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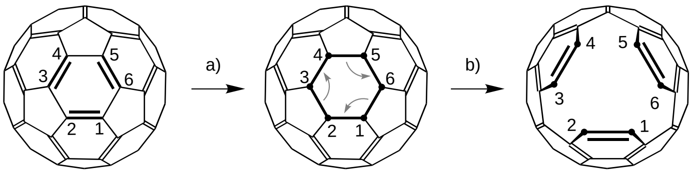
Formation of an Effective Opening within the Fullerene Core of C_{60} by an Unusual Reaction Sequence**

Georg Schick, Thibaut Jarrosson, and Yves Rubin*

With the formation of a large orifice in the fullerene shell, the potential arises to introduce practically any atom inside these hollow structures. This constitutes a critical step for the development of a powerful method to produce endohedral fullerene complexes.[1] Thus far, the task of opening an effective aperture on the surface of fullerenes has proven very challenging.[1, 2] Although up to three bonds[2f] are cleaved in current ring-opening reactions, the relative positions of the fullerene carbon atoms are maintained by bridging addends, whose steric requirement can further hinder accessibility of the cavity.

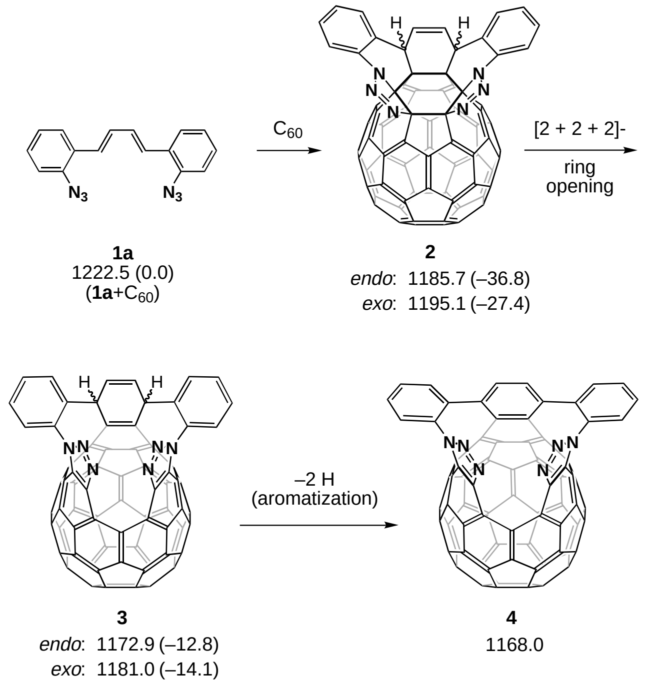
These restrictions can be eliminated by placing three adding groups within a relatively rigid, preorganized reactant such as a macrocycle.[1b] Threefold addition of the reactive moieties to three endocyclic $C{=}C$ bonds of C_{60} ([6,6] junctions) results in a fully saturated, strained planar cyclohexane moiety (Scheme 1).



Scheme 1. a) Addition of six saturating groups. b) [2+2+2] ring-opening reaction.

This arrangement promotes a facile [2+2+2] ring-opening reaction following a mechanism similar to that of all presently known fullerene ring scission reactions, for example, those leading to [5,6] ring-opened methanofullerenes (fulleroids).[3]

The system chosen for this initial study is based on the relatively rigid diazidobutadiene system **1a** (Scheme 2). Azide and Diels–Alder cycloadditions to C_{60} have been studied extensively.[3–5] Possible side reactions of the fragile triazoline moieties formed by azide additions include the formation of [5,6]-iminofullerenes and/or [6,6]-aziridinofullerenes under loss of N_2.[6] Semiempirical calculations on the



Scheme 2. Conceptual set of reactions at the origin of this work with calculated (AM1) heats of formation [$kcal\,mol^{-1}$] (the relative energies at each step are given in parentheses).

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putative intermediates **2**–**4** predict that the critical [2+2+2] ring opening of **2** to **3** is favored (Scheme 2). In this fragmentation, three [5,6] bonds within the saturated six-membered ring are cleaved, assisted by the aromatization of two triazoline moieties in **2** to the triazoles of compound **3**. Aromatization of the cyclohexadiene ring in **3** by oxidation to afford **4** further enlarges the orifice to a point that leaves enough space for any atom or ion to pass through (Figure 1).

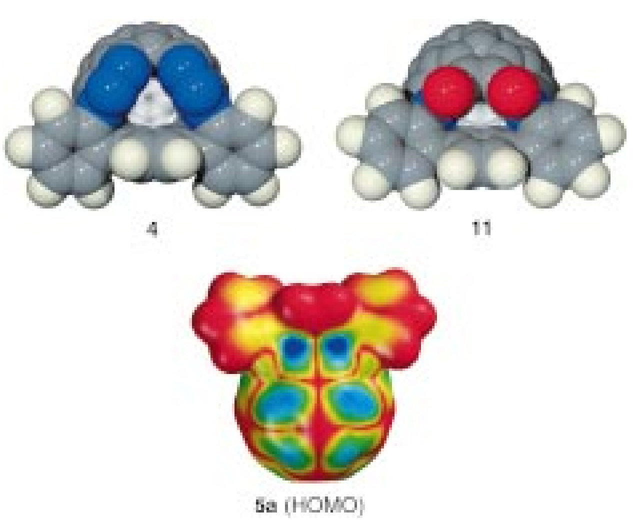
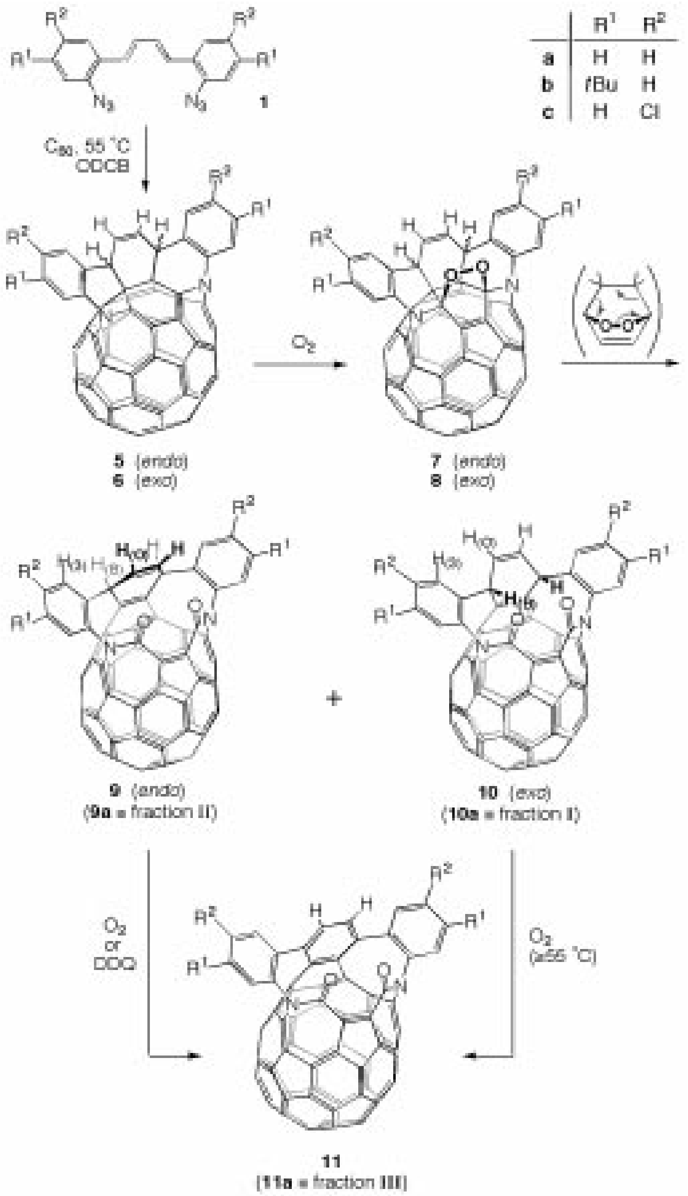


Figure 1. Space-filling representations of the open fullerenes **4** and **11**, and the HOMO density of **5a** projected on an electron potential surface (0.002 electron Å^{-2}).

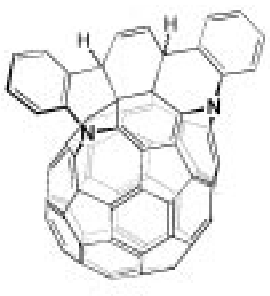
Comparison with a known complex of a [2.2.2]paracyclophane having a gallium(I) ion lodged deep inside the cyclophane cavity reveals that the three phenylene rings have practically identical spacing as the triazole and benzene moieties of **4**.[7, 8]

The reaction of diazidobutadiene **1a**[8] with C_{60} was carried out at 55 °C for four days in *ortho*-dichlorobenzene (ODCB) under exclusion of air (argon), resulting in a brown solution containing three major products (TLC, SiO_2, toluene/EtOAc 8/2). After flash chromatographic isolation (toluene/EtOAc 99/1 →80/20), ^1H and ^{13}C NMR spectra provided encouraging data for all three compounds, showing that they are part of a homologous C_s-symmetric series.[8] The higher polarity fraction (**III**, $R_f = 0.20$) has two benzylic hydrogen atoms less than the two lower polarity products **I** and **II** ($R_f = 0.53$ and 0.40, respectively), confirming that a dehydrogenation takes place and that the two possible *endo* and *exo* Diels–Alder products are formed. On the other hand, the presence of ^{13}C carbonyl resonances at $\delta \approx 162$ for all three products and a carbonyl stretch at 1691 cm^{-1} (**II** and **III**) and at 1682 cm^{-1} (**I**) in the IR spectra indicates the presence of a lactam moiety.[2a] High-resolution FAB mass spectra reveal that all three compounds have four nitrogen atoms less than the putative products *endo*-**3**, *exo*-**3**, and **4**, and addition of two extra oxygen atoms.

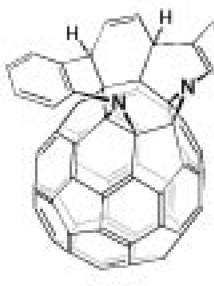
Since the loss of nitrogen and addition of oxygen to form two symmetrically disposed amide groups indicates that side reactions of the primary adduct(s) must take place, alternative pathways were examined to explain these results.[9] As explained below, it was determined that products **I**, **II**, and **III** are in fact the unusual bisamides **10a**, **9a**, and **11a**, respectively (Scheme 3). We found initially that the 1,4-diarylbutadiene moiety[10] does not react with C_{60} by itself, showing that the azide group must add first to give a triazoline. Subsequent Diels–Alder addition should be favored by the intramolecular effect,[11, 12] affording the corresponding azide + diene addition product and possibly compound **2**. Either of these intermediates can rearrange at any time to form [5,6]-iminofullerene or [6,6]-aziridinofullerene moieties. Of the corresponding C_s-symmetric structures (Table 1), the *endo*/*exo* isomers **5a** and **6a** with bis([5,6])-iminofullerene moieties are greatly favored over the strained [6,6]-aziridinofullerene isomers **5′a** and **6′a** . Alternative modes of azide + diene + azide additions of **1a** to C_{60} were rejected based on AM1 product energies and the restriction to C_s symmetry.



Scheme 3. Reaction pathway leading to products **9**, **10**, and **11**.



5a/6a



5'a/6'a

Table 1. Calculated (AM1) heats of formation [kcal mol^{-1}] (relative energies are given in parentheses) for two reaction pathways starting from compound **2** (or partially cyclized precursors) and affording C_s-symmetric products with loss of four nitrogen atoms.

Regioisomer	*endo*[a]	*exo*[a]
[5,6/5,6]	**5a**: 1078.52 (0.0)	**6a**: 1083.17 (4.7)
[6,6/6,6]	**5′a**: 1088.97 (10.5)	**6′a**: 1195.92 (117.4)

[a] Relative stereochemistry with respect to the HC=CH bridge resulting from the Diels–Alder step.

The two nitrogen atoms bridging the former [5,6] bonds of **5** and **6** are part of a very electron rich 1,4-diaminobutadiene moiety on the fullerene framework.[13] This unprecedented situation places HOMO orbital lobes with very large coefficients at the 1- and 4-carbon atoms attached to the nitrogens (Figure 1, Scheme 3). Hence, attack of these positions by singlet oxygen[14] affords the endoperoxides **7** and **8**, which rearrange by spontaneous [2+2+2] ring opening under the formation of two amide moieties in **9** and **10**. AM1 calculations largely favor this fragmentation by 130–136 kcal mol^{-1} (Table 2). This reaction is not a common fragmentation pathway for endoperoxides, but has precedent when a leaving group can be ejected.[15] The leaving group in **7/8** is the relatively strained sp^3–sp^3 C–C moiety of the nascent cyclohexadiene rings. The rearrangement concurrently forms the two amide groups of **9/10** that are stabilized by resonance.

Table 2. Calculated (AM1) heats of formation [kcal mol^{-1}] (the relative energies at each step are given in parentheses) for the unsubstituted series **5a**–**11a**.

Compound	*endo*[a]	*exo*[a]
C_{60} + **1a**	1222.52 (0.0)	
5a/6a	1078.52 (−144.0)	1083.17 (−139.4)
7a/8a	1090.70 (+12.9)[b]	1092.88 (+9.0)[b]
9a/10a	954.93 (−135.8)	962.84 (−130.0)
11a	951.04	

[a] Relative stereochemistry with respect to the HC=CH bridge resulting from the Diels–Alder step. [b] The AM1 heat of formation for $^1O_2$ (0.73) is included with those of **5a** and **6a** for these numbers.

The aromatized bislactam **11** (Figure 1, Scheme 3), which is isolated in up to 12% yield as the major product when some oxygen is present, is the dehydrogenation product of **9** and **10**. Dehydrogenation of *endo*-**9a** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) occurs instantaneously at 25 °C, while *exo*-**10a** does not react over 48 h due to the relative inaccessibility of its benzylic hydrogen atoms. Dehydrogenation of *exo*-**10a**, however, occurs under air over the course of 2 h at 100 °C in ODCB.

The *endo/exo* configurations of **9a** and **10a** can be assigned based on NOE interactions in 2D T-ROESY experiments.[11] The *exo*-isomer **10a** has strong interactions between $H_{(3)}$ and $H_{(O)}$ ($\delta = 7.77$ and 7.20) and between $H_{(O)}$ and $H_{(B)}$ ($\delta = 5.59$). The *endo*-isomer **9a** displays strong interactions of the aromatic hydrogen atoms $H_{(3)}$ ($\delta = 7.60$) with the benzylic hydrogen atoms $H_{(B)}$ ($\delta = 4.47$), which themselves show a cross-peak with the olefinic hydrogen atoms $H_{(O)}$ ($\delta = 6.18$). The ^1H NMR spectra of **9a** and **10a** have quite different chemical shifts of either set of benzylic or olefinic absorptions, reflecting the different environments in the two isomers. In particular, the *endo* benzylic hydrogen atoms $H_{(B)}$ of **10a** pointing directly toward the amide oxygen atoms are deshielded by 1.12 ppm compared to those of **9a**.

The two other series of derivatives were prepared for their higher solubility and for crystallization attempts.[9] In all these reactions, the 1,4-diaminobutadiene systems **5a**–**c** or **6a**–**c** are never observed, pointing to their extreme reactivity even under relatively good exclusion of air. However, their intermediacy was confirmed by trapping **5a/6a** with the dienophile *p*-benzoquinone (**12**), which itself does not react with the diene or azide moieties of **1a** under the conditions of the experiment (**12** + **1a** + C_{60}, ODCB, 55 °C, 4 d). Remarkably, the two products **13** and **14** were obtained as the only products in a ratio of 6:1 in 13 and 2% yield, respectively (Figure 2). The stereochemistry of both compounds was established from 2D T-ROESY data, showing in particular that benzoquinone adds only in a *syn* fashion relative to the 1,4-diaminobutadiene moieties of *endo*-**9a** and *exo*-**10a**. The presence of a signal for an sp^3 carbon atom at $\delta = 75.5$ (**13**) and $\delta = 72.5$ (**14**) in the ^{13}C NMR spectra leaves no doubt as to the conversion of the nitrogen-attached sp^2 carbon atoms into sp^3 carbon atoms. The latter set of Diels–Alder and singlet oxygen additions constitute the first examples of a diene moiety within the fullerene core participating as a 4π-electron system in a cycloaddition reaction.[3]

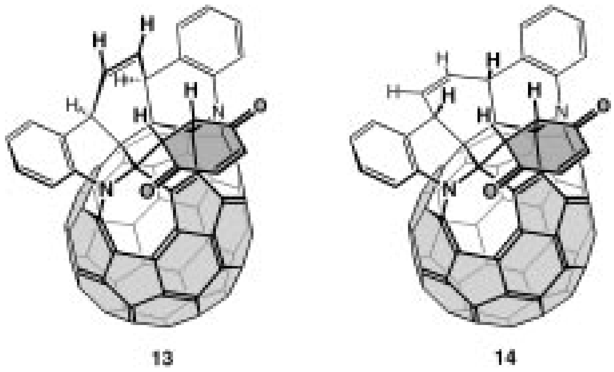


Figure 2. Structures of the Diels–Alder trapping adducts **13** and **14**.

The scission of four bonds within the fullerene cage in this reaction sequence provides very efficient formation of the largest orifice created so far on a fullerene. The opening of **11** may be large enough to allow the smallest atoms, molecules, or ions (He, H_2, Li^+, Be^{2+}) to pass through, a possibility that is currently under investigation. The cavity of **11** is essentially restrained only by the third unopened five-membered ring bearing an unfavorable endocyclic [5,6] double bond, and oxidation or other addition reactions may be able to cleave this bond. More importantly, the fragile azide functions of dienes **1a–c** can be replaced with other 1,3-dipoles to effect a reaction course similar to that of Scheme 2. Preliminary experiments with the bis-nitrile oxide system analogous to **1a** provide encouraging results.

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Self-Assembly of a Tetrahedral Lectin into Predesigned Diamondlike Protein Crystals[**]

Nir Dotan, Dorit Arad, Felix Frolow, and
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The implementation of chemical and structural principles for the construction of supramolecular one-, two-, and three-dimensional arrays was demonstrated by the self-assembly of synthetic organic molecules.[1–8] The analogous use of nucleic acids or proteins as building blocks offering uniform molecular population, larger structures, and specific intermolecular recognition is, however, far from being fully exploited. Branched DNA molecules were successfully ligated into a cube[9] and a truncated octahedron,[10] or self-assembled into a two-dimensional array.[11] Two-dimensional protein crystals were readily assembled by reconstruction of bacterial cell surface layers on a solid support,[12] two and three distinctive "unidirectionally" oriented protein layers were assembled on metallic surfaces or liposomes,[13, 14] and bispecific antibodies were employed for the construction of an oriented monolayer of bacteriorhodopsin on a metalic surface.[15]

To the best of our knowledge, self-assembly of proteins into a predesigned three-dimensional protein lattice has not been described. The development of methodologies for the for-

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