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Approaches to Open Fullerenes: Synthesis and Kinetic Stability of Diels−Alder Adducts of Substituted Isobenzofurans and C_{60}

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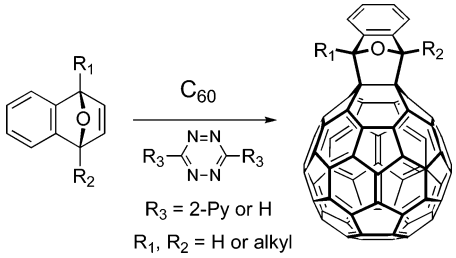

We have examined the reactions of 1,3-disubstituted isobenzofurans with the fullerene C_{60} in the context of an approach to open a large orifice on the fullerene framework. A variety of substituted isobenzofurans (**6a**−**h**), generated from the reaction of 1,4-substituted 1,4-epoxynaphthalenes **3a**−**h** with 3,6-bis(2-pyridyl)-1,2,4,5-tetrazine (**4a**) or 1,2,4,5-tetrazine (**4b**), were added to C_{60} to afford the Diels−Alder adducts **7a**−**h**. The thermal stability of these adducts toward retro-Diels−Alder fragmentation differs greatly in solution from that in the solid state. In solution, the relatively facile retro-Diels−Alder fragmentation of monoadducts **7a** and **7c**, to give C_{60} and the free isobenzofurans **6a** and **6c**, have rate constants (and activation barriers) of $k = 9.29 \times 10^{-5}$ s^{-1} at 70 °C ($E_a = 32.6$ kcal mol^{-1}) and $k = 1.36 \times 10^{-4}$ s^{-1} at 40 °C ($E_a = 33.7$ kcal mol^{-1}), respectively, indicating that the addition of isobenzofurans to C_{60} is readily reversible at those temperatures. In the solid state, thermogravimetric analysis of adduct **7a** indicates that its decomposition occurs only within the temperature range of 220−300 °C. As a result, these compounds can be stored at room temperature in the solid state for several weeks without significant decomposition but have to be handled within several hours in solution.

Introduction

Because of their unusual and novel properties, endohedral metallofullerenes have remained attractive targets ever since the initial discovery of the fullerenes.[1] Access to endohedral fullerenes is limited, however, because conventional preparation methods generally provide very low yields, often involving tedious purification. Thus, alternative, synthetic approaches to endohedral fullerenes, e.g., by creating an opening on the fullerene sphere, inserting a guest entity, closing the cage, and removing any remaining functionality ("molecular surgery"), have attracted increasing attention during the past few years.[2−4] These methods should eventually provide access to a wider array of elements trapped inside fullerene cages than those currently available.[5]

One strategy toward opening an orifice within the carbon framework of a fullerene involves saturating three adjacent double bonds within one of its six-membered rings (Figure 1).[5] Because of the very limited availability of adducts of type **B**,[6,7] this type of opening mechanism remains untested. Nevertheless, several precedents involving highly strained cyclohexanes have been described;[8] the concept should be transferable to fullerenes thanks to the inherently strained 1,2,3,4,5,6-hexaaddition pattern. One advantage of this approach is that hexasubstituted adducts of type **B** could be isoenergetic or slightly higher in energy with respect to either open forms **C(5o)** and **C(6o)**, such that the closed fullerene framework could be in equilibrium with the open one. Ideally, the added functional groups should be removable after insertion of the guest entity to provide pristine endohedral fullerenes ($M@C_{2n}$) as recently demonstrated by Komatsu et al.[3b]

These considerations motivated us to prepare various preorganized multifunctional reagents containing linked diene and/or dipolar subunits, for addition to C_{60} (Chart 1). The three possible opening strategies outlined in Chart 1 all involve the

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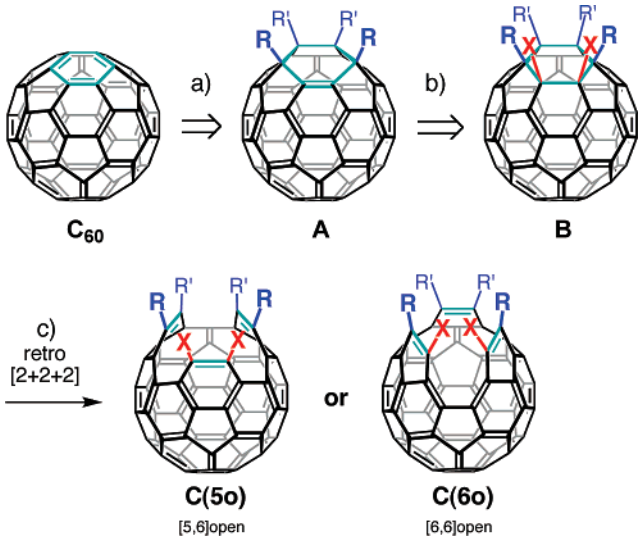
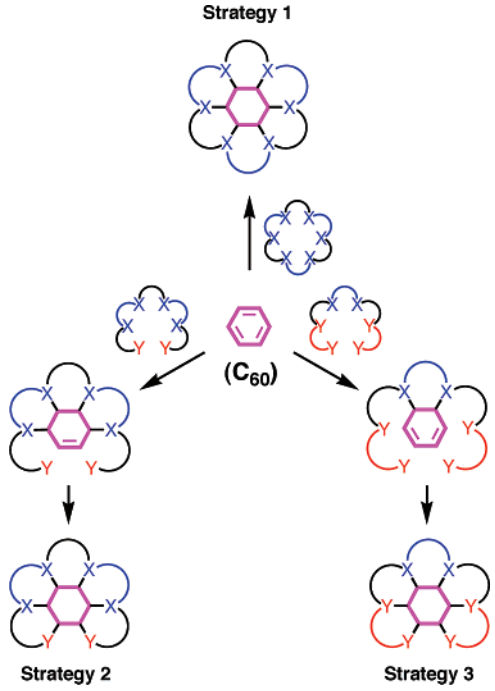


FIGURE 1. A generic strategy to open an orifice on the surface of fullerene C_{60} by a two-step saturation of three adjacent C=C bonds of a single six-membered ring: (a) Addition of four saturating groups from a tethered reagent. (b) Addition of two saturating groups through a reactive intermediate on substituents R,R. (c) [2 + 2 + 2] Ring opening of the 1,2,3,4,5,6-hexaadduct at either the [5,6] or [6,6] ring junctions.

CHART 1. Three Conceptual Strategies for the Stepwise Addition Of Tethered Reactive Units to Three Adjacent C=C Bonds of a Single Six-Membered Ring of C_{60}



challenging eventual full saturation of one of the fullerene six-membered rings followed by a [2 + 2 + 2] ring opening. These strategies differ only in the number of C=C bonds that are saturated during the first step(s); the functional groups must be well-chosen and separated by suitable linkers. Strategies 2 and 3 involve more than one step; reactive moieties, such as alkoxyl radicals, carbon radicals, nitrenes, or carbenes, must be formed from their initial intermediates to further saturate the remaining C=C bonds. Alternatively, less reactive groups such as dienes or 1,3-dipoles (azides, azomethine ylides, nitrilimines, etc.) may be invoked if the C=C bond to be saturated is reactive enough. Not surprisingly and as our recent results have shown,[6] saturating the last bond turns out to be the most challenging aspect of this project.

The tethered stepwise cycloadditions depicted in Chart 1 necessitate a good degree of preorganization imparted by tethers of appropriate length and rigidity.[9] Side reactions of the functional groups with undesired double bonds of C_{60} need to be restrained by favoring the best transition state geometries. Our first published opening approach described the reaction of a diene-bisazide to effect a tandem series of 1,3-dipolar/Diels–Alder/1,3-dipolar cycloadditions on C_{60}, conceptually following the YY–XX–YY format of Strategy 3.[2a] We found that the open bislactam **1** was formed instead through a complex set of rearrangements involving the loss of two nitrogen molecules and the addition of molecular oxygen, due to the high lability

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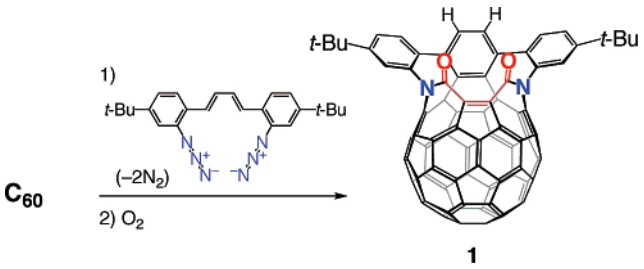
(7) A C_{3v}-tris-epoxide $C_{60}O_3$ has been isolated and partially characterized. From its UV–vis absorption features, it is likely the assigned structure; see: Tajima, Y.; Takeuchi, K. *J. Org. Chem.* **2002**, *67*, 1696–1698.

of intermediate triazoline rings formed by 1,3-dipolar cycloadditions between azide and fullerene systems. The open fullerene **1**, with its first *effective* orifice,[2a,10] gave us the opportunity to study the introduction of small gases such as helium and molecular hydrogen (H_2) inside it.[2b] It became clear, however, that much larger openings on fullerene surfaces would be needed to provide endohedral access to larger species, especially for the transition metals, which have much greater potential to exhibit unusual and novel properties.[1−4] The approach presented in Figure 1 should provide access to appropriately large openings, since the addends impart sufficient strain to push apart the three C═C double bonds formed through [2 + 2 + 2] ring opening.[5,8m]



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The judicious selection of the adding groups is key to the success of this synthetic project. Hence, we became interested in the reactivity of substituted isobenzofurans (IBFs)[11] and their potential for undergoing multiple additions with C_{60} thanks to the ease of substitution of their furan precursors, the possibilities for large-scale synthesis, and perhaps more importantly, their ease of removal through retro-Diels−Alder reactions. The physical stability of the isobenzofuran-C_{60} adducts is also important: if they are too labile, the Diels−Alder adducts may be difficult to handle; if they are too stable, the addends may be difficult to remove at a later stage. As seen in the accompanying paper,[12] a variety of *cis-1* bisadducts of C_{60} can be prepared through double Diels−Alder cycloadditions of bis-isobenzofurans following the methodology described in the present paper; their unusual thermal stability gave us the opportunity to examine different strategies for saturating the remaining double bond by reactions of convergent functional groups at both ends of the addend framework.[6]

The Diels−Alder reaction of the parent isobenzofuran with C_{60} was initially reported by Wudl.[13] However, the addition of substituted isobenzofurans to C_{60} has not been adequately explored; we wanted to optimize these reactions to apply them to the preparation of open C_{60} adducts. For example, the addition of the commercially available 1,3-diphenylisobenzofuran to C_{60} has been reported to provide an isolable monoadduct,[14] but we were unable to reproduce this result, possibly because of the high propensity for reversibility of the adduct.

We have developed a general approach for the preparation of mono- and bis-substituted isobenzofurans using an optimization of the methodology of Warrener.[15] The isobenzofuran precursors **3a**−**h** were readily available in up to 50 g quantity through the reaction of benzyne with furans **2a**−**h**, respectively. The reactive isobenzofurans were generated in situ through the cycloaddition of the bicyclic adducts **3a**−**h** with 3,6-bipyridyl-1,2,4,5-tetrazine (**4a**) or with the much more reactive parent 1,2,4,5-tetrazine (4**b**). Since all of the monoadducts **7a**−**h** showed a propensity for cycloreversion, we examined the kinetic stability of two representative systems (**7a** and **7c**) toward retro-Diels−Alder fragmentation in solution by ^{1}H NMR spectroscopy and in the solid state by thermogravimetric analysis (TGA).

Results and Discussion

Formation of the Isobenzofuran Monoadducts. The 1,4-disubstituted 1,4-epoxynaphthalenes **3a**−**h** were prepared by in situ generation of benzyne in the presence of the respective substituted furans **2a**−**h** (Table 1). Although benzyne can be prepared by a number of methods,[16] we found that it was most readily obtained from the thermal decomposition of benzene-

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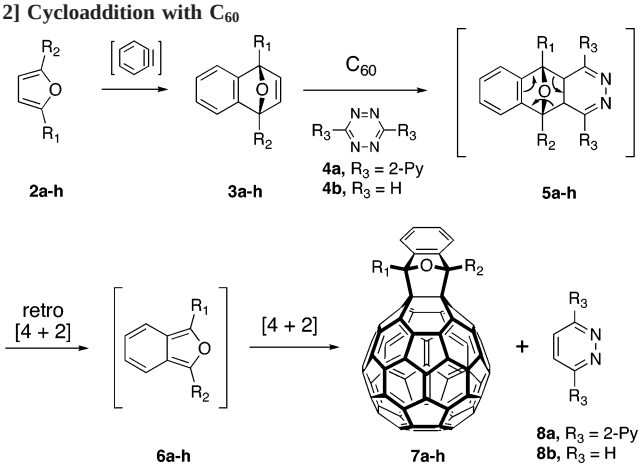
TABLE 1. Formation of Reactive Isobenzofurans and Their [4 + 2] Cycloaddition with C_{60}



substrate	R_1	R_2	yield (%)[a] (**4a**, 45 °C)	yield (%)[a] (**4b**, 25 °C)
7a	H	H	58 (66)	62 (72)
7b	H	CH_2OAc	31 (48)	40 (56)
7c	H	CO_2Me	43 (57)	51 (60)
7d	Me	Me	85 (89)	78 (86)
7e	$(CH_2)_3COCH_3$	$(CH_2)_3COCH_3$	18 (52)	39 (62)
7f	CH_2OTBS	CH_2OTBS	*b*	44 (76)
7g	CH_2OH	CH_2OH	*b*	32 (50)
7h	H	CH_2OH	15 (47)	33 (55)

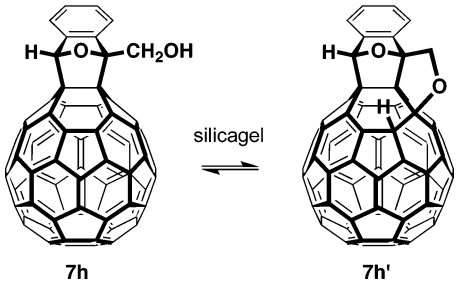
[a] Yields in parenthesis are based on recovered C_{60}. [b] Pyrazoline side-products **9a** or **9b** obtained instead.

diazonium-2-carboxylate,[17] which we prepared freshly and used immediately under appropriately safe conditions. A small amount of propylene oxide was added to remove any acidic contaminants. Good yields (60−80%) of adducts **3a**−**h** were obtained after heating a slurry of benzenediazonium-2-carboxylate under reflux in the presence of the respective furan (**2a**−**h**) in dry THF.

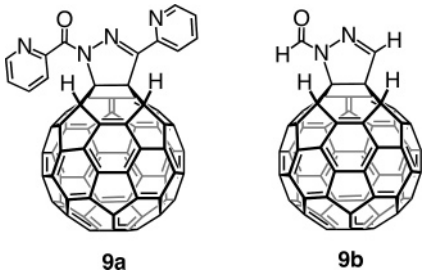
Warrener's methodology[15] was subsequently applied to bicyclic adducts **3a**−**h** to generate the isobenzofurans **6a**−**h** in situ through reactions with either 3,6-bipyridyl-1,2,4,5-tetrazine (**4a**) or 1,2,4,5-tetrazine (**4b**). Most of the isobenzofuran precursors **3a**−**h** underwent facile inverse-electron-demand [4 + 2] cycloaddition with 3,6-bipyridyl-1,2,4,5-tetrazine (**4a**) to form the intermediate adducts **5a**−**h** after the initial extrusion of N_2, although the more sterically hindered precursors **3e**−**g** were slow to react with 3,6-bipyridyl-1,2,4,5-tetrazine (**4a**) and suffered competing addition of the tetrazine moiety to C_{60}.[18] Subsequent [2 + 2 + 2] retrocycloaddition generated the reactive isobenzofurans **6a**−**h**, with pyridazines **8a** or **8b** as side products. The corresponding cycloadducts **7a**−**h** were obtained in overall good yields (47−89%, based on recovered C_{60}).

The characterization of monoadducts **7a**−**h** is based on their ^1H, ^{13}C, and MS spectral data. For example, compound **7f** displays two sets of doublets at 5.03 and 5.15 ppm (J = 11.8 Hz) for the diastereotopic methylene protons of the CH_2O group in the ^1H NMR spectrum, in addition to the expected multiplet centered at 7.5 ppm for the ortho-substituted phenyl ring and the signals of the TBS group at 0.16, 0.19 (diastereotopic $SiMe_2$), and 0.93 ppm (Si*t*-Bu). The C_s-symmetry of this compound is revealed also in the ^{13}C NMR spectrum: a single oxa-bridge sp^3 carbon is found at 80.46 ppm, while the two directly connected sp^3 carbons on the fullerene appears at 95.08 ppm. The related C_s-symmetric compounds **7d**, **7e**, and **7g** show similar features, while the C_1-symmetric compounds **7a**−**c** and **7h** have doubled signals in the substituent patterns. Satisfactory mass spectral data for most of these adducts was very difficult to obtain in most instances due to their thermally labile nature.

SCHEME 1



Substituent Effects. The steric effects that various substituents on isobenzofurans **6a**−**h** have on the rates of cycloaddition with C_{60} and on the thermal stability of the corresponding adducts **7a**−**h** can be extrapolated from their yields. For the parent system, the formation of adduct **7a** is readily achieved in 58% yield (66% based on recovered C_{60}) through the reaction of C_{60} and 3,6-bipyridyl-1,2,4,5-tetrazine (**4a**) at room temperature for 16 h. With the isobenzofuran precursor **3d** having methyl groups at the 1,3-positions, formation of the corresponding adduct **7d** was considerably more difficult. It was necessary to increase the reaction temperature to 40−45 °C to facilitate the formation of 1,3-dimethyl isobenzofuran (**6d**) as seen by the slow buildup in concentration of product **7d** by ^1H NMR. This shows that steric factors intervene in the reaction between **3d** and tetrazine **4a** at the onset of the series of cycloadditions before the formation of isobenzofuran **6d**, which reacts quickly with C_{60} (*vide infra*). Although increasing the reaction temperature generally overcame the steric factors, a further slight increase in temperature (to ca. 50 °C) resulted in a remarkable acceleration of the competing reaction of tetrazines **4a** and **4b** with C_{60} to give the unexpected side products **9a** and **9b**, respectively.[18]



To further understand the effects of various substituents at the 1 and 3 positions of isobenzofuran, we studied the reactions of the remaining isobenzofuran precursors **3b**−**h** (Table 1). We found that the rates of isobenzofuran formation in reactions with 3,6-bis(2-pyridyl)tetrazine (**4a**) were substantially slower when spatially demanding substituents were present at either one or both of the oxabicyclic bridgehead carbon atoms of the isobenzofuran precursors **3b**−**e** and **3h**, as evidenced by the

(17) Stiles, M.; Miller, R. G. *J. Am. Chem. Soc.* **1960**, *82*, 3802.
(18) (a) Murata, Y.; Suzuki, M.; Rubin, Y.; Komatsu, K. *Bull. Chem. Soc. Jpn.* **2003**, *76*, 1669−1672. (b) Miller, G. P.; Tetreau, M. C.; Olmstead, M. M.; Lord, P. A.; Balch, A. L. *Chem. Commun.* **2001**, 1758−1759.

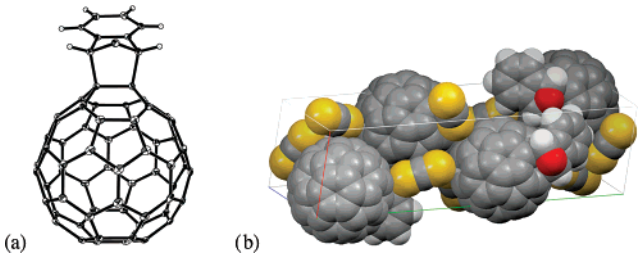


FIGURE 2. (a) Crystal structure of the mono(isobenzofuran)-C_{60} adduct **7a**, with two CS_2 molecules of crystallization omitted for clarity. (b) Packing structure of adduct **7a**; red = oxygen, yellow = sulfur.

moderate-to-low yields of **7b**−**e** and **7h** and the requirement for higher reaction temperatures. For instance, the reaction of diketone **3e** with tetrazine **4a** and C_{60} had to be performed at a temperature of 45 °C or higher, or otherwise no isobenzofuran-C_{60} adduct **7e** was observed.

Interestingly, we found that the parent tetrazine **4b** was much more reactive and the reaction could be performed at room temperature, with yields of the isobenzofuran-C_{60} adducts increasing substantially.[19] Although the relative reactivities of these two tetrazines in inverse-electronic-demand Diels−Alder reactions with isobenzofuran precursors has yet to be quantified,[20] it appears that steric hindrance between the C1/C4 substituents of **3a**−**h** and the C3/C6 substituents of tetrazine **4a** is the main factor influencing the rates of these cycloadditions.

The lower yields for adducts **7f**−**h** in the reaction with the parent tetrazine **4b** are due to the appearance of byproduct **9b** as well as the secondary reversible addition of the hydroxyl group of compound **7h** to form the *cis-1* bisadduct **7h′** that occurs before and during the purification of compound **7h** (Scheme 1). 3,6-Dihydro-1,2,4,5-tetrazine (**4b**) was prepared following the method described by Sauer et al.[19] Unfortunately, this synthesis usually provides the tetrazine in an overall yield below 10% and as a CH_2Cl_2 solution. Despite the added complication of preparing the parent tetrazine **4b**, its use has the great advantage of facilitating the reaction rates and improving yields, both of which were critical to the success of this project and the subsequent formation of Diels−Alder bisadducts.[6,12]

Crystal Structure of Monoadduct 7a. The single-crystal X-ray structure of the isobenzofuran monoadduct **7a** has not been described. Slow evaporation of a CS_2 solution of **7a** yielded unusually large black prisms (up to ca. 2- to 3-mm crystals).[21] The structural information provided by this isobenzofuran-C_{60} adduct is interesting (Figure 2). The only $C(sp^3)-C(sp^3)$ single bond in this C_{60} derivative has a length of 1.603 Å, which is very close to those of the $C(sp^3)-C(sp^3)$ bonds of other monofunctionalized C_{60} derivatives.[22] This $C(sp^3)-C(sp^3)$ bond is particularly longer, by ca. 0.50 Å, than the corresponding bond lengths of the 2,3-dihydro-1,4-epoxynaphthalene-chromium complex[23] or the 2-mono- or 2,3-disubstituted-1,4-epoxynaphthalenes,[24,25] reflecting a relief of bond strain in the functionalized C=C bond of C_{60} as is usually observed. The ease with which we obtained such large crystals may arise from the rigid, polar structure of **7a** coincidentally favoring packing interactions in the crystal,[26] together with the presence of the highly polarizable solvent molecules of CS_2 which maintains many fullerene derivatives in solution at relatively high concentrations and far better than aromatic solvents. The crystal packing structure contains two molecules of CS_2 in the unusually long crystallographic cell (*b*-axis, 31.615 (10) Å).

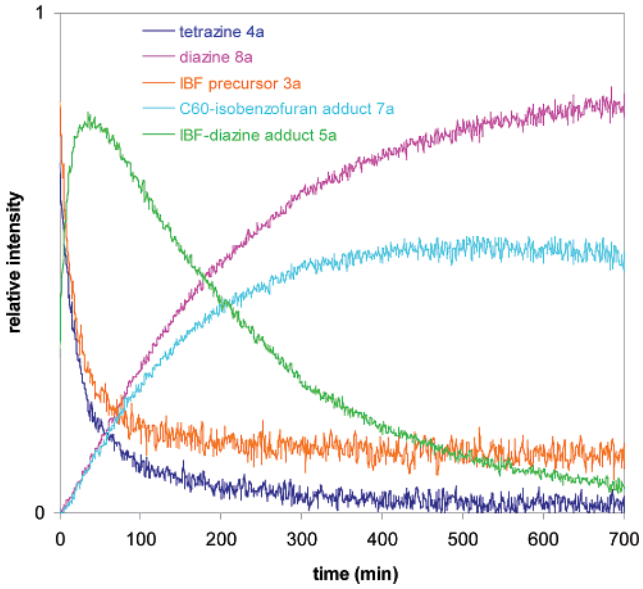


FIGURE 3. Real-time ^1H NMR observation of the concentrations of products in the reaction between 3,6-bis(2-pyridyl)-1,2,4,5-tetrazine (**4a**) and C_{60}. The observed intermediates or products are 1,4-dihydro-1,4-epoxynaphthalene (**3a**), the C_{60}-isobenzofuran adduct **7a**, intermediate adduct **5a**, and 4,5-bis(2-pyridyl)-pyridazine (**8a**); see Table 1 for structures. *Y*-axis: intensity of each species relative to the integration intensity of 3,6-bis(2-pyridyl)-1,2,4,5-tetrazine (**4a**) at time zero.

Real-Time Observation of the Reaction Course. We used ^1H NMR spectroscopy to monitor the reaction course of the cycloaddition of 3,6-bis(2-pyridyl)-1,2,4,5-tetrazine (**4a**) with isobenzofuran precursor **3a** and the subsequent formation of the isobenzofuran-C_{60} adduct **7a** (Figure 3). This experiment also permitted us to observe intermediate **5a** and its decomposition prior to the formation of the C_{60}-adduct **7a**, showing that it is the rate-limiting step in the series of cycloadditions (Table 1).

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(21) Black prism, approximate dimensions 0.40 × 0.20 × 0.10 mm, space group *P*2(1)/*n*, *Z* = 4, *a* = 9.927(3) Å, *b* = 31.615(10) Å, *c* = 12.614(4) Å, *β* = 108.654(6)°, *V* = 3751(2) Å^3, temp = 100(2) K, *R*1 = 0.059, *Rw* = 0.1089, GoF = 1.039.

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(25) (a) Kohnke, F. H.; Stoddart, J. F.; Slawin, A. M. Z.; Williams, D. J. *Acta Crystallogr., Sect. C* **1988**, *44*, 742−745. (b) Schlemper, E. O.; Shinmyozu, T.; McCormick, J. P. *Acta. Crystallogr., Sect. B* **1982**, *38*, 2981−2983.

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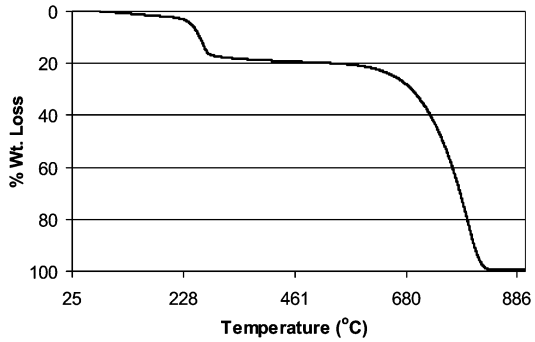


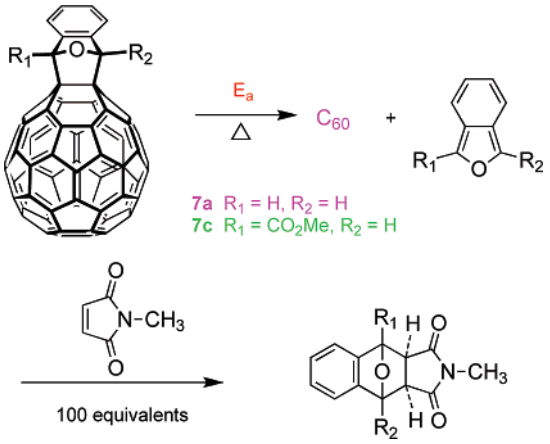
FIGURE 4. Thermogravimetric (TGA) analysis of the isobenzofuran-C_{60} adduct **7a**.

The reaction of 3,6-bis(2-pyridyl)-1,2,4,5-tetrazine (**4a**) with isobenzofuran precursor **3a** was complete within just 40 min at 25 °C; the observed rates of disappearance of **3a** and **4a** were 6.61×10^{-4} and 6.53×10^{-4} s^{-1}, respectively. The concentration of intermediate **5a** ($k_{obs} = 1.85 \times 10^{-3}$ s^{-1}) reached its maximum value within 40 min, and then the isobenzofuran **6a** began to form slowly. Upon its formation, **6a** reacted with C_{60} instantly to provide the isobenzofuran-C_{60} adduct **7a** ($k_{obs} = 9.47 \times 10^{-5}$ s^{-1}); accordingly, it was not possible to observe **6a** directly in the NMR spectra. The decomposition of intermediate **5a** was complete within 12 h ($k_{obs} = 6.98 \times 10^{-5}$ s^{-1}), which is consistent with the time necessary for the reaction to reach completion when performed on larger scales. Thus, this single NMR spectroscopy experiment provided the full kinetic scope for the one-pot synthesis of the isobenzofuran-C_{60} adduct **7a**. The maximum yield of this reaction, as evidenced from the integral intensities, was ca. 60−70%, which is a value consistent with the yield calculated from the weight of the isolated compound.

Practical Considerations on the Thermal Stability of Isobenzofuran-C_{60} Adducts. The flash chromatographically purified isobenzofuran-C_{60} monoadducts **7a**−**h** were all stable in the solid state at room temperature for long periods of time, but their stability in solution was only moderate because they tended to undergo slow to moderately fast [4 + 2]cycloreversion at temperatures from 20 to 80 °C. For example, the adduct **7a** was fairly stable at room temperature but began to decompose gradually at 45 °C in solution. The retro-Diels−Alder reactions of all of the synthesized adducts **7a**−**h** were quite fast in solution at temperatures above 80 °C.[27]

In the solid state, thermogravimetric (TGA) analysis showed that **7a** decomposes at temperatures between 220 and 300 °C, undergoing a weight loss of 17% (theoretical weight loss 14%) corresponding to the loss of the isobenzofuran moiety with an onset at 200 °C. Further heating to 840 °C caused the complete loss of C_{60} through sublimation (Figure 4).[1a,28] Long-term storage (>2 years) of **7a** at room temperature led to the appearance of C_{60} and some species that were more polar than **7a**, as monitored by TLC (SiO_2; toluene/hexanes, 1:1; $R_f = 0.2$−0.4). One of the more polar compounds, a brown-colored species, was possibly a mixture of regioisomeric bis(isobenzofuran)-C_{60} adducts formed through slow isobenzofuran transfer to a neighboring molecule in the solid state. This phenomenon

SCHEME 2. Retro-Diels−Alder Reaction of Isobenzofuran Adducts 7a and 7c in the Presence of Excess *N*-Methylmaleimide



may occur along the lines of the solid state anthracene transfer reaction reported by Kräutler et al.[29]

In solution, the 1,3-dimethylisobenzofuran monoadduct **7d** underwent cycloreversion to give C_{60} upon treatment with maleic anhydride (10 equiv) in toluene under reflux; ca. 90% of free C_{60} was recovered within 25 min. The least-stable monoadduct **7c** decomposed slowly in solution, even at room temperature, as a result of both electronic and steric effects imparted by the ester groups. In the gas phase, as monitored through mass spectrometry, we could not obtain signals for the molecular ions of any of the mono(isobenzofuran)-C_{60} adducts **7a**−**h** when using MALDI-FT-ICR, MALDI-TOF, or FAB ionization methods, once again reflecting the labile nature of these adducts. In general, each of these isobenzofuran monoadducts was stable in the solid state but gradually decomposed in solution at higher than room temperature.

Kinetics of Isobenzofuran-C_{60} Adduct Formation. The varying degrees of thermal stability of the isobenzofuran-C_{60} adducts **7a**−**h** with their different substituents prompted us to use NMR spectroscopy to determine the activation energies for the cycloreversion (retro-Diels−Alder reaction) of two representative compounds, **7a** and **7c**. We quantified these rates of decomposition by observing the decrease in integral intensity for the oxa-bridge methine protons in the ^1H NMR spectra recorded in $C_2D_2Cl_4$ and $CDCl_3$ at fixed temperatures. The liberated isobenzofurans **6a** and **6c** were trapped by their reaction with a large excess (100×) of *N*-methylmaleimide to form stable isobenzofuran−maleimide adducts that do not undergo retro-Diels−Alder reaction under the experimental conditions (Scheme 2).[30] Spectra were acquired at fixed time intervals over a range of temperatures that were appropriate for observing the decomposition within a practical time scale. For both **7a** and **7c**, the kinetics of decomposition fit well to exponential decays within the studied range of temperatures. Table 2 displays the rate constants calculated for the decompositions of the adducts **7a** and **7c** at different temperatures;[31] it is quite evident that adduct **7a** is more stable than adduct **7c**.

Arrhenius plots (ln k vs $1/T$) for the decompositions of the C_{60}-isobenzofuran adducts **7a** and **7c** exhibited excellent linear

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(31) Lonhienne, T.; Gerday, C.; Feller, G. *Biochim. Biophys. Acta* **2000**, *1543*, 1−10.

TABLE 2. Rate Constants and Activation Parameters Calculated from Time-Resolved ^{1}H NMR Spectroscopy Data on Adducts 7a (in $C_2D_2Cl_4$) and 7c (in $CDCl_3$)

adduct	T (K)	k (s^{-1})[a]	$\Delta H^{\ddagger} = E_a - RT$ (kcal mol^{-1})	$\Delta G^{\ddagger} = RT(23.76 + \ln T - \ln k)$ (kcal mol^{-1})	$\Delta S^{\ddagger} = (\Delta H^{\ddagger} - \Delta G^{\ddagger})/T$ (cal mol^{-1} K^{-1})
7a	343	9.29×10^{-5}	31.8	26.6	15.2
	348	1.74×10^{-4}	31.8	26.6	15.0
	353	3.69×10^{-4}	31.8	26.4	15.2
	358	7.56×10^{-4}	31.8	26.3	15.3
	363	1.34×10^{-3}	31.8	26.3	15.2
	368	2.16×10^{-3}	31.8	26.3	14.9
7c	313	1.36×10^{-4}	33.2	24.0	29.5
	318	2.41×10^{-4}	33.2	24.0	28.9
	323	6.63×10^{-4}	33.2	23.8	29.2
	328	1.67×10^{-3}	33.2	23.5	29.4
	333	2.98×10^{-3}	33.2	23.5	29.0

[a] The kinetics of fragmentation were measured in tetrachloroethane-d_2 (**7a**) and chloroform-d (**7c**).

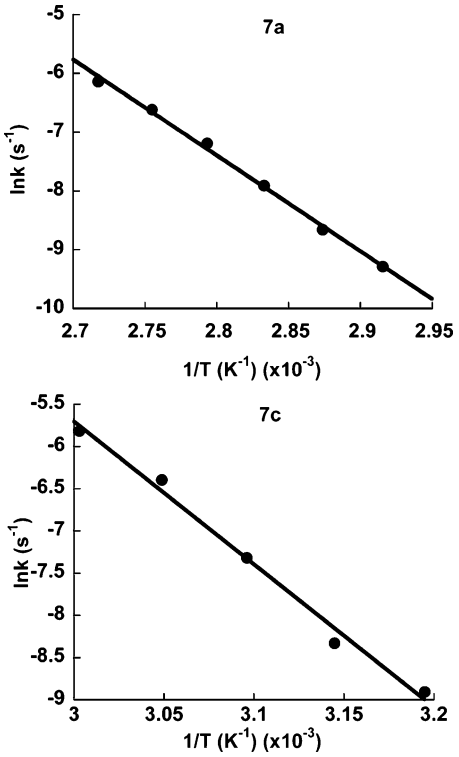

FIGURE 5. Arrhenius plots for the retro-Diels−Alder fragmentation of adducts **7a** and **7c**.

fits, giving the corresponding activation energies: 32.6 ± 0.9 and 33.7 ± 1.9 kcal mol^{-1}, respectively (Figure 5). These activation energies are within the range of energies required for typical retro-Diels−Alder reactions,[32] i.e., 31−42 kcal mol^{-1}.[33] In contrast, the decomposition of the C_{60}-cyclopentadiene adduct occurs with an activation energy of only 26.7 kcal mol^{-1}.[34]

Conclusion

Isobenzofuran monoadducts of C_{60} are readily available by optimizing Warrener's methodology for the generation of reactive isobenzofurans in the presence of C_{60}. This approach allows adducts to be prepared from isobenzofuran precursors featuring various functional groups at the 1 and 3 positions. In general, these isobenzofuran-C_{60} adducts were stable in the solid state but slowly decomposed in solution at temperatures above 25 °C. Thus, isobenzofurans could be used as reagents for blocking reactive C═C bonds of C_{60}, i.e., their function may be similar to that of 9,10-dimethylanthracene (DMA) but at higher temperature.[35,36] DMA has been used at room temperature to reversibly block the addition sites of C_{60} to allow, for example, stepwise functionalization toward O_h-symmetric hexakisadducts. Because the 9,10-dimethylanthracene adduct of C_{60} is very labile already at 25 °C, high selectivity cannot be imparted fully in all of the steps leading to the final hexakisadduct; it is possible that this problem may be alleviated through the use of isobenzofurans. Further investigation into the applications of isobenzofurans for this goal and for the preparation of open fullerenes remains ongoing and will be reported in due time.

Experimental Section

General Procedure A. Preparation of Isobenzofuran Precursors 3a−h. The benzyne precursor was prepared using the following typical procedure. Generally, ∼1.5 equiv of anthranilic acid was used with respect to 1 equiv of furan derivative. Isoamyl nitrite (5.0 mL, 38 mmol) was added to a solution of anthranilic acid (2.45 g, 17.9 mmol) and trichloroacetic acid (34 mg, 0.21 mmol) in THF (30 mL) at 0 °C. The resulting solution was stirred vigorously for a few minutes at 0 °C and then warmed to room temperature. After stirring for 1 h at room temperature, the color of the suspension had turned pale yellow. The solid (**Caution! Danger of explosive decomposition!** No metal spatula) was collected by filtration and washed with dry THF into a flask containing a furan derivative (12.0 mmol). Propylene oxide (2 mL) and dry THF were added until the total volume was ca. 60 mL. The resulting mixture was then gradually heated to 60 °C. The diazonium salt decomposed gradually to generate benzyne. After 1 h, the decomposition of the diazoniumcarboxylate salt was complete, and the solution was heated under reflux for several minutes. The solution was then concentrated to a volume of ca. 4 mL and purified by silica gel chromatography using appropriate eluents. Compounds **3a**,[37] **3b**,[38] **3c**,[39] **3d**,[40] **3e**,[41] and **3f** were prepared using this method through the reactions of compounds

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2a, **2b**,[42] **2c**, **2d**, **2e**, and **2f**, respectively, with benzyne. Compounds **3g** and **3h** were obtained after deprotection of the TBS group of **3f** (with TBAF) and the acetyl group of **3b** (with LiOH), respectively. See experimental description and spectral data for compounds **3b**−**e** and **3 g,h** in Supporting Information.

1,8-Bis(*tert*-butyldimethylsilyloxymethyl)-11-oxatricyclo-[6,2,1,0^{2,7}]undeca-2,4,6,9-tetraene (3f). According to general procedure A, the silylated furan **2f** (5.35 g, 15 mmol) was converted to pure adduct **3f** (5.70 g, 88%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 0.12 (s, 12H), 0.92 (s, 18H), 4.26 (d, J = 11.0 Hz, 2H), 4.41 (d, J = 11.0 Hz, 2H), 6.91−6.95 (m, 2H), 7.21−7.23 (m, 2H). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ (ppm) −5.2, 18.4, 25.8, 61.7, 92.3, 119.5, 124.8, 143.9, 151.1. IR (neat) ν (cm^{-1}) 2955, 2929, 2858, 1472, 1256, 1105, 838. EI-MS *m*/*z* (rel. intensity) 431 (70, [M − H]$^+$), 375 (42), 271 (48), 243 (88), 229 (71), 213 (62), 145 (57), 115 (100), 90 (87). HRMS (*m*/*z*) calcd for $C_{24}H_{39}O_3Si_2$, 431.2438, found 431.2429.

General Procedure B. Isobenzofuran Additions to C_{60} To Give Adducts 7a−h. An isobenzofuran precursor (**3a**−**h**; 1 equiv relative to C_{60}) and a tetrazine (**4a** or **4b**;[19] 1.1 equiv relative to **3a**−**h**) were added to a solution of C_{60} in freshly distilled dry toluene (1−1.5 mg C_{60}/mL toluene) at 20 °C. This reaction mixture was then stirred under Ar for 16 h at either 45 °C (whenever **4a** was used) or 25 °C (whenever **4b** was used). The resulting brown solution was then subjected to flash chromatography (toluene/EtOAc, 9:1). The purple fraction containing C_{60} eluted first, followed by the fraction containing the desired C_{60}-isobenzofuran adduct (**7a**−**h**), which was then concentrated. The residual brown solid was redissolved in an appropriate solvent (e.g., CS_2 or $CHCl_3$; 1 or 2 mL). This solution was then added to stirred pentane (20−30 mL) to precipitate the cycloadducts and remove any oily solvent impurities (mostly phthalate plasticizers). Finally, the slurry was centrifuged, the resulting solid was collected, resuspended in pentane, and centrifuged again, and the collected solid was dried under vacuum.

As noted in the text, all of these Diels−Alder monoadducts decomposed in solution through retro-Diels−Alder reactions, with rates depending on the temperature. Therefore, purification must be performed carefully without exceeding a temperature of 40 °C, particularly during evaporation on the rotary evaporator. In addition, it was not possible to obtain satisfactory mass spectral data for most of these adducts. Although some M$^+$ and MH$^+$ ions were detected when using FAB or MALDI-MS, their intensities were not sufficiently high to allow determination accurate masses. See experimental description and spectral data for compounds **7b**−**e** and **7g,h** in Supporting Information.

9,10-(1,8-Bis(*tert*-butyldimethylsilyloxymethyl)-11-oxa-tricyclo-[6.2.1.0^{2,7}]undeca-2,4,6-trieno)-1′,2′-buckminsterfullerene (7f). A mixture of compound **3f** (51.8 mg, 0.12 mmol), a solution of tetrazine **4b** in CH_2Cl_2 (0.37 mmol/mL, 0.4 mmol), and C_{60} (72 mg, 0.1 mmol) in toluene (100 mL) was stirred at 20 °C for 24 h. Chromatography on SiO_2 with toluene/cyclohexane 1:1 (R_f = 0.7) gave the pure adduct **7f** (49.0 mg, 44%; 76% based on recovered C_{60}) as a brown solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 0.16 (s, 6H), 0.19 (s, 6H), 0.93 (s, 18H), 5.03 (d, J = 11.8 Hz, 2H), 5.15 (d, J = 11.8 Hz, 2H), 7.49−7.52 (m, 2H), 7.82−7.85 (m, 2H). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ (ppm) −5.3, −5.2, 18.5, 26.0, 64.3, 80.5, 95.1, 122.4, 127.8, 137.6, 137.9, 139.2, 139.5, 141.7, 141.8, 142.18, 142.21, 142.25, 142.29, 142.7, 143.1, 144.2, 144.6, 145.0, 145.2, 145.3, 145.4, 145.57, 145.63, 145.9, 146.0, 146.2, 146.4, 146.7, 147.0, 147.3, 153.4. IR (KBr) ν (cm^{-1}) 2951, 2925, 2853, 1460, 1252, 1112, 835, 526.

Tetrazine Adduct 9b. Compound **9b** was observed in the reaction whenever **4b** was used as the tetrazine source. It was also prepared by treating C_{60} (72 mg, 0.10 mmol) with tetrazine **4b** (16.4 mg, 0.20 mmol) in toluene (80 mL) at room temperature for 5 days. The color of the mixture turned from purple to brown. Silica gel was added, and the whole mixture was stirred for 5 h. The reaction mixture was then poured onto a silica gel column. Elution with toluene gave recovered C_{60}. Further elution with toluene/EtOAc (9:1) gave compound **9b** (26 mg, 33%, 64% based on recovered C_{60}). ^{1}H NMR 500 MHz (CS_2/$CDCl_3$, 9:1) δ (ppm) 6.13 (d, J = 2.0 Hz, 1H), 6.53 (d, J = 2.0 Hz, 1H), 7.52 (s, 1H), 9.20 (s, 1H). ^{13}C NMR 125 MHz ($C_2D_2Cl_4$) δ (ppm) 52.0, 54.5, 71.5, 75.5, 135.8, 136.5, 136.7, 139.3, 140.0, 140.3, 140.4, 142.69, 142.73, 143.1, 143.4, 143.5, 143.8, 143.9, 144.0, 144.1, 144.31, 144.32, 144.34, 144.36, 144.38, 144.45, 144.49, 144.53, 144.6, 144.67, 144.69, 144.8, 144.9, 145.10, 145.13, 145.2, 145.5, 145.9, 146.0, 146.3, 146.6, 146.7, 147.0, 147.18, 147.24, 147.3, 147.40, 147.43, 148.2, 148.7, 148.8, 149.1, 149.5, 149.6, 151.2, 160.8. IR (KBr) ν (cm^{-1}) 2917, 1673, 1600, 1270. MS-FAB *m*/*z* (rel. intensity) 720 (100, C_{60}^+), 793 (53, MH$^+$). HRMS (*m*/*z*) calcd for M$^+$ $C_{62}H_4N_2O$ 792.0324, found 792.0335.

Kinetic Experiment Monitoring the Formation of Compound 7a. Real-time observation of the course of the reaction between C_{60} (7.26 mg, 0.01 mmol), 3,6-bis(2-pyridyl)-1,2,4,5-tetrazine (**4a**; 2.36 mg, 0.01 mmol), and the isobenzofuran precursor **3a** (1.44 mg, 0.01 mmol) was conducted in a solution of d_4-*o*-dichlorobenzene and carbon disulfide (1:1; 1 mL) at 25 °C. A total of 729 FIDs were collected with 30° angle pulses. The acquired FID data were then transformed into a 2D data set. The peaks of interest were integrated and exported in ASCII files. The data were imported into Microsoft Excel and analyzed.

Kinetics of the Decompositions of Adducts 7a and 7c. *N*-Methylmaleimide (100 equiv) and mesitylene (0.25 mg, internal standard) were added to a solution of adduct **7a** (2.0 mg) in $C_2D_2Cl_4$ (1 mL). The decomposition of adduct **7a** was monitored at 343, 348, 353, 358, 363, and 368 K using ^{1}H NMR. The corresponding measurements for compound **7c** (3.0 mg) in $CDCl_3$ (1 mL) were conducted at 313, 318, 323, 328, and 333 K. The decompositions of compounds **7a** and **7c** were monitored using a method similar to that described above for conducting the real-time observations. The resulting ASCII data were imported into Excel. The Excel data set was then plotted using KaleidaGraph (Synergy Software) to obtain the rate constants.

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Supporting Information Available: Experimental description and spectral data for compound **3b**−**e,g,h** and **7b**−**e,g,h** and crystallographic information files in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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