

A new stabilised form of isobenzofuran, rack-mounted on an alicyclophane

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New stable, crystalline isobenzofurans **9a** and **9b** linked through the 1,3-positions and incorporated into alicyclophanes have been prepared from the related furano-alicyclophane **5** in three steps (i) addition of benzyne or 4,5-bis(trimethylsilyl)benzyne (ii) hydrogenation of the π -bond (iii) ejection of ethylene by flash vacuum pyrolysis, and shown to yet retain high 1,3-diene character and form adducts with dienophiles, e.g. dimethyl acetylenedicarboxylate or *N*-methyl maleimide; the corresponding off-rack 1,3-dimethylisobenzofurans were too unstable for isolation.

Many cyclic polyene compounds that resist isolation in monomeric form, do so because of their propensity to react with themselves, e.g. dimerisation of cyclobutadiene¹ or polymerisation of isobenzofuran.² Specialised techniques to generate the monomer species in a controlled environment have been reported, e.g. flash vacuum pyrolysis or matrix isolation at liquid helium temperatures. The most ingenious way to isolate such a highly reactive monomer, however, was reported by Cram and co-workers who were able to corral cyclobutadiene inside a hemicarcerand (**1**, Fig. 1), study its chemistry and even record its NMR spectrum.³ This method succeeded since it kept the cyclobutadiene molecules separated from each other, and confirmed the inherent stability of cyclobutadiene itself. In principle, this technique should be suitable for the study of isobenzofuran systems, a class of unstable monomeric compounds characterised by the presence of the *o*-xylylidene chromophore.⁴ In practice, our efforts to achieve this goal using the Cram technique have been unrewarding because of the difficulty in preparing hemicarcerand hosts large enough to encase photosubstrates currently required for such isobenzofuran system generation.^{5†} Accordingly, we have sought ways to stabilise these highly reactive monomers other than having them so heavily substituted that their natural chemistry could be compromised.⁶

We report herein a new technique for stabilising isobenzofurans (rack-IBFs) by incorporating them into an alicyclophane macrocycle (**2**, Fig. 1).⁷ The concept depends on the rack section of the alicyclophane acting as a steric shield ($6.65 \times 6.81 \text{ \AA}$ in rack **3**, X-ray data⁸) that by its presence in rack-IBFs **9a** and **9b** inhibits intermolecular self-dimerisation or polymerisation processes. This motif should be applicable to other isobenzofuran systems (isoindoles, isoindenes and isobenzofulvenes) as well as elusive monomers such as cyclobutadiene and cyclopentadienones. The new rack-IBFs **9a** and **9b** are stable, high melting solids that could be isolated, handled as regular compounds and stored in solution for several days at 5 °C and for many months in the solid state.

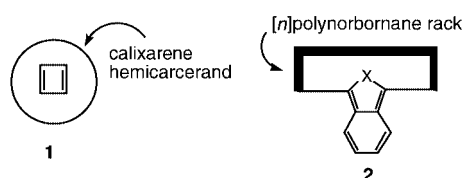


Fig. 1

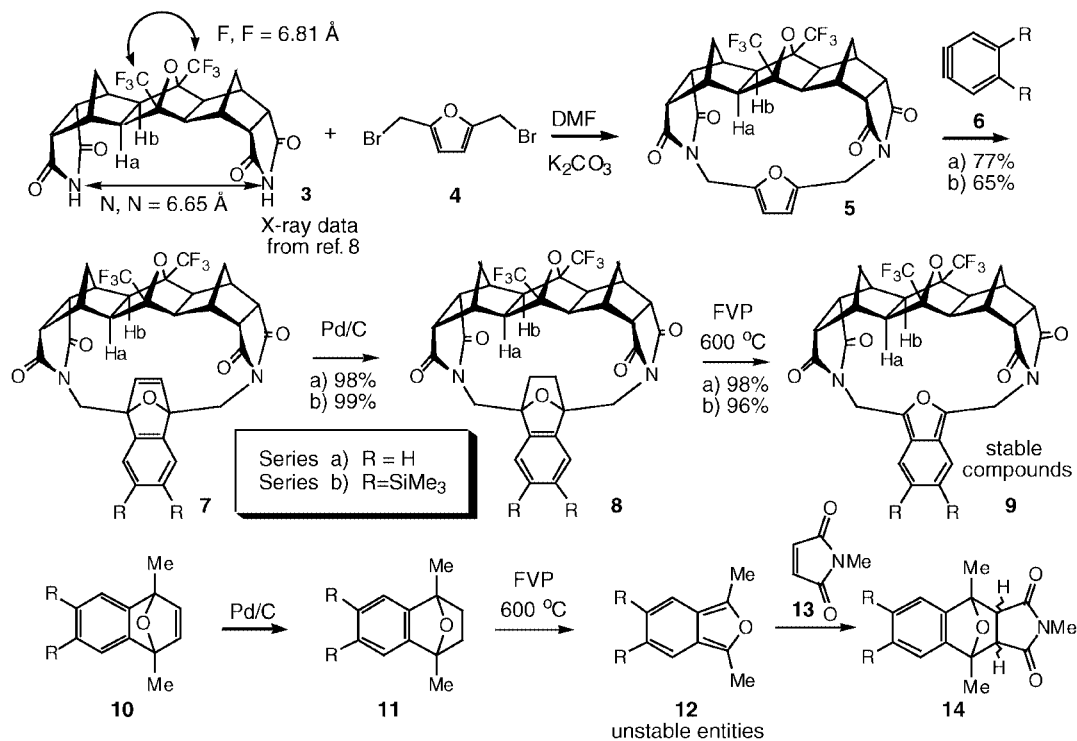
The synthesis of the parent rack-IBF **9a** commenced from the bis(succinimide) rack **3**⁷ which was reacted with 2,5-bis-(bromomethyl)furan **4** in dimethylformamide containing solid potassium carbonate to produce the furano-alicyclophane **5**⁹ in 84% yield (Scheme 1). Reaction of rack-furan **5** with benzyne **6a**, generated by diazotisation of anthranilic acid, gave the 1,4-epoxy-1,4-dihydronaphthalene derivative **7a** which was hydrogenated (Pd/C, H₂, 50 psi, 3 days) to the 2,3-dihydro compound **8a** and this subjected to flash vacuum pyrolysis (FVP, 500 °C, 0.001 mbar) to afford the rack-IBF **9a**, mp 199–201 °C, in 98% yield.^{10‡} The stability of rack-IBF **9a** contrasted strikingly with the structurally similar 1,3-dimethylisobenzofuran **12a** which, when generated under the same FVP conditions from **11a**, was found to form a polymer upon attempted isolation.§

The ¹H NMR spectrum of rack-IBF **9a** revealed that the rack *endo*-protons Ha, Hb were equivalent (δ 1.70) and upfield-shifted relative to those in rack-IBF **3** (δ 2.30) owing to the ring-current of the 10 π -isobenzofuran while the other rack protons occurred as overlapping resonances at δ 3.01 (bridgehead, succinimide) and an AB doublet (δ 2.19, δ 1.33 $J = 11$ Hz) for the methano bridges. Also, the aromatic protons appeared as an AA'BB' pattern at δ 6.99 and 7.59 while the *N*-methylene protons displayed a singlet resonance at δ 4.93 indicative of a rapid, pendulum motion of the IBF ring about the long σ -plane of the molecule.¶

While the isobenzofuran component of rack-IBF **9a** was stabilised against polymerisation (or homocycloadditions) by incorporation into the rack, it still retained the ability to react as a 4 π -diene with small 2 π -dienophiles to form [4 π + 2 π] Diels–Alder cycloadducts, e.g. reaction with *N*-methylmaleimide **13** was complete in 2 minutes (quantitative yield) and gave exclusively the *endo*-adduct (*N*-Me δ 2.25). In contrast, *N*-methylmaleimide **13** reacted more slowly (1 hour, RT) with the unstable 1,3-Me₂IBF **12a** and produced a 1:5 mixture of *exo*- (*N*-Me δ 3.03) and *endo*- (*N*-Me δ 2.23) isomers of **14** in 55% yield.

This rack-mounting strategy was general and FVP (500 °C, 0.001 mbar) of **8b** yielded rack-(TMS)₂IBF **9b** [¹H NMR δ 7.93 (s, 2H), 4.93 (s, 4H), 3.02 (s, 8H), 2.19 (d, $J = 11$ Hz, 2H), 1.73 (s, 4H), 1.56 (s, 4H), 1.28 (d, $J = 11$ Hz, 2H), 0.42 (s, 18H)], isolated as a stable crystalline product (96% yield), mp 312–314 °C. In a model study, 5,6-(TMS)₂-1,3-Me₂IBF **12b** was prepared by FVP (620 °C, 0.001 mbar) of the 1,4-epoxy-1,2,3,4-tetrahydro (TMS)₂ naphthalene **11b**. The non-crystalline product **12b** [¹H NMR δ 7.55 (s, 2H), 2.57 (s, 6H), 0.35 (s, 18H)] rapidly decomposed in CDCl₃ solution but could be characterised by treating the pyrolysate immediately after deposition with a solution of *N*-methyl maleimide **13** in CDCl₃ as its *endo*-adduct **14b** (67% yield).

In conclusion, we have demonstrated that incorporation of isobenzofurans into alicyclophanes to produce rack-IBFs dramatically increases their stability, yet achieves this without compromising the Diels–Alder capacity of the IBF component. This strategy should be applicable to other reactive monomers with a propensity for self-dimerisation, and experiments to test



Scheme 1

this proposal are currently being undertaken and results will be reported in due course.

Notes and references

† We have conducted a theoretical study (AM1) on the size compatibility of guests with Cram-type hemicarcerands as an aid to selecting hemicarcerands for photosubstrate incorporation (ref. 7).

‡ The incorporation of trifluoromethyl substituents into the alicyclophane improved their volatility and thermal stability, key factors required for application of this FVP technique.

§ Substituents at the 1,4-positions of 1,4-epoxy-1,4-dihydronaphthalene are known to restrict access of 3,6-di-2-pyridyl-s-tetrazine (ref. 11) to the π -bond and often preclude the use of this route to produce the corresponding IBF (ref. 12) in this study, attempts to prepare rack-IBF **9a** from **7** failed (too crowded), yet it is known that 1,3-Me₂IBF **12a** can be formed from **10a**. Removal of one or both 1,4-substituents allows the reaction to proceed, *e.g.* Wong and co-workers used the method successfully for the preparation of 5,6-(TMS)₂IBF and trapped it with *N*-phenylmaleimide (ref. 13).

¶ Protons Ha, Hb are non-equivalent in **7** and **8**, but are equivalent in **5** and **9**. The significance of these observations will be discussed elsewhere, (ref. 14).

|| The 4,5-bis(trimethylsilyl)benzynes **6b** required for the formation of **7b** from **5b** was generated from 1,2,3,4-tetra(trimethylsilyl)benzene by treatment with diacetoxyiodobenzene (ref. 15).

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9 All new compounds gave high-resolution mass spectra, ¹H and ¹³C NMR spectra corresponding to their assigned structures. Compound, mp (°C): **5**, >350; **7**, >350; **8**, >350; **9a**, 199–201; **9b**, 312–314; **14a** (*exo*), 105–106; **14a** (*endo*), 122–123; **14b** (*endo*) 186–187.

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