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Facile, Completely Regioselective 1,4-Hydrogenations of C_{60}-Diaryltetrazine Monoadducts

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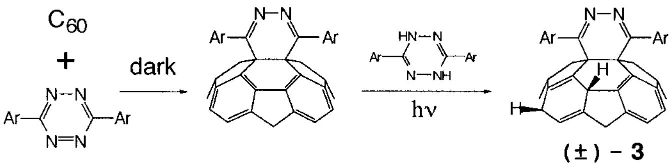
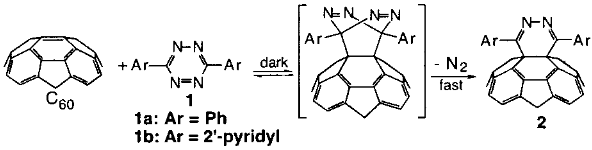
ABSTRACT



Thermal Diels–Alder reactions between C_{60} and electron-deficient 3,6-diaryl-1,2,4,5-tetrazines yield monoadducts possessing a diaryldihydropyridazine function nested atop the fullerene. The diaryldihydropyridazine functions direct a completely regioselective 1,4-hydrogenation, resulting in a racemic mixture of bifunctional bisadduct (±)-3.

C_{60} behaves as an electron-deficient dienophile in Diels−Alder reactions with numerous electron rich dienes including anthracene,[1] pentacene,[2] cyclopentadiene,[3] and *o*-quinodimethane.[4] Interested in appending electron deficient functionalities onto a fullerene[60], we began an investigation of the Diels−Alder reactivity between C_{60} and electron-deficient 3,6-diaryl-1,2,4,5-tetrazines **1**. We now report that reactions between C_{60} and **1** proceed in modest yield to produce diaryldihydropyridazine monoadducts **2** which in turn undergo facile, *completely regioselective* 1,4-hydrogenations to produce racemic mixtures of bifunctional bisadducts (±)-**3**. The hydrogenations are photoinduced (ambient light) and rely upon the formation of catalytic dihydrotetrazine (vide infra). Dihydrotetrazine is readily formed in situ via reaction between photoexcited **1** and fortuitous water adsorbed on glass.

Synthesis and Structure of 2. Upon reacting 3,6-diphenyl-1,2,4,5-tetrazine, **1a**, or 3,6-di(2′-pyridyl)-1,2,4,5-tetrazine, **1b**, with 1 equiv of C_{60} in refluxing toluene in the dark, the initial Diels−Alder product undergoes a rapid retro-Diels−Alder reaction with loss of N_2 to afford the corresponding monoadduct, **2a** or **2b**, respectively (eq 1). N_2 extrusion from the tetraazabicyclo[2.2.2] intermediate renders the cycloaddition irreversible.



[1]

The crude product is rinsed thoroughly with acetone to remove unreacted tetrazine and other nonfullerene[60]

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(1) (a) Schlueter, J. A.; Seaman, J. M.; Taha, S.; Cohen, H.; Lykke, K. R.; Wang, H. H.; Williams, J. M. *J. Chem. Soc., Chem. Commun*. **1993**, 972. (b) Komatsu, K.; Murata, Y.; Sugita, N.; Takeuchi, K.; Wan, T. S. M. *Tetrahedron Lett*. **1993**, *34*, 8473. (c) Tsuda, M.; Ishida, T.; Nogami, T.; Kurono, S.; Ohashi, M. *J. Chem. Soc., Chem. Commun*. **1993**, 1296.

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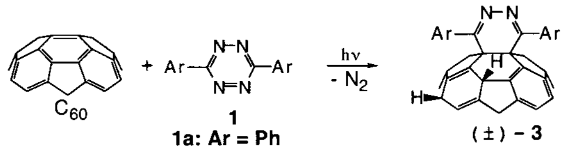
byproducts including dihydrotetrazine (vide infra). Chloroform-soluble monoadduct **2** is then obtained in approximately 50−60% yield via simple chloroform rinsing. Small quantities of unreacted C_{60} remain in the chloroform layer, and these can be removed, if desired, via flash silica column chromatography. Products of multiple tetrazine addition (e.g., bistetrazine adducts, tristetrazine adducts, etc.) are not observed under these conditions. ^{1}H and ^{13}C NMR spectra confirm formation of C_{2v} symmetric structures[5] consistent with cycloaddition across 6,6 π-bonds in starting fullerene[60]. Electrospray MS yields an MH^+ ion at m/z 929 for monoadduct **2b**.

Regioselective Formation of (±)-3. When the same reactions are performed in refluxing toluene and ambient light rather than darkness, a different set of products is produced. As before, each reaction gives only one fullerene[60] product whose spectroscopy is consistent with a single tetrazine cycloaddition. The new products show enhanced solubility in a variety of organic solvents, are decidedly less symmetric than **2**, and otherwise possess spectroscopic features[5] consistent with hydrogenated structures (±)-**3a** and (±)-**3b** (eq 2) in which carbon atoms 4 and 15 each bear a new C−H bond.[6]



[2]

1
1a: Ar = Ph
1b: Ar = 2'-pyridyl

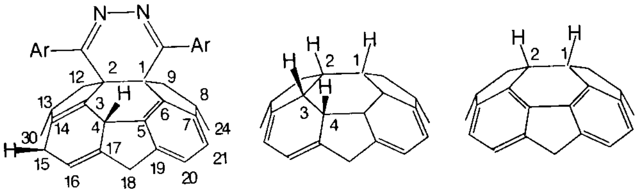
(±) – 3

Ample data demonstrate that the Diels−Alder addition of diaryltetrazine precedes hydrogenation. Thus, ^{1}H NMR analyses of crude reaction mixtures show **2** alone for reactions run in the dark and either mixtures of **2** and (±)-**3** or more typically (±)-**3** alone for reactions run in ambient light. Moreover, isolated **2** readily hydrogenates in regioselective fashion to afford (±)-**3** under comparable reaction conditions (vide infra). We have never observed 1,4-dihydrofullerene[60] as an intermediate.

The hydrogenation of **2** proceeds with *complete regioselectivity*. Reactions run under a variety of conditions with variable solvent, temperature, and reaction time repeatedly produce but one product, (±)-**3**. Apparently, the diaryldihydropyridazine addend exerts a strong directing influence over hydrogenation. Likewise, hydrogenated (±)-**3** should possess a structure in which the new C−H bonds are located close to the diaryldihydropyridazine addend. If hydrogenation occurred at sites well removed from the diaryldihydropyridazine addend, then there would be no reason to expect a regioselective addition. In this case, formation of multiple hydrogenation regioisomers, all energetically similar, would be expected.

Structure of (±)-3. ^{1}H NMR spectra for (±)-**3a** and (±)-**3b** show 10 and 8 aromatic resonances, respectively, indicating the absence of a symmetry plane. Moreover, each spectrum contains a pair of AB doublets at approximately 6.5 ppm with each doublet integrating for a single proton. The AB coupling constant is 1.8 Hz, consistent *only* with a 1,4-arrangement of hydrogen atoms on (±)-**3** and ^5J coupling. Comparable ^5J, ^4J, $^3J(6,6)$, and $^3J(5,6)$ constants are available[7a,b] from the published spectra for 1,2,3,4-tetrahydrofullerene[60], **4**, and they are +1.7, −0.2, +14.1, and +9.8 Hz, respectively (Table 1). ^{13}C NMR spectra for (±)-**3a** and (±)-**3b** show 60+ carbon signals each, including occasional coincidental overlap in the sp^2 region and a set of 4 resolved signals at higher field in the sp^3 region. Decoupled ^{13}C NMR spectra show nuclear overhauser enhanced intensities for the two highest field signals, and these resonances are thus assigned to the fullerenic methines (C4 and C15) rather than the fullerenic quaternary carbons (C1 and C2) on (±)-**3**. Comparable ^{13}C NMR shifts are not available for **4**, but the published ^{13}C spectrum[7c] for 1,2-dihydrofullerene[60], **5**, includes a fullerenic methine signal at 54.1 ppm, in close agreement with the fullerenic methine shifts (54−57 ppm) for (±)-**3**. Select ^{1}H and ^{13}C NMR features of (±)-**3a**, (±)-**3b**, **4**, and **5** are summarized in Table 1.

Table 1. Select ^{1}H and ^{13}C NMR Data (δ, ppm) for (±)-**3a**, (±)-**3b**, **4**, and **5** in CS_2 or $CS_2/CDCl_3$ Solvent



(±) – 3 **4** **5**

	^{1}H NMR					^{13}C NMR
		coupling constants (Hz)				
	C_{sp^3}-H	$^3J(6,6)$	$^3J(5,6)$	^4J	^5J	C_{sp^3}-H
(±)-**3a**	6.40				1.8	54.1
	6.56					56.9
(±)-**3b**	6.62				1.8	54.2
	6.65					55.7
4[a]	5.73	14.1	9.8	−0.2	1.7	
	6.32					
5[b]	6.97					54.1

[a] See ref 7b. [b] See ref 7c.

While ^{1}H NMR coupling constant data convincingly point to a 1,4-hydrogenation pattern, the ^{1}H NMR spectra offer little other regiochemical information[8] except to rule out a select few 1,4-hydrogenation patterns which would require

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[5] UV/vis, ^{1}H NMR, and ^{13}C NMR data are available as Supporting Information for **2a**, **2b**, (±)-**3a**, and (±)-**3b**.

[6] The numbering scheme utilized is that proposed by IUPAC. See: Godly, E. W.; Taylor, R. *Pure Appl. Chem.* **1997**, *69*, 1411.

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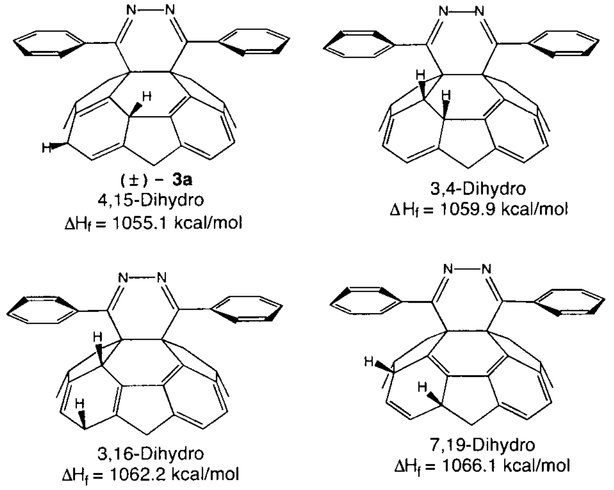
a product of higher symmetry than that observed (e.g., hydrogenation at C15 and C30). To narrow the number of potential structures for (±)-**3**, AM1 semiempirical calculations were utilized. Upon confining our search to structures in which new C−H bonds are placed within close proximity of the diaryldihydropyridazine function, the calculations unambiguously lead to the structure shown for (±)-**3** in which carbon atoms 4 and 15 each bear a hydrogen atom (Figure 1). The calculations demonstrate that the relative stabilities of (±)-**3** and its dihydro regioisomers are primarily influenced by two factors: (a) the presence of 6,5 π-bonds on the fullerene[60] surface and (b) a potentially close van der Waals encounter between one or both of the methine hydrogens and an aromatic ring of the diaryldihydropyridazine function. It is well established that 6,5 π-bonds on fullerene[60] are somewhat destabilized relative to their 6,6 π-bond counterparts. Accordingly, most additions to C_{60} occur in a 1,2-fashion across an existing 6,6 π-bond such that no new 6,5 π-bonds are produced. Hydrogenation reactions on bare C_{60} are not an exception.[7,9] Thus, the only dihydrofullerene[60] isomer isolated to date is the 1,2-dihydrofullerene[60] in which addition occurs across a 6,6 π-bond. Because a 1,4-hydrogenation pattern necessarily creates a destabilizing 6,5 π-bond (e.g., between C3 and C14 in (±)-**3**), the 4,15-, 3,16-, and 7,19-dihydro isomers (Figure 1) all suffer energetically. Of these structures, however, only the 4,15-dihydro regioisomer, (±)-**3**, avoids the van der Waals strain resulting from close contact between a methine H and an aromatic ring of the diaryldihydropyridazine addent. AM1 calculations predict this van der Waals interaction to be energetically more costly than a 6,5 π-bond as evidenced by the fact that (±)-**3** is nearly 5 kcal/mol more stable than the 3,4-dihydro regioisomer despite the fact that the latter structure has no destabilizing 6,5 π-bonds (Figure 1). Our confidence in the AM1 assignment of H's to C4 and C15 in (±)-**3** is reinforced by the fact that we do not observe formation of the 3,4-dihydro regioisomer nor any other regioisomer in which hydrogenation occurs in a 1,2-fashion.


(±) - 3a
4,15-Dihydro
ΔH_f = 1055.1 kcal/mol

3,4-Dihydro
ΔH_f = 1059.9 kcal/mol

3,16-Dihydro
ΔH_f = 1062.2 kcal/mol

7,19-Dihydro
ΔH_f = 1066.1 kcal/mol

Figure 1. AM1-calculated heats of formation for (±)-**3a** and other dihydro regioisomers.

Recent work by Haddon, Meier, and co-workers[10] concerning enhanced reactivity of π-bonds surrounding the bridging atom(s) of a [5,6]-fulleroid structure are relevant to the present discussion. Theory[10a] indicates that pyramidalization angles for carbon atoms in the immediate vicinity of fulleroid addends are actually reduced compared to C_{60} (11.6°). However, π-orbital misalignment angles are greatly increased (0° for C_{60}). Consequently, π-bonds adjacent to the bridging atom(s) in a [5,6]-fulleroid are somewhat twisted and more reactive than other π-bonds in the structure. Experiment[10b] confirms enhanced reactivity of bridgehead (anti-Bredt) alkene functions in $C_{61}H_2$, a [5,6]-fulleroid. Hydrogenation of $C_{61}H_2$ is regioselective, the major product having new C−H bonds at C1 and C2, site of a former bridgehead alkene. **2** is not a fulleroid and contains no anti-Bredt alkene functions. Nonetheless, π-orbital misalignment angles at π-bonds surrounding the diaryldihydropyridazine addend are likely significant and may enhance reactivity in this region of the molecule.

Mechanism for Formation of (±)-3. In separate experiments with either toluene, benzene, CS_2, or toluene-d_8 as solvent, *protio*-**(±)-3** is consistently produced. Consequently, solvent can be ruled out as the source of hydrogen. Considering that both hydrazine[9d] and diimide[7b] are known to reduce C_{60} and that the synthesis of 3,6-diaryl-1,2,4,5-tetrazine culminates with an oxidation of the corresponding dihydrotetrazine, **6**, we considered the possibility that **6** may be responsible for the observed hydrogenation of **2**. **6** was not, however, detected by ^{1}H NMR spectroscopy in our tetrazine reactant and was certainly not present in quantities sufficient for *stoichiometric* hydrogenation of **2**. Control experiments revealed two important facts: (1) monoadduct

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(8) Some additional regiochemical information can be gathered from the ^{1}H NMR spectra of (±)-**3a** and (±)-**3b**. The ^{1}H NMR spectrum for (±)-**3b** includes 8 pyridyl proton resonances, two of which coincidentally overlap at approximately 8.0 ppm. These 8 resonances exist as 4 pairs of ^{1}H signals, one pair for the 2 unique 3′-protons, one pair for the 2 unique 4′-protons, etc. By analogy to the known spectrum for bis(2′-pyridyl)-1,2,4,5-tetrazine, the quasi-doublets at lowest field are safely assigned to the 2 unique 3′-protons on (±)-**3b**. The remaining set of quasi-doublets at 8.21 and 7.98 ppm must then be assigned to the two unique 6′-protons. The chemical shift differences between the individual resonances of each pair are decidedly larger for the 6′-protons ($\Delta\delta \sim 0.23$ ppm) than for the other pairs (0.10−0.16 ppm), suggesting significantly different electronic environments for the 6′-protons. These data is consistent with structure (±)-**3b** in which the fullerenic methine protons are spatially close to one (and only one) of the pyridyl 6′-protons. The ^{1}H NMR spectrum for (±)-**3a** is more compelling: 6 phenyl proton resonances are observed with all but the 4 *o*-protons coincidentally overlapping between 7.56 and 7.67 ppm. The chemical shift differences between the individual resonances of the *m*- and *p*-protons is small. By contrast, the 4 *o*-protons, 2 of which are closest to the fullerenic methines in (±)-**3a**, exist as a pair of quasi-doublets centered at 8.29 and 8.68 ppm ($\Delta\delta = 0.39$ ppm).

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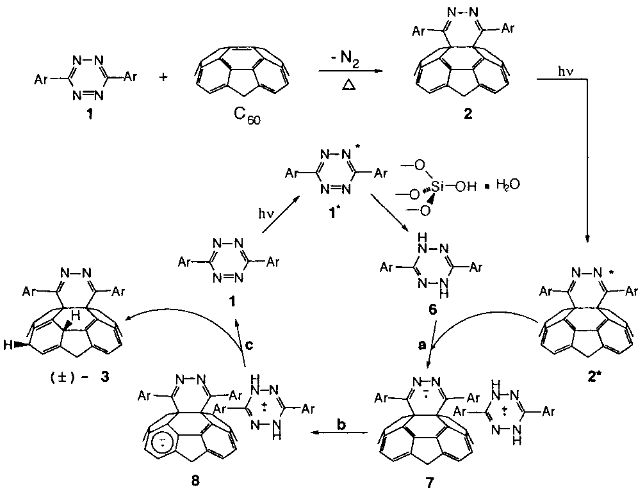
2 is regioselectively hydrogenated to (±)-**3** by dihydrotetrazine **6**, but only in the presence of light, and (2) **6** is generated in situ upon refluxing the corresponding tetrazine **1** in neat solvent for prolonged times, but only in the presence of light. The identity of **6** prepared in this fashion was verified by independent synthesis. Thus, we propose that the unexpectedly facile hydrogenation of **1** in refluxing solvent and ambient light provides a small quantity of **6** sufficient for the *catalytic*, *regioselective* hydrogenation of **2** according to Scheme 1.

Scheme 1



a: intermolecular e- transfer; **b**: intramolecular e- transfer;
c: protonation, H-atom abstraction

Dihydrotetrazines are well-known organic electron donors.[11] Electron transfer from **6** to **2** must require initial photoexcitation of **2** since **2** is not converted to (±)-**3** in the dark but under otherwise identical conditions. Electron-transfer yields the tight (organic solvent) radical ion-pair **7** which can undergo a subsequent intramolecular electron transfer to give the structurally unique tight radical ion-pair, **8**. A protonation−hydrogen atom abstraction sequence completes the synthesis of (±)-**3** and regenerates tetrazine **1** for further reaction. In the absence of better H atom donors, the ultimate source of hydrogen required for the reduction of **1** to **6** appears to be fortuitous water adsorbed on the glassware. Although initially reluctant to accept this conclusion, several control experiments point squarely to adsorbed water. For example, upon running the reaction in ambient light using glassware that has been either heated for prolonged times at 200 °C or exhaustively oxidized with KMnO$_4$, no (±)-**3** is observed to form. In these cases, the reaction stops at **2**. Extensive heating and/or KMnO$_4$ oxidation removes physically adsorbed water and some surface hydroxyl groups from silica.[12] Moreover, upon running the reaction in ambient light using glassware that has been thoroughly soaked in NaOD/D$_2$O solution followed by D$_2$O rinsing and careful drying, (±)-**3**-d_2 is formed in which carbon atoms 4 and 15 each bear a deuterium. The ^{1}H NMR spectrum for (±)-**3a**-d_2 is nearly identical to that observed for (±)-**3a** save the absence of the two fullerenic hydrogen signals at 6.40 and 6.56 ppm. Since ambient light is required to form **6** from **1**, it appears that photoexcited **1**, **1***, is a good hydrogen atom acceptor.

In summary, fullerene[60] monoadducts generated from the reaction between C$_{60}$ and 3,6-diaryl-1,2,4,5-tetrazines contain a diaryldihydropyridazine function nested atop the fullerene which directs a subsequent 1,4-hydrogenation with *complete regioselectivity* producing a racemic mixture of bifunctional bisadduct (±)-**3**. The new C−H bonds in (±)-**3** are formed exclusively at carbon atoms 4 and 15 of the fullerene[60] skeleton. A photoinduced electron-transfer mechanism has been proposed to account for the regioselective hydrogenation.

Acknowledgment is made to the University System of New Hampshire for financial support and to Professors Gary Weisman, Robert Rosenberg, and Richard Johnson for helpful discussions.

Supporting Information Available: Detailed experimental procedures and spectroscopic data for **1**, **2**, and (±)-**3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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