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Novel 'Windscreen Wiper' Cavity Structures Formed by the Cycloaddition of *N*-substituted Isoindoles onto Molrac *bis*-Alkenes

John R. Malpass,*[1] Guangxing Sun,[a] John Fawcett[b] and Ronald N. Warrener*[a]

a) Centre for Molecular Architecture, Central Queensland University, Rockhampton, Qld, 4702, Australia
b) X-Ray Crystallographic Unit, Department of Chemistry, University of Leicester, LE1 7RH, UK

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Abstract: A strong *N*-substituent effect is observed in the reaction of isoindoles with cyclobutene-1,2-diesters: *N*-alkyloxycarbonyl derivatives react to form adducts with bent-frame stereostructures; *N*-alkylisoindoles produce both extended-frame (stable) and bent-frame (unstable) stereoisomers, but require high-pressure conditions (10-15 kbar); *N*-acyl isoindoles fail to react. Reaction of *N*-benzyl tetrafluoroisoindole **6c** with *bis*-alkene **13** produced the first 'windscreen wiper' *N*-bridged cavity compound **12**, the structure of which was confirmed by X-ray analysis.

Several new types of organic molecules reported over recent years possess shapes and functions which have been modelled after traditional mechanical analogues. These include the train stations for rotoxane shuttles,[2] molecular ratchets,[3] molecular gears,[4] brakes,[5] turnstiles[6] and our own bell and clapper as a model for a molecular switch.[7] In the present communication, we report on a novel type of bridged nitrogen cavity molecule (Figure 1) based on a windscreen wiper analogy, where conformational change at the nitrogen atom acts as a mechanical fulcrum to modify access to the cavity (**A-D**). Interconversion between invertomers can occur in several ways: independent, single *N*-inversion, eg **B**↔**C** or by a dual windscreen wiper transition where both inversions occur in concert either in a conrotatory sense (**D**↔**C**) or disrotatory sense (**A**↔**B**).[8]

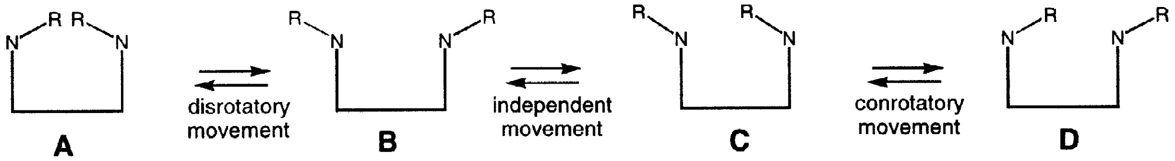

Figure 1. 'windscreen wiper' inversion of dual *N*-bridged cavity molecules

We have described several routes to rigid cavity structures,[10] but none of these has incorporated a *N*-bridge. Accordingly, we needed to develop appropriate chemistry to achieve this goal and we elected to investigate the role of isoindoles in cycloadditions onto rigid molrac *bis*-alkenes.[11] This approach allowed exploitation of our background in simple *N*-bridged chemistry[12] and draws on some related cycloaddition chemistry where isobenzofurans were used as delivery agents in the construction of cavity crown ethers.[14] Isoindole chemistry is an important but relatively unexplored area of cycloaddition chemistry,[15] and even simple questions relating to the effect of *N*-substituents on diene reactivity had not been investigated systematically.

We find that *N*-benzyloxycarbonylisoindole **6a** and *N*-methoxycarbonylisoindole **6b** are much better cycloaddition reagents than their simple *N*-alkyl counterparts *N*-benzylisoindole **6c** or *N*-methylisoindole **6d**, and that *N*-acetyl isoindole **6e** or *N*-benzoylisoindole **6f** are completely unreactive with dienophiles such as **8**.

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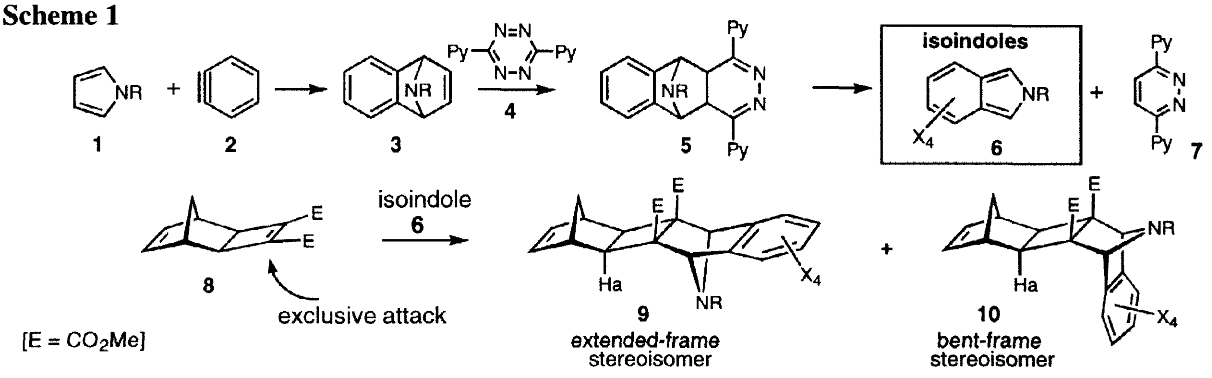
Table 1 Reaction of **8** with isoindoles **6a-6f**

6	X	R	conditions	9 (yield %)	Ha(δ)	10 (yield %)	Ha(δ)
6a	H	CO_2Bn	RT, $CHCl_3$	0		38	1.1
6b	H	CO_2Me	not conducted				
6c	F	Bn	14 kbar, DCM	61-69	2.14	28-31	1.04
6d	F	Me	14 kbar, DCM	34	2.11	0	
6e	H	COMe	no reaction thermally; too unstable for high pressure study				
6f	H	COPh	no reaction thermally; too unstable for high pressure study				

Scheme 1



Thus, the *N*-alkyloxycarbonyl isoindole **6a**, generated using the *s*-tetrazine route shown in Scheme 1,[11] was reacted *in situ* with the test ambident dienophile **8** to yield cycloadduct **10**. The *N*-alkyl isoindoles **6c** and **6d** are more stable and no reaction occurred at temperatures up to 100 °C (with or without Lewis acid catalysts) at atmospheric pressure. As the tetrafluroisoindoles **6c** and **6d** can be isolated as crystalline solids,[11] cycloadditions were conducted under ultra high-pressure (14 kbar)[16] and this allowed access to cycloaddition products **9c**, **9d** and **10c**, **10d**.

In each case, exclusive site selectivity occurred at the cyclobutene π-system where formation of the extended-frame stereoisomers[18] is favoured with the *N*-alkyl isoindoles, while the bent-frame stereoisomers[18] dominated almost exclusively in the *N*-alkyloxycarbonyl isoindole cycloadditions (see Table 1).

Thus stereoselectivity can be controlled in these cycloaddition reactions simply by modifying the *N*-substituent of the isoindole. Removal of *N*-CO_2R and *N*-Bn groups to give secondary amines is well precedented and should allow access to a wide range of derivatives.[12] Bent-frame isomers formed as coproducts in the *N*-alkyl isoindole cycloadditions, eg **10c** and **10d**, are not stable in solution at atmospheric pressure and revert to starting materials at room temperature.[19]

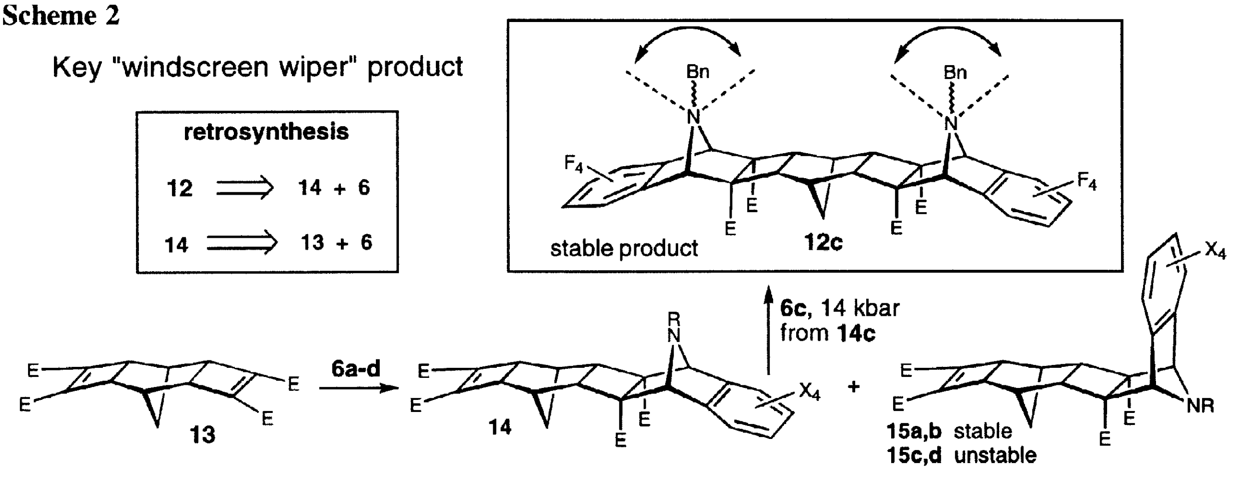
Stereostructural assignments to these products are readily made on the basis of chemical shift data. The *endo*-methine protons (Ha) move significantly upfield when shielded by the proximate benzene ring (bent-frame isomers) compared with those where this ring is remotely positioned (extended-frame isomers). Similar shielding effects operate on the ester-methyl groups, but they are not so pronounced.

Retroanalysis of 'windscreen wiper' cavity structure **12** (Scheme 2) shows that the extended-frame isomer stereoselectivity is required in the isoindole cycloaddition step, so the reactions between *N*-alkyl isoindoles **6c** and **6d** with molrac *bis*-alkenes **13** and **17** were investigated. The most successful reaction occurred between *bis*-alkene **13** and *N*-benzylisoindole **6c**. Both 1:1-adducts and 1:2-adducts were produced, and by using excess isoindole and a Lewis acid (see Table 2), a significant proportion of the required 1:2-adduct **12c** could easily be obtained as a stable, crystalline compound. The structure of this 'windscreen wiper' product **12c** was confirmed by X-ray crystallography (Figure 2),[21] which showed that the outward-facing conformation of the *N*-substituents, eg **B** in Figure 1, was favoured in the crystalline state. NMR analysis on the solution conformations of **12c** is still being investigated, but line broadening indicates that substituent mobility is occurring at room temperature.[22]

Table 2 Reaction of **13** with isoindoles **6a** - **6d**

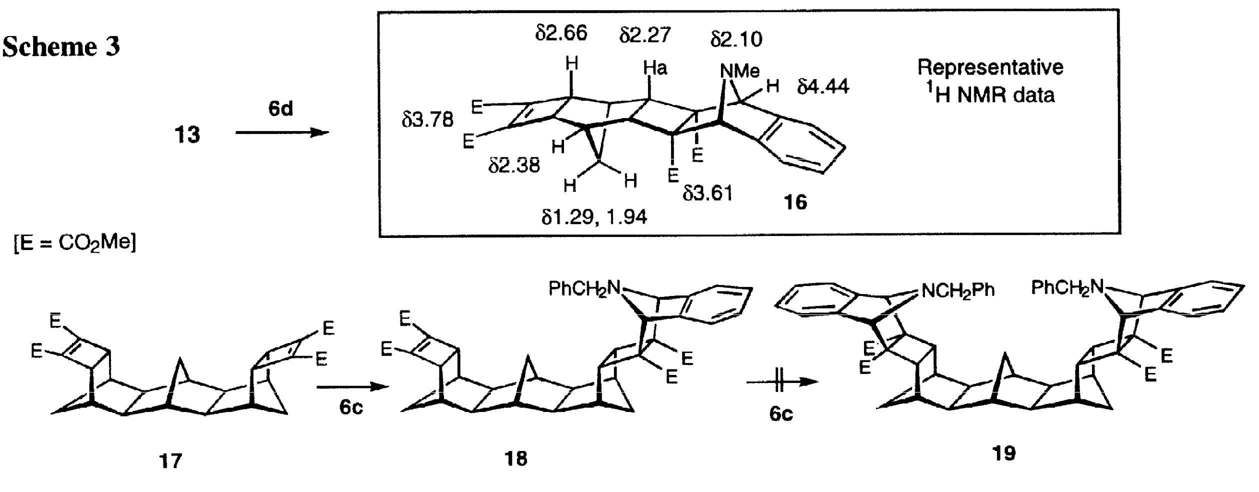
isoindole	conditions	12 (%)	14 (%)	15 (%)	recovered 13
6a	$CHCl_3$, RT, 12h	0	0	41	-
6b	$CHCl_3$, RT, 12h	0	7	21	-
6c	DCM, 14 kbar, 3d, **13**:**6**=1:2	0	26	53	20
6c	DCM, 14 kbar, 4d, **13**:**6**=1:3	17	51	24	8
6c	DCM, 14 kbar, 4d, **13**:**6**=1:3, $ZnCl_2$	36	44	15	5
6d	DCM, 14 kbar, 4d, 13:6=1:3	0	34	0	-

Scheme 2



Attempts to prepare the *N*-methyl analogue of **12** from reaction of **6d** with **13** produced only the 1:1-adduct **16**. The ^{1}H NMR data (see annotations on **16**, Scheme 3), in particular the chemical shift of Ha, support the stereostructural assignment to **16**. Similarly, the reaction of *N*-benzyl isoindole **6c** with cavity *bis*-alkene **17**[23] (Scheme 3) stopped at the 1:1-stage and yielded only the mono cycloadduct **18**, albeit with the required stereostructure. In each case, further investigation is being conducted to achieve better models for studying the potential of 'windscreen wiper' molecules to be used in host, guest chemistry.

Scheme 3



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21. Crystal data for **12c**: $C_{50}H_{38}Cl_8F_8N_2O_8$, M=1017.7, colourless plate, 0.59x0.27x0.12mm, Triclinic, space group $P\bar{1}$, a=11.892(3), b=14.141(3), c=15.159(4)Å, α=83.00(2), β=77.76(2), γ=66.62(2)°, U=2284.7(9) $Å^3$, Z=2, D_c =1.479gcm^{-3}, F(000)=1044, μ=(Mo-K_α) 0.233mm^{-1}. Intensity data were collected on a Siemens P4 diffractometer using ω scans and graphite monochromated Mo-K_α radiation (λ=0.71069Å) to $2\theta_{max}$ of 50°. 7648 unique reflections were measured with 4482 having $F>4\sigma(F)$. Refinement on F^2 with anisotropic displacement parameters for all non-hydrogen atoms converged to R_1=0.0629 and wR_2=0.185 (all data).
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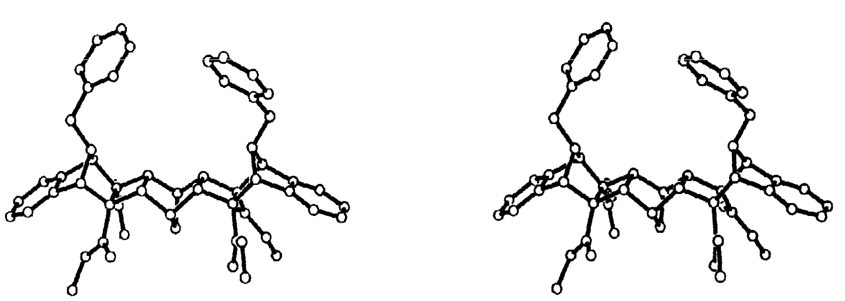

Figure 2 Stereoview of X-Ray structure of 'windscreen wiper' cavity structure **12c**.