.9(2) Å$^3$, $Z$ = 4, $D_c$ = 1.616 g cm$^{-3}$, $\mu$(Mo Ka) = 0.150 mm$^{-1}$, 10968 reflections collected, $R(F)$ = 0.0907, $R(wF^2)$ = 0.1209 for all 4696 independent reflections, [$R(F)$ = 0.0518, $R(wF^2)$ = 0.1078 for 3168 data with $F > 4\sigma(F_O)$].

*Crystal data* for **9** $C_{30}H_{24}O_5F_6N_2$, $M$ = 606.51, orthorhombic, space group $Fdd2$ (No. 43), $T$ = 150(1) K, $a$ = 18.4480(2), $b$ = 28.7380(4), $c$ = 9.6088(8) Å, $U$ = 5094.2(4) Å$^3$, $Z$ = 8, $D_c$ = 1.582 g cm$^{-3}$, $\mu$(Mo Ka) = 0.137 mm$^{-1}$, 7636 reflections collected, $R(F)$ = 0.0459, $R(wF^2)$ = 0.0818 for all 1553 independent reflections, [$R(F)$ = 0.0330, $R(wF^2)$ = 0.0762 for 1326 data with $F > 4\sigma(F_O)$].

*Crystal data* for **10** $C_{34}H_{32}O_6F_6N_2$, $M$ = 678.62, triclinic, space group $P\bar{1}$ (No. 2), $T$ = 150(1) K, $a$ = 10.1160(7), $b$ = 10.8820(7), $c$ = 14.0090(11) Å, $U$ = 1451.40(4) Å$^3$, $Z$ = 2, $D_c$ = 1.553 g cm$^{-3}$, $\mu$(Mo Kα) = 0.131 mm$^{-1}$, 11411 reflections collected, $R(F)$ = 0.0911, $R(wF^2)$ = 0.1435 for all 5116 independent reflections, [$R(F)$ = 0.0586, $R(wF^2)$ = 0.1292 for 3671 data with $F > 4\sigma(F_O)$].

For all structures the data (collected on a Nonius Kappa-CCD instrument) were integrated and scaled using the DENZO-SMN package (Z. Otwinowski and W. Minor, *Methods in Enzymology*, 1997, **276**, 307). The structures were solved and refined using SHELXTL V5.0 (G. M. Sheldrick, SHELXTL\PC V5.1, Bruker Analytical X-ray Systems, Madison, Wisconsin, U.S.A). CCDC 182/1868. See http://www.rsc.org/suppdata/cc/b0/b008178g/ for crystallographic files in .cif format.

†† The IUPAC name for durene is 1,2,4,5-tetramethylbenzene.

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