Synthesis of [60]- and [70]Fullerene-Fused Tetrahydroquinoxaline Derivatives by Oxidative [4+2] Cycloaddition with Unusual Reactivity and Regioselectivity

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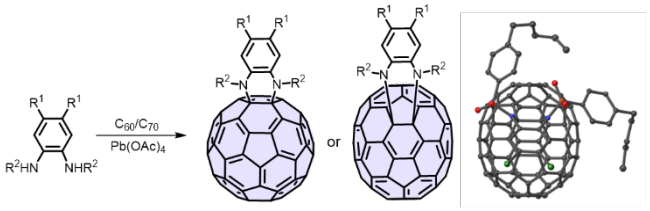
Supporting Information Placeholder



ABSTRACT: The oxidative [4+2] reaction of *o*-phenylenediamine-derived disulfonamides with fullerene C_{60} and C_{70} is reported, in which electron-deficient reactants showed high reactivity. The reaction of C_{70} exhibited unusual regioselectivity, yielding a [5,6]-adduct as the major product, which was characterized by ^{1}H, ^{13}C NMR, and single-crystal X-ray diffraction. DFT calculations revealed the reaction is an inverse-electron-demand Diels-Alder (IEDDA) reaction, and the [5,6]-adduct of C_{70} is a kinetic product.

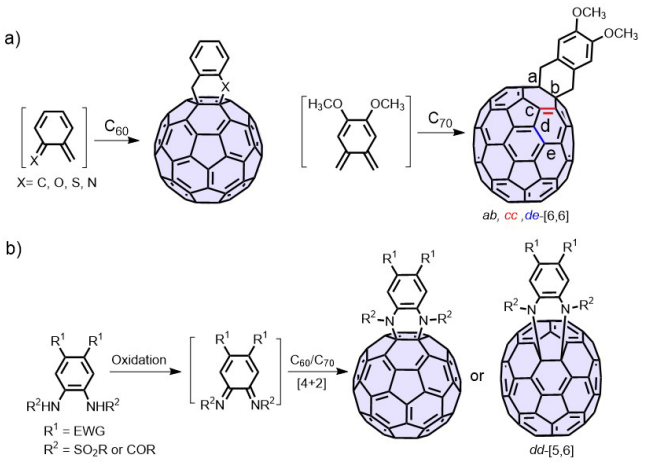
Chemical functionalization of fullerenes is a powerful approach to introduce desirable properties.[1] In the past two decades, various cycloaddition reactions to modify fullerenes have been developed as highly robust, modular, and functional-group-tolerant methods, including the Diels-Alder cycloaddition,[2] Bingel-Hirsch cyclopropanation,[3] Prato 1,3-dipolar addition,[4] diazoaddition,[5] etc. In these reactions, fullerenes typically play a similar electron-accepting role, so their reactivity and regioselectivity are highly consistent: generally, electron-rich molecules are more reactive towards fullerenes; C_{60} tends to react on the [6,6] bond, while C_{70} typically gives *ab, cc*-[6,6] adducts as major products (see Scheme 1a for position assignment on C_{70}).[6] Although other minor adducts of C_{70} such as *de*-[6,6] or *dd*-[5,6] can be obtained,[7] the overall consistent regiochemistry still presents a limitation of structural diversity of products in cycloadditions. On one hand, for lower symmetry cages like C_{70}, it is difficult to selectively obtain certain isomers in high yields. On the other hand, existing cycloaddition reactions tend to have lower reactivity for higher fullerenes[8] or endohedral metallofullerenes.[9] In this regard, new chemical reactions that reverse the reactivity and regioselectivity, could provide an "out of the box" approach to obtain traditionally minor products or derivatives of less reactive fullerenes.

Diels-Alder cycloadditions have been one of the most intensively used reactions to prepare fullerene derivatives (Scheme 1a).[10] The versatility of the [4+2] cycloaddition to introduce heteroatoms[11] makes it very valuable to access diverse fullerene-based materials. While there are a few precedents of hetero Diels-Alder reactions to yield fullerene derivatives with a heteroatom attached to the cage,[12] attaching multiple heteroatoms directly to a fullerene cage via [4+2] cycloaddition[13] remains very rare.

Recently one reactive intermediate diimine, oxidized from protected *o*-phenylenediamines, was reported to diaminate the double bonds of various alkenes.[14] Here we report a hetero Diels-Alder cycloaddition to synthesize [60] and [70]fullerene-fused tetrahydroquinoxaline derivatives, with the reactive diimines from an oxidative process in situ, as shown in Scheme 1b. We note that the reaction showed IEDDA behavior, i.e., more electron-deficient reactants are more reactive,[9g, 15] which is the opposite of typical fullerene cycloadditions. Furthermore, the C_{70} reaction yielded the *dd*-[5,6] isomer as the major product in which the addition happened close to the central belt instead of the caps. While *dd*-[5,6] C_{70} adducts were reported in [2+2] and [3+2] cycloadditions as minor products,[7c, 7f] it is the first time that a *dd*-[5,6] product was observed in a [4+2] cycloaddition, and the first time that the *dd*-[5,6] adduct was the major cycloadduct on C_{70}. These results were

rationalized by the frontier orbitals of C_{70} and computation of the activation energy for different reaction paths.

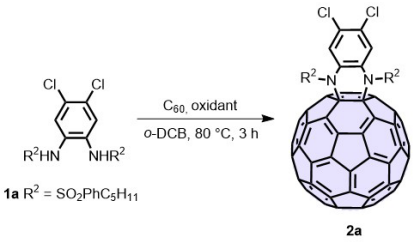
Scheme 1. a) Reported addition pattern of [4+2] reaction of fullerenes and b) this work



This reaction was initially investigated by optimizing the reaction conditions using the *N,N′*-(4,5-dichloro-1,2-phenylene)bis(4-pentylbenzenesulfonamide) **1a** as the model substrate to react with C_{60} (Table 1). The reactive quinone diimine intermedates,[16] oxidized from protected *o*-phenylenediamines in situ, were expected to be reactive towards double bonds on a fullerene cage. Therefore, our initial task was to identify an appropriate oxidant. The optimal oxidant in a recent report,[14b] $PhI(OAc)_2$ was firstly examined which successfully led to the formation of adduct **2a**, nevertheless in low yields regardless of the presence of a Lewis acid (Table 1, entry 1, 2). Product **2a** was purified by flash chromatography and characterized by ^1H, ^{13}C and ^1H-^{13}C heteronuclear multiple quantum coherence (HMQC) NMR spectroscopy to confirm the corresponding [4+2] adduct. A series of other oxidants were then attempted as shown in Table 1, with each entry optimized for the best concentration, reaction time, and temperature. While most oxidants gave higher yields than $PhI(OAc)_2$, $Pb(OAc)_4$ (which was also used in other fullerene reactions[17]) stood out with significantly higher yields (Table 1, entry 10). Besides, the reaction was not improved by adding acid (Table 1, entry 11), and did not occur in the presence of base (Table 1, entry 12). Therefore, $Pb(OAc)_4$ was used as the oxidant in further reactions.

Under optimized conditions, the substrate scope of the oxidative [4+2] reaction (Scheme 2) was then investigated. Compounds **1a-1i** were synthesized and characterized by NMR (Figs. S1–S20). First, different substituents on the phenyl ring were studied to understand the influence of electronic properties of the disulfonamides. The reaction of 4,5-dinitrobenzene-1,2-diamine-derived disulfonamide (**1b**) and C_{60} gave the expected product **2b**, with a similar structure to **2a**. No reaction occurred with o-phenylenediamine-derived disulfonamide (**1c**) or 4,5-dimethylbenzene-1,2-diamine-derived disulfonamide (**1d**). Moreover, the unsymmetrical 4-nitrobenzene-1,2-diamine-derived disulfonamide (**1e**) was also found amenable to this reaction to give product **2ea** and **2eb** in 16% and 13% yield, respectively. In the formation of **2eb**, one nitro group was replaced by excess ^-OAc. Besides phenylenediamines, the pyridine-2,3-diamine and pyridine-3,4-diamine-derived disulfonamides **1f** and **1g** also reacted with C_{60} to give the similar [4+2] adducts **2f** and **2g** in relatively lower yields.

Table 1. Optimization of the reaction conditions[a]



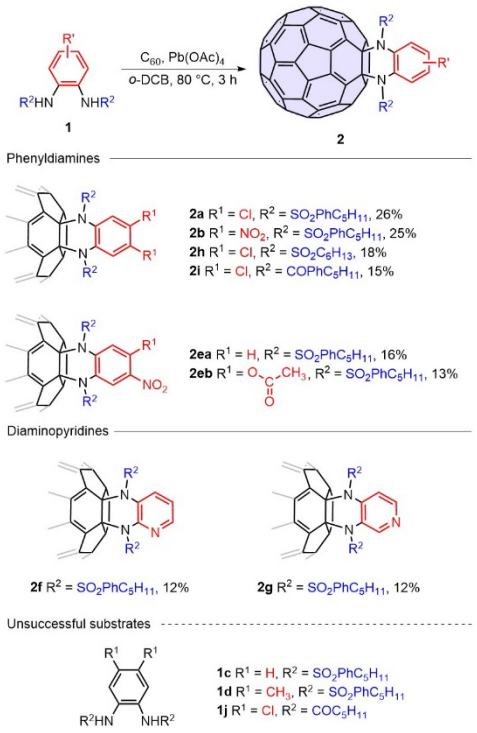
entry	oxidant	additive	yield[b](%)
1	$PhI(OAc)_2$	NA	7
2	$PhI(OAc)_2$	$Zn(OAc)_2$	9
3	$PhI(OCOCF_3)_2$	NA	15
4	MnO_2	NA	13[c]
5	$Mn(OAc)_3$	NA	14[c]
6	$KMnO_4$	NA	20[c]
7	NFSI	NA	13[d]
8	Dess-Martin periodinane	NA	trace
9	$Pd(OAc)_2$	4 Å MS	NR
10	$Pb(OAc)_4$	NA	26
11	$Pb(OAc)_4$	CF_3COOH	24
12	$Pb(OAc)_4$	pyridine	NR

[a]Reactions were performed with C_{60} (0.017 mmol) and 1a (0.050 mmol) in the presence of oxidant (0.053 mmol) and additive in *o*-DCB (1.0 mL) at 80 °C for 3 h, unless otherwise noted. [b]Isolated yield. [c]Yield at 120 °C; [d]Yield at 140 °C

Meanwhile, the diamine derivatives with different substituents on the nitrogen atoms were also studied. The *N,N′*-(4,5-dichloro-1,2-phenylene)bis(hexane-1-sulfonamide) **1h** and 4-pentylbenzamide **1i** reacted with C_{60} to give the products **2h** and **2i** in similar yields. Full spectroscopic characterizations were performed for **2a–2i** (Figs. S21–S63). No reaction occurred with the dihexanamide **1j**.

Matrix-assisted laser-desorption ionization time-of-flight mass-spectrometry (MALDI-TOF-MS) was conducted to confirm the molecular weights of products. Notably, the adducts with sulfonyl groups readily undergo fragmentation in MALDI-TOF-MS as shown in the spectrum of **2f** (Fig. S46). Though the adduct **2i** with carbonyl groups showed better stability under MALDI-TOF condition, the peaks of fragments were still observed in the MS spectrum (Fig. S62). As expected, the UV-Vis spectra of compounds **2a-2i** (Fig. S64) are highly similar and match reasonably well with the reported [6,6] cycloadducts of C_{60}.[18]

Scheme 2. Substrate scope with respect to diamine derivatives



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With the understandings about this reaction on C_{60}, the oxidative [4+2] reaction was then performed on C_{70}. The reaction of C_{70} was carried out under essentially the same reaction conditions with slightly lower equivalences of **1a** and $Pb(OAc)_4$. After silica gel column chromatography, one major product and a mixture of several minor products were obtained in a ratio of 53:47. Compound **3** (Fig. 1a) was isolated as the major product in 13% yield (31% conversion yield), which was characterized by ^1H, ^{13}C NMR, UV-vis spectra and single-crystal X-ray diffraction (Figs. S65-70). The minor products that showed as one single spot in TLC and one symmetric peak on HPLC (5-PYE, Fig. S71) contain at least three isomers, based on ^1H NMR of the mixture (Fig. S72), that we were not able to isolate with reasonable yields.

The ^{13}C NMR spectrum of **3** (Fig. S66) showed one peak of the two sp^3 addition sites at 80.8 ppm which suggests these two carbon atoms are equivalent, i.e., not the *ab*-[6,6] adduct, but one of *aa*-[5,6], *cc*-[6,6], or *dd*-[5,6] adducts. To further investigate the addition pattern, the UV–vis spectrum of **3** was recorded in chloroform (Fig. 1b). The characteristic peaks in the absorption spectrum of **3** are in good agreement with those of the products with the same addition sites reported by Yamakoshi et al.[7f] Ultimately, single-crystal X-ray diffraction unambiguously confirmed that the product was the *dd*-[5,6]-adduct (Fig. 1c). The structure appeared well ordered.

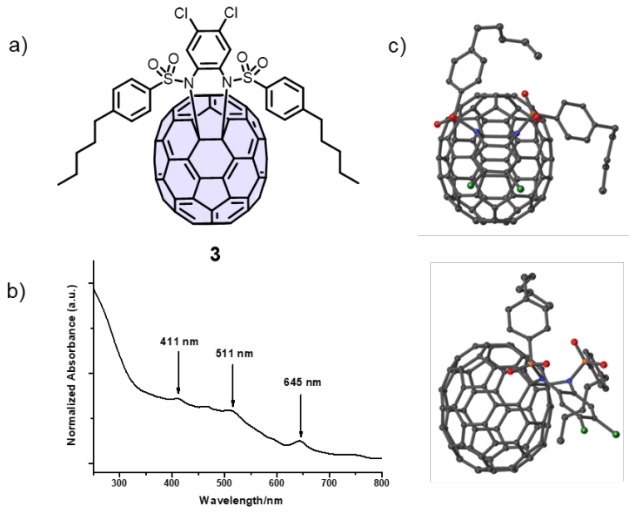


Figure 1. (a) Molecular structure of Compound **3**. (b) UV/Vis spectrum of Compound **3** in $CHCl_3$. (c) Single-crystal X-ray Structure of Compound **3** (Top: front; bottom: side). Hydrogen atoms are not shown.

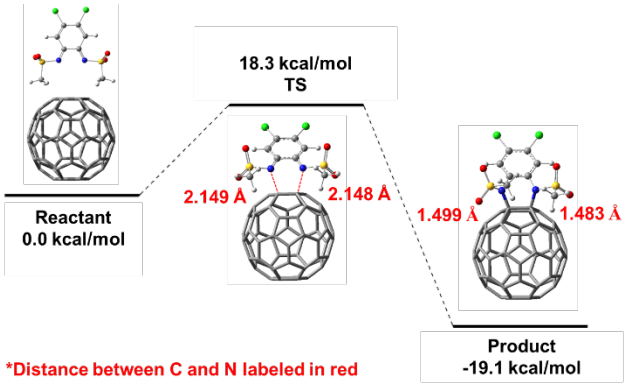
It is noted that the reactions of C_{60} showed overall unusual reactivity. In the reactions of C_{60} with *o*-phenylenediamine-derived disulfonamides **1a**-**1d**, it turned out that **1b** (with -NO_2) reacted with C_{60} at room temperature, but **1a** (with -Cl) could not react without heating and got optimal yield at a reaction temperature of 80 °C. Meanwhile, **1c** (with -H) or **1d** (with -CH_3) did not react even at higher temperatures. It can be concluded that the presence of electron withdrawing groups (EWGs) facilitates the reaction, while electron donating groups (EDGs) hamper the reaction, which is in contrary to what is expected in a normal Diels-Alder reaction on fullerenes. We hypothesize that this reaction is going through an IEDDA reaction pathway with the diene (diimine) being electron poor and the dienophile (fullerene) being electron rich.

This hypothesis is further corroborated by the substituent effect on the nitrogen atoms. With the electron-withdrawing chloro groups on the phenyl ring and sulfonyl groups on the nitrogen atoms, the reaction could occur with either aromatic (**1a**) or alkyl (**1h**) groups attached to the sulfonyl groups, with **1a** giving higher yield than **1h** (26% vs 18%), likely due to the increased electron delocalization caused by the phenyl rings. However, replacing the sulfonyl groups with carbonyl groups, the reaction only happened with aromatic groups attached (**1i**) with lower yield, and the alkyl counterpart (**1j**) did not react. Clearly, the stronger EWG sulfonyl group made the reactants more reactive than those with a weaker EWG like a carbonyl group.

DFT calculations were then performed to confirm the inverse electron demand, on reactants with methylsulfonyl diimine intermediates bearing different substituents on the phenyl ring (Table 2). We placed the diimine molecule close to the [6,6] bond of C_{60} and obtained the optimal structures of the products and transition states in *o*-DCB. The transition state with chloro groups is shown as an example in Table 2.

We then computed the activation energies as $\Delta G^{\ddagger(s)} = G_{TS}^{(s)} - (G_{C_{60}}^{(s)} + G_{diimine}^{(s)})$ and the reaction free energies as $\Delta G_{rxn}^{(s)} = G_{product}^{(s)} - \left(G_{C_{60}}^{(s)} + G_{diimine}^{(s)}\right)$ at 80 °C. Here $G_{product}^{(s)}$, $G_{TS}^{(s)}$, $G_{C_{60}}^{(s)}$, $G_{diimine}^{(s)}$ are the free energies of the product, transition state, C_{60} and diimine, respectively, and the subscript (s) labels the solvation environment for the calculations.

Table 2. Activation energies and change in free energies for the [4+2] reactions between C_{60} and methylsulfonyl diimines with different substituents



substituent	$\Delta G^{\ddagger(s)}$ (kcal/mol)	$\Delta G_{rxn}^{(s)}$ (kcal/mol)
NO_2	14.9	-23.9
Cl	18.3	-19.1
H	20.2	-17.0
CH_3	21.1	-13.8

From Table 2, the Diels-Alder reactions are all exothermic with the activation barrier varying between 14-22 kcal/mol depending on the substituent on the phenyl ring. As the electron withdrawing ability of the substituent increases, the reactivity increases (i.e., lower $\Delta G^{\ddagger(s)}$) and the reaction driving force ($-\Delta G_{rxn}^{(s)}$) becomes larger. Therefore, the IEDDA cycloadditions are kinetically and thermodynamically more favorable when EWGs are present, in good agreement with the experimental observations.

DFT calculations were then performed on the reactions of C_{60} or C_{70} with the diimine intermediate, oxidized from the *N,N'*-(4,5-dichloro-1,2-phenylene)dimethanesulfonamide, to rationalize the formation of the [6,6]-C_{60} and *dd*-[5,6]-C_{70} products (Tables S1, S2 and Figs. S73, 74). Since the transition states and products formed from different addition sites are structural isomers, we report $\Delta G^{\ddagger(s)}$ and $\Delta G_{rxn}^{(s)}$ by taking the lowest free energy values as references in Table 3. As expected, the addition on the [6,6] bond of C_{60} has lower $\Delta G^{\ddagger(s)}$ and $\Delta G_{rxn}^{(s)}$ than that on the [5,6] bond. In comparison, the *ab*-[6,6] adduct on C_{70} has the most stable structure, consistent with the findings of previously reported cycloadditions on C_{70}.[6c,7f] The *dd*-[5,6] and *cc*-[6,6] adducts are also relatively stable with the free energies higher than the *ab*-[6,6] adduct by 5 kcal/mol. However, the pathway to form the *dd*-[5,6] adduct possesses the lowest activation barrier, which is smaller than that of the *ab*-[6,6] and *cc*-[6,6] adducts by 6.4 and 1.8 kcal/mol, respectively. Therefore, the formation of the *dd*-[5,6] adduct is kinetically favored among all the reaction sites on C_{70}, making it the major product in the experimental synthesis.

Finally, the computed frontier molecular orbitals also suggest the IEDDA reaction pathway is more favorable than a normal electron demand alternative. As shown in Fig. S75, the gap between the HOMOs of fullerenes and the LUMO of diimines is significantly lower than the gap between the HOMO of diimines and the LUMOs of fullerenes, suggesting the fullerenes are the electron donors. This analysis is consistent with the observed regioselectivity on C_{70}. The HOMO of C_{70} is located on the *cc*, *cd* and *dd* bonds (Fig. S76), not on the *ab* bond where other cycloadditions tend to select. While the addition on *dd* bond yielding the major product is confirmed by the crystal structure, we suggest the *cc*-adduct is likely in our minor product mixture from the frontier orbital (Fig. S76), activation energy (Table 3), and molecular symmetry (Fig. S72) points of view. Further assignment of the minor products will be very challenging without the capacity to isolate them. Moreover, our computation shows that both the HOMO and LUMO of the C_{60} or C_{70} derivatives are located on the fullerene cage (Fig. S77).

Table 3. Relative activation energies and change in free energies for the [4+2] reactions. For C_{60} and C_{70}, the reactions with the lowest activation energies and free energies are used as references

C_{2n}	reaction site	relative $\Delta G^{\ddagger(s)}$ (kcal/mol)	relative product energy (kcal/mol)
C_{60}	**[6,6]**	**0.0**	**0.0**
	[5,6]	5.1	3.0
C_{70}	*aa*-[5,6]	5.2	13.9
	ab-[6,6]	6.4	0.0
	bc-[5,6]	5.9	19.2
	cc-[6,6]	1.8	5.0
	cd-[5,6]	8.7	23.8
	***dd*-[5,6]**	**0.0**	**5.0**
	de-[6,6]	8.6	18.6
	ee-[6,6]	14.4	45.5

In summary, an oxidative [4+2] reaction of *o*-phenylenediamine-derived disulfonamides with C_{60} or C_{70} was developed, which we found to be an oxidation reaction followed by an IEDDA reaction. EWGs in the disulfonamides facilitated the reaction experimentally and computationally, which is the opposite of most fullerene cycloadditions. Indeed, a [4+2] adduct on the [5,6]-junction of C_{70} was isolated as a major product for the first time, which was confirmed by NMR and X-ray diffraction. DFT studies revealed that the *dd*-[5,6]-C_{70} adduct is a kinetically favored product. In addition to accessing new regioselectivity on C_{70}, this new reaction can be used to functionalize traditionally inert reactants in the future, such as endohedral fullerenes or fullertubes.[19]

ASSOCIATED CONTENT

Supporting Information

This material is available free of charge via the Internet at http://pubs.acs.org.
Experimental procedures, spectroscopic data, and ^{1}H and ^{13}C NMR spectra for all new compounds.

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Notes

The authors declare no competing financial interest.

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