Mechanistic Implications of the Stereochemistry of the Cation Radical Diels−Alder Cycloaddition of 4-(*cis*-2-Deuteriovinyl)anisole to 1,3-Cyclopentadiene

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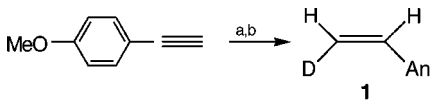
The cation radical Diels−Alder cycloaddition of *trans*-anethole to 1,3-cyclopentadiene, catalyzed by tris(4-bromophenyl)aminium hexachloroantimonate, yields both the trans-endo and trans-exo products, but no traces of cis adducts are found (<0.1%).[1] In sharp contrast, the addition of *cis*-anethole to cyclopentadiene is nonstereospecific, forming all four Diels−Alder cycloadducts in substantial amounts. These contrasting results are especially dramatic because of the very high degree of suprafacial stereoselectivity established in the cycloaddition of *trans*-anethole. Since *cis*-anethole obviously adds via a stepwise process, it is natural to assume that *trans*-anethole does likewise. However, if this is the case it is necessary to postulate that the cyclization of the distonic cation radical intermediate is at least 1000 times as rapid as bond rotation. Presumably, bond rotation in the trans isomer could be appreciably slowed by the steric hindrance encountered by the anisyl substituent as it rotates into the less stable cisoid conformations, but the existence of a cyclization step that is so much faster than bond rotation would be at least somewhat surprising and would constitute an important precedent in cation radical cycloaddition chemistry. An alternate, but admittedly less likely, possibility is that while the cis isomer reacts in stepwise fasion, the trans isomer reacts via a concerted mechanism; i.e., there is a mechanistic change between these two geometric isomers.

Results and Discussion

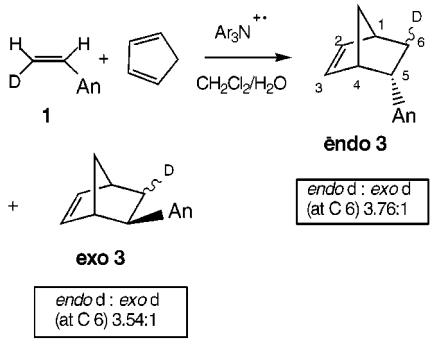
To distinguish between the two previously mentioned mechanistic possibilities, and specifically to remove the effect of the methyl substituent upon the rate of bond rotation, the stereochemistry of the cation radical Diels−Alder cycloaddition of 4-(*cis*-2-deuteriovinyl)anisole (**1**$^{\cdot+}$) to 1,3-cyclopentadiene was studied. Since the reaction of 4-vinylanisole with cyclopentadiene had not previously been reported, we first carried out the reaction of this substrate with an excess (10-fold) of 1,3-cyclopentadiene in the presence of tris(4-bromophenyl)aminium hexachloroantimonate (**2**$^{\cdot+}$) in dichloromethane solution at 0 °C.[2] The reaction afforded a mixture of endo and exo Diels−Alder adducts (**3**; endo/exo =3:1), which could be separated by column chromatography. The ^{1}H NMR, COSY, and NOESY spectra of both pure isomers were examined, and it was established that the endo and exo protons at C6 were well resolved from each other and from other absorptions for both isomers. The deuterated substrate was then prepared from 4-ethynylanisole as shown in Scheme 1.

Scheme 1



a.BuLi,THF,78°; D_2O
b.H_2,MeOD,Pd/$CaCO_3$,Pb,quinoline

Scheme 2



The results of the reaction of the deuterated substrate with cyclopentadiene are shown in Scheme 2. The reaction is significantly nonstereospecific in the case of both adduct diastereoisomers. Although the main cycloaddition stereochemistry involved in the formation of the endo isomer is the expected suprafacial addition, the exo isomer is formed predominantly by an antarafacial path. This latter observation, although initially somewhat surprising, is consistent with the proposal that the exo adduct is predominantly formed via an initial approach from the endo face, followed by rotation to give the exo product. Precedent for a preferred endo approach mode has previously been established.[3]

These results clearly establish that the addition of the vinylanisole cation radical to cyclopentadiene, like that of the *cis*-anethole cation radical, is a stepwise process, and they thus strongly suggest that the addition of *trans*-anethole is also stepwise, even though both the endo and exo adducts in the latter case are formed with complete (>99.9%) suprafacial stereoselectivity. The list of nonstereospecific and thus obviously stepwise cation radical Diels−Alder cycoadditions thus continues to grow longer.[3,4] These results further emphasize that, especially in the case of cation radical Diels−Alder cycloadditions, even very high reaction *stereoselectivity* may not necessarily be a strong indicator of reaction concertedness. However, the uncoupling of concertedness and high reaction *stereospecificity* (highly stereoselective addition of both cis and trans dienophile geometric isomers), although also theoretically possible, still has not been observed and appears unlikely. It is therefore appropriate to note that

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the cation radical Diels−Alder cycloadditions of the three geometric isomers of 2,4-hexadiene to cyclohexadiene are highly stereospecific[5] as are those of the cis,trans isomers of 1,2-diaryloxyethenes to 1,3-cyclopentadiene.[6]

Experimental Section

Chemicals and Solvents. All chemicals used as starting materials were purchased from the Aldrich Company and used as received unless otherwise specified. The dichloromethane solvent was dried by refluxing it over calcium hydride. The catalyst, tris(4-bromophenyl)aminium hexachloroantimonate, was synthesized according to the literature procedure.[2]

Synthesis of 1-(2′-Deutero)ethynyl-4-methoxybenzene. To 1.32 g (0.01mol) of 1-ethynyl-4-methoxybenzene[7,8] dissolved in 20 mL of dry THF at −78 °C was added 7.54 mL (0.012 mol, 1.6 M in hexane) of *n*-BuLi. The mixture was stirred for 18 min and then quenched with 2.5 mL of D_2O at −78 °C. The usual two-phase water/dichloromethane workup yielded 1.33 g (99%) of the pure product: ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.75 (s, 3H), 6.82 (2H, dd, J = 8.82, 2.05 Hz), 7.40 (2H, dt, J = 8.87, 2.07 Hz); HRMS calcd for C_9H_7DO 134.071617, found 134.071724.

Synthesis of *cis*-2-Deuteriovinylanisole (1). To 100 mg (0.75 mmol) of 1-(2′-deutero)ethynyl-4-methoxybenzene of dissolved in 8 mL of CH_3OD was added 5 mg of Lindlar catalyst and 50 mg of quinoline. Hydrogen gas contained in a balloon was bubbled into the reaction mixture at room temprature for about 16 min (monitored by GC). Workup gave the pure product (100 mg; 98.5% yield), which was found by NMR to be at least 98.8% *cis*-2-deuteriovinylanisole: ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.8 (3H, s), 5.13 (1H, dd, J = 10.97, 3.25 Hz), 6.66 (1H, m), 6.84 (2H, d, J = 8.56 Hz), 7.32 (2H, d, J = 8.74 Hz); HRMS calcd for C_9H_9DO 1.36.087267, found 136.087118.

Reaction of 4-Vinylanisole with 1,3-Cyclopentadiene. To tris(4-bromophenyl)aminium hexachloroantimonate (274 mg; 0.335 mmol) dissolved in 20 mL of dichloromethane and 5 mL of water at 0 °C was added a solution of 300 mg (2.24 mmol) of 4-vinylanisole and 1.48 g (22.4 mmol) of 1,3-cyclopentadiene dissolved in 5 mL of dichloromethane, all in one portion. After 1.5 min, the reaction mixture was quenched with saturated methanolic potassium carbonate. After aqueous workup and purification by column chromatography (silica gel; elution with hexanes/dichloromethane = 10:1), the mixture of endo and exo DA adducts (3:1) was obtained (313 mg, 70%). Endo adduct (**3a**): ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.21 (1H, m, H6 endo), 1.42 (1H, m, H7 anti), 1.50 (1H, m, H7 syn), 2.18 (1H, m, H6 exo), 2.91 (1H, s, H1), 3.02 (1H, s, H4), 3.32 (1H, m, H5), 3.78 (3H, s, OCH_3), 5.75 (1H, m, H3), 6.22 (1H, m, H2), 6.76 (2H, d, J = 8.63 Hz), 7.03 (2H, d, J = 8.23 Hz); HRMS calcd for $C_{14}H_{17}O$ 201.127940, found 201.127755. Exo adduct (**3b**): ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.40 (1H, m, H7 anti), 1.57 (1H, m, H7 syn), 1.61 (1H, m, H6 endo), 1.70 (1H, m, H6 exo), 2.65 (1H, dd, J = 8.63, 4.62 Hz, H5), 2.82 (1H, s, H4), 2.97 (1H, s, H1), 3.79 (3H, s, OCH_3), 6.14 (1H, dd, J = 5.62, 2.81 Hz, H2), 6.23 (1H, dd, J = 5.62, 3.01 Hz, H3), 6.82 (2H, d, J = 8.83 Hz), 7.18 (2H, dq, J = 8.23, 0.6 Hz); HRMS calcd for $C_{14}H_{17}O$ 201.127940, found 201.127745.

Reaction of 4-(*cis*-2′-Deuteriovinyl)anisole with Cyclopentadiene. To tris(4-bromophenyl)aminium hexachloroantimonate (326.6 mg; 0.4 mmol) in 20 mL of dichloromethane and 5 mL of H_2O at 0 °C was added a solution of 300 mg (2.24 mmol) of 4-(*cis*-2′-deuteriovinyl)anisole and 1.76 g (26.7 mmol) of 1,3-cyclopentadiene in 5 mL of dichloromethane in one portion. The reaction mixture was then quenched with saturated methanolic potassium carbonate after 1.5 min. After aqueous workup, the adducts were purified by column chromatography (silica gel; hexanes/dichloromethane = 10:1), giving 285 mg (63.8% yield) of the endo and exo DA adducts. Pure fractions of both adducts were obtained by this means. Endo adduct: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.21 (21% H, m, H6 endo), 1.42 (1H, m, H7 anti), 1.50 (1H, m, H7 syn), 2.18 (79% H, m, H6 exo), 2.91 (1H, s, H1), 3.02 (1H, s, H4), 3.30 (1H, dd, J = 9.5, 3.5 Hz, H5), 3.78 (3H, s, OCH_3), 5.76 (1H, dd, J = 5.75, 3 Hz, H3), 6.22 (1H, dd, J = 5.5, 3 Hz, H2), 6.76 (2H, d, J = 8.83 Hz), 7.03 (2H, dd, J = 8.83, 0.6 Hz); HRMS calcd for $C_{14}H_{15}DO$ 202.135765, found 202.134651. Exo adduct: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.40 (1H, m, H7 anti), 1.57 (1H, m, H7 syn), 1.60 (78% H, m, H6 endo), 1.70 (22% H, m, H6 exo), 2.62 (1H, d, J = 8.5 Hz, H5), 2.81 (1H, s, H4), 2.92 (1H, s, H1), 3.79 (3H, s, OCH_3), 6.12 (1H, dd, J = 5.5, 3 Hz, H2), 6.22 (1H, dd, J = 5.5, 3 Hz, H3), 6.82 (2H, d, J = 8.5 Hz), 7.19 (2H, d, J = 8.53 Hz); HRMS calcd for $C_{14}H_{15}DO$ 202.135765, found 202.134655.

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Supporting Information Available: NMR spectra of obtained compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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