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Reaction of Fullerenes and Benzyne

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Summary: Benzyne reacts with C_{60} to form a series of compounds $[C_{60} + (C_6H_4)_n]$, $n = 1,2,3,4$, identified by mass spectrometry; the monoaddition product was isolated by chromatography and structurally characterized by ^{1}H- and ^{13}C-NMR spectroscopies.

Electron-deficient pyracyclene bonds are the sites of attachment in the preponderance of fullerene addition reactions. Metal reagents add here,[1] as do a variety of dienes and dipolar compounds,[2] carbenes,[3] and oxygen atoms.[4] However, *o*-benzyne typically reacts with polycyclic aromatic compounds by adding across the 1,4-positions within a ring, not between rings, thus participating in [2 + 4] cycloaddition reactions.[5] The common 1,2-mode of attachment to C_{60} might not be the exclusive regiochemistry followed in a reaction of benzyne with buckminsterfullerene. Here, we describe the preparation of benzyne adducts of C_{60} and C_{70}, as well as the isolation of the monoaddition product (*m*/*z* 796) to C_{60} and its spectroscopic characterization.

Fullerenes were prepared and purified using standard procedures described previously.[6] A benzene solution containing C_{60} and isoamylnitrite was stirred vigorously. Benzyne, 10 equiv, was generated in situ by adding anthranilic acid at room temperature.[7]

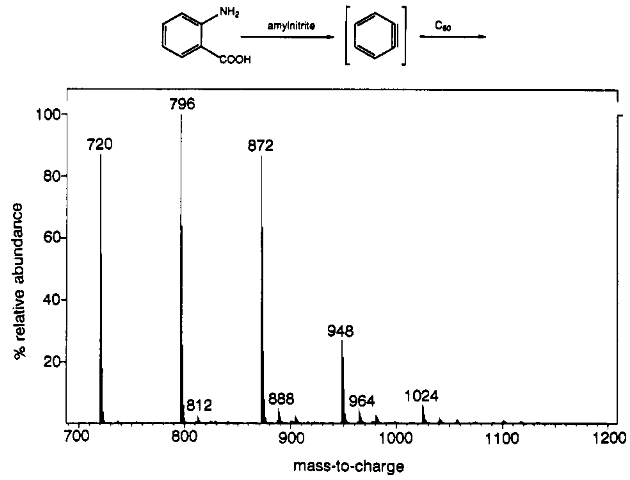

Figure 1. Electron attachment mass spectrum[8] of the benzyne adducts of C_{60}: *m*/*z* 720 = C_{60}, *m*/*z* 796 = $C_{60} + C_6H_4$, *m*/*z* 872 = $C_{60} + (C_6H_4)_2$, *m*/*z* 948 = $C_{60} + (C_6H_4)_3$, *m*/*z* 1024 = $C_{60} + (C_6H_4)_4$.

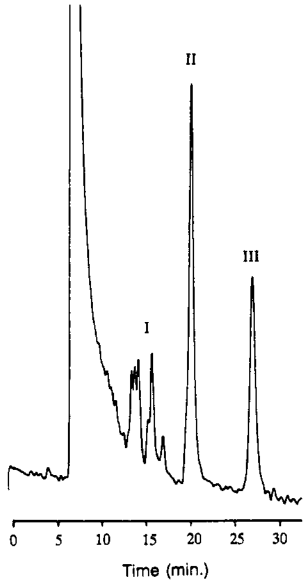

Figure 2. High-performance liquid chromatogram[13] showing the peaks corresponding to the dibenzyne adducts (I), monobenzyne adduct (II), and C_{60} (III).

Mass spectrometric analysis[8] of the reaction mixture showed that ~72% of the C_{60} had been consumed, of which ~45% was converted to monobenzyne product (*m*/*z* 796), ~38% to dibenzyne product (*m*/*z* 872), ~12% to tribenzyne product (*m*/*z* 948), and ~2% to tetrabenzyne product (*m*/*z* 1024) (Figure 1).[9] Fragmentation of the benzyne adducts by tandem mass spectrometry[10] occurs by successive losses of benzyne, ultimately restoring C_{60}. The major peaks in the spectrum are associated with

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(7) Friedman, L.; Logullo, F. M. *J. Am. Chem. Soc.* **1963**, *85*, 1549. C_{60} (10 mg, 0.014 mol) was dissolved in 40 mL of methylene chloride in a 100-mL round-bottom flask fitted with a drying tube. Isoamyl nitrite (20 mL, 0.014 mol) was added via syringe. Anthranilic acid (20 mg, 0.015 mol) was added as a solid, and the reaction mixture was stirred for 3 h at room temperature, after which the mixture had assumed a deep brown color. The solution was then concentrated by evaporation.

(8) Mass spectra were recorded using a Finnigan TSQ Model 700. Samples were introduced by desorption from a probe which was ramped from ambient temperature to 800 °C in 20 s. Electron attachment was performed using NH_3 as a reagent gas to moderate electron energies and to allow nondissociative electron attachment. See: von Ardenne, M.; Steinfelder, K.; Tummler, R. *Elektronenanlagerungs-massenspektrometric Organischer Substanzen*; Springer-Verlag: Berlin, 1971. Hunt, D. F.; Sethi, S. K. *J. Am. Chem. Soc.* **1980**, *102*, 6953. Dillard, J. G. *Chem. Rev.* **1973**, *73*, 589.

(9) Yields were estimated by integrating the respective mass chromatograms over the full desorption profile and assuming equal ionization and transmission efficiencies.

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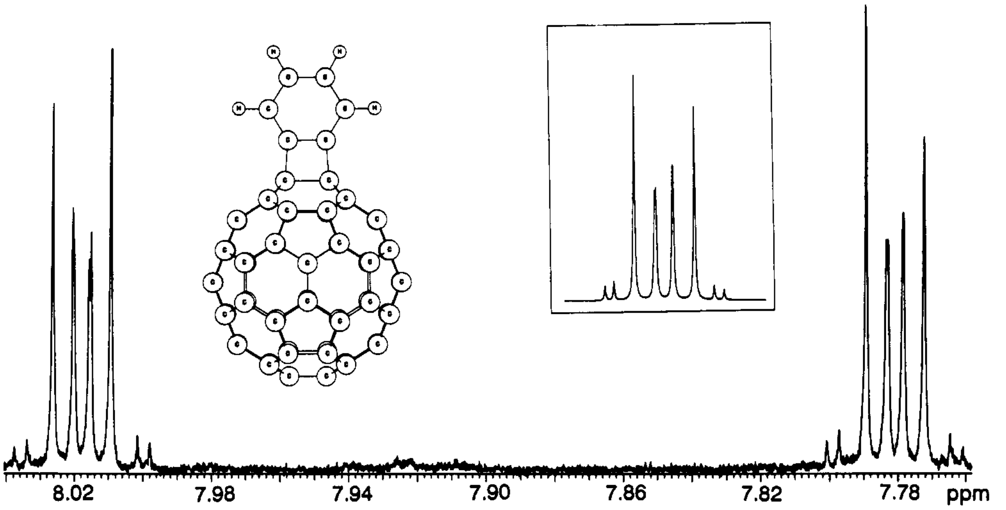

Figure 3. 500-MHz ^{1}H-NMR spectrum[14] of the monobenzyne adduct of C_{60} in CD_2Cl_2. The inset shows the simulated line shape to scale but offset. Also inset is the calculated structure, based on the AM1 Hamiltonian,[17] for the product resulting from addition across the pyracyclene bonds.

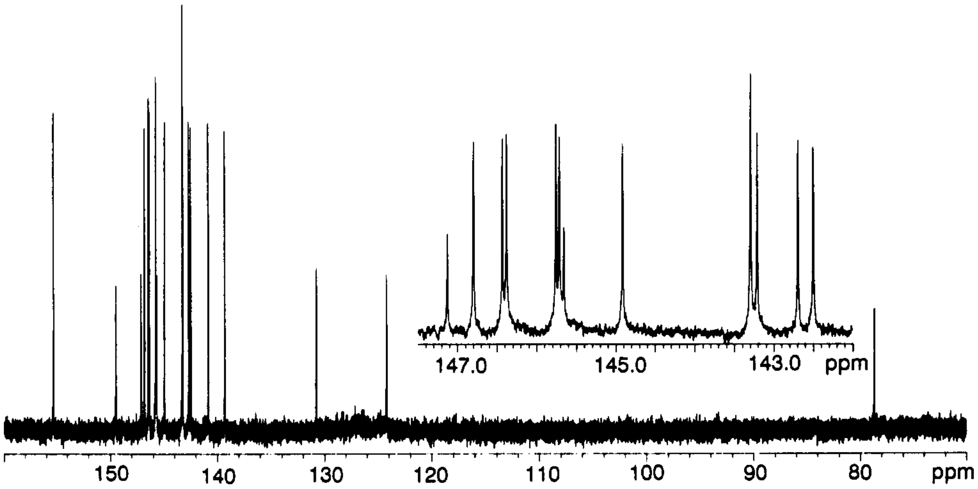

Figure 4. The ^{13}C-NMR spectrum of the monobenzyne adduct of C_{60} in 3:1 CS_2/acetone-d_6 with 0.03 M Cr(acac)$_3$ as a relaxation agent.[18] ppm (number of carbons): δ 155.34 (4), 149.48 (2), 147.13 (2), 146.80 (4), 146.43 (4), 146.38 (4), 145.76 (4), 145.72 (4), 145.66 (2), 144.91 (4), 143.30 (6), 143.21 (4), 142.70 (4), 142.5 (4), 140.85 (4), 139.31 (4), 130.76 (2), 124.22 (2), 78.75 (2).

satellites that are 16 Da higher, presumably resulting from the pernicious epoxidation of fullerenes observed previously under a variety of conditions.[11] C_{70} also reacts with benzyne to give a monoaddition product (*m/z* 916).

Previously, we showed that aromatic hydrocarbons undergo electrophilic substitution with C_{60} and C_{70}.[12] The resulting mixtures of fullerenated aromatics were difficult to purify because (1) multiple additions (up to 20) occurred and were difficult to control under the Friedel–Crafts conditions described, (2) the aryl adducts were accompanied by ions resulting from multiple stages of dehydrogenation, and (3) the pendant groups were unstable to some analytical conditions. The benzyne adducts of C_{60} suffered from none of these deficiencies.

Milligram quantities of the mixtures resulting from the reaction of benzyne and C_{60} were chromatographed on a semipreparative C_{18} column.[13] Figure 2 shows the chromatogram with peaks corresponding to the separated di- and monobenzyne adducts of C_{60}, as well as C_{60}. The identities of the respective fractions were confirmed by negative ion desorption chemical ionization mass spectrometry.

The major feature in the ^{1}H-NMR spectrum[14] of the fraction corresponding to monoaddition of benzyne was an AA′BB′ multiplet in the aromatic region characteristic of a mirror symmetric product. Transitions were observed in CD_2Cl_2 at δ 8.038, 8.034, 8.026, 8.020, 8.015, 8.014, 8.009,

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(10) Collision-induced dissociation was performed in the negative-ion mode with a Q2 DC offset of 150 V and a xenon target at 0.6 mTorr (uncorrected): Busch, K. L.; Glish, G. L.; McLuckey, S. A. *Mass Spectrometry/Mass Spectrometry*; VCH: New York, 1988.

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(13) A Vydac 201TP, 5-μm, C_{18}, 250- × 10-mm i.d. column protected by a C_{18} guard column was used in the HPLC separations. Isocratic elution was achieved on a Perkin-Elmer Series 400 liquid chromatograph at a flow rate of 2 mL/min with a 60:40 mixture of Fisher HPLC-grade acetonitrile and Baker spectrophotometric-grade chloroform. After reconcentration of the reaction mixture and filtration with a nylon 66, 0.45-μm membrane filter, the brown reaction solution was injected using a Rheodyne Model 7120 injector with a 50-μL injection loop. Elution was monitored by ultraviolet absorption at 254 nm with a Altex mercury vapor detector.

(14) ^{1}H-NMR and ^{13}C-NMR spectra were obtained on Varian VXR 500 and VXR 600 NMR spectrometers, respectively. The FTIR spectrum was recorded with a Perkin-Elmer 1800 spectrometer and the UV/vis spectrum with a Hewlett-Packard 8451A diode array spectrometer.

8.002, 7.998, 7.801, 7.797, 7.789, 7.784, 7.783, 7.778, 7.772, 7.764, and 7.761. This spectrum was simulated with the following chemical shifts and coupling constants: $\nu_a = \delta$ 8.018, $\nu_b = \delta$ 7.780, J_{AB} = 7.6 Hz, $J_{AB'}$ = 1.2 Hz, $J_{BB'}$ = 6.7 Hz, and $J_{AA'}$ = 0.8 Hz (Figure 3). The ^{1}H-NMR spectrum of the collected diadduct fractions was complex (more than 100 transitions from δ 7.5–8.2) resulting from the many regiochemical possibilities for adding a second benzyne molecule to [C_{60} + C_6H_4].

The ^{13}C[^{1}H]-NMR spectrum (Figure 4) showed 19 transitions. A tabulation of the peaks is given in the figure caption. The C_{2v} structure, corresponding to benzyne addition across the pyracyclene bonds, should give rise to 20 peaks in the spectrum; seven independent carbon atoms sit on mirror planes and 13 have unit occupancy. Correspondence between the proposed structure and the NMR spectrum would be achieved if the missing line, one of the expected weak signals, is isochronous with the peak at δ 143.30, thus contributing to its unique intensity. Symmetry considerations force us to conclude that addition occurs across bonds between fused six-membered rings. The coupled spectrum reveals that the peaks at δ 124.22 and δ 130.76 correspond to carbons carrying the protons. The signal at δ 78.75 is assigned to the quaternary bridgehead carbons of the fullerene cage which are the sites of attachment of the benzyne moiety. The upfield value confirms that the structure is the closed, rather than the open [10]annulene, isomer.[15] Complete analysis of the connectivity via the INADEQUATE sequence is in progress.[16]

The monoadduct of C_{60} and benzyne is yellow in color; the UV/vis spectrum in *n*-hexane showed λ_{max} at 320 nm with a weak visible band at 428 nm. The FTIR spectrum (KBr pellet) showed C–H absorption bands at 2924 and 2854 cm^{-1}. Additional frequencies were recorded at 1458, 1278, and 1024 cm^{-1}.

In one anomalous reaction of benzyne and buckminsterfullerene, we observed two AA′BB′ spin systems in the aromatic region for the separated product that gave rise to a predominant ion (*m/z* 796) in the mass spectrometer. The major product showed eight major transitions at δ 7.627, 7.620, 7.616, 7.609, 7.480, 7.473, 7.468, and 7.462. We are investigating the possibility that even the monoaddition of benzyne to C_{60} may be regiononspecific and subtly dependent on reaction conditions.

The isolated monoaddition product, corresponding to the downfield AA′BB′ spin system, crystallized from CS_2 as dark red spars (mp >400 °C). Structure analysis by X-ray diffraction is in progress.

Acknowledgment. We thank Stanley Dostal for his assistance. This work was supported by the National Science Foundation (CHE-9114265, CHE-87-21768, and DIR 8912612). S.H.H. thanks BASF for a contribution to a National Needs Fellowship. J.M. thanks Purdue University Department of Chemistry for a QUEST Fellowship. D.D. was supported by a postdoctoral fellowship from Michelin from where she was on leave.

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Synthesis of the 9,10-Acetonide of 9-Dihydro-FK-506[1]

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Summary: The synthesis of the analog FKANAL (I) of the immunosuppressant FK-506 in which the central features are the spiroenone system B which masks the α-allyl aldol portion of FK-506 and the spiroketal D which mimics the α-keto amide portion is described.

In the course of work directed toward the total synthesis of the immunosuppressant FK-506,[2] it appeared that the spiroketal I (FKANAL[3]) might be a close, stable analog of the natural product itself. Many of the salient features that effect the binding[4] of FK-506 to its receptor FKBP are preserved in this analog and the effector domain[4] remains identical to that of the natural product. The synthesis of this material became the first target of this work and this goal has now been achieved.

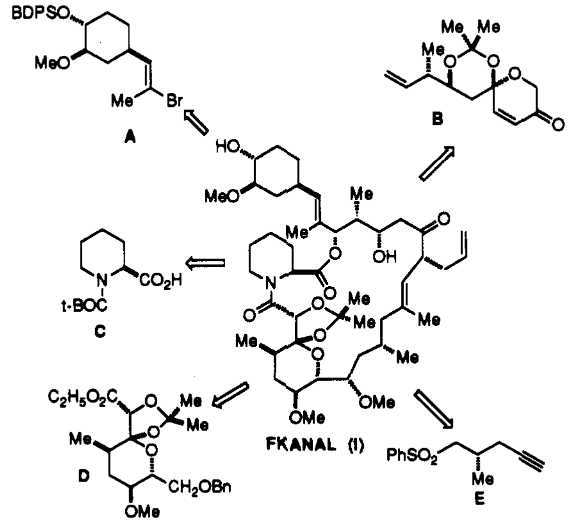

Figure 1. Parts for the synthesis of FK-506 analog.

The main features of the retrosynthetic plan for the analog I are the vinyl bromide A, the spiroenone B, and the spiroketal D (Figure 1). The assemblage of these parts

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