Approaching a possible stepwise/concerted mechanistic crossover point in the cation radical cycloadditions of *cis*- and *trans*-anethole

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Received (in Cambridge, UK) 15th February 2000, Accepted 6th March 2000

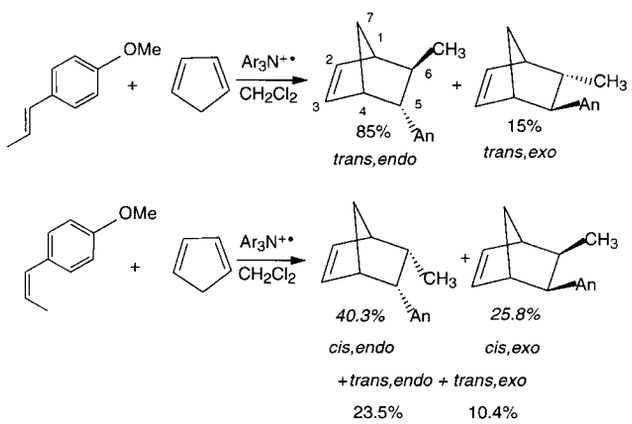
The Diels–Alder cycloadditions of the *cis*- and *trans*-anethole cation radicals to cyclopenta-1,3-diene have carefully been examined and are found to produce sharply different stereochemical results. The *cis*-anethole cation radical adds *via* a distinctly stepwise mechanism, yielding comparable amounts of all four diastereoisomeric Diels–Alder adducts. In contrast, the *trans*-anethole cation radical yields only *trans* adducts, with the *endo* isomer predominating. None of the *cis* adducts could be detected, and the percentage of *cis* adducts formed, if any, is significantly less than 0.1%. This result stands in contrast to the additions of aryl *cis*- and *trans*-propenyl ethers to the same diene, in which both geometric alkene isomers yield all four adducts in comparable amounts. Consequently, if *trans*-anethole also reacts by a stepwise mechanism, the rate of cyclization in the intermediate distonic cation radical must be of the order of 1000 times the rate of bond rotation. Alternatively, although it is less likely, the *trans* cation radical could react *via* a concerted reaction path.

Introduction

Cycloadditions of the cation radicals of aryl *cis*- and *trans*-propenyl ethers[1] and also of *N*-*cis*-β-deuteriovinylcarbazole[2] to cyclopenta-1,3-diene have recently been found to be non-stereospecific and thus to involve distonic cation radical intermediates which undergo bond rotation at a rate comparable to or even greater than cyclization. On the other hand, the cation radical cycloadditions of the three geometric isomers of hexa-2,4-diene to cyclohexa-1,3-diene are quite stereospecific,[3] indicating either a concerted reaction mechanism or, conceivably, a stepwise one in which the cyclization step is very much faster than the bond rotations (around single bonds) in the intermediate which would engender stereorandomization. The stabilization of the carbocation site of a distonic cation radical intermediate by a strongly electron donating aryloxy or amine function would, of course, be expected both to favor a stepwise mechanism and to provide a longer lived intermediate which would therefore have much greater opportunity for bond rotations. In order to investigate further the effect of structural changes upon the potential competition between stepwise and concerted cycloadditions, to look for a possible crossover point in the mechanistic competition, and ultimately to probe the subtle distinction between concerted mechanisms and stepwise ones involving extremely rapid cyclization, it appeared desirable to study the cation radical cycloadditions of *cis*- and *trans*-anethole to cyclopenta-1,3-diene. The anetholes were selected based upon the likelihood that the stabilization provided by a *p*-anisyl group to a cationic site should be intermediate between that provided by a simple alkene π bond on one hand and an ether or amine function on the other.

Results and discussion

trans-Anethole was obtained from the Aldrich Company and contained less than 0.1% of the *cis* isomer. *cis*-Anethole of similar purity was obtained by careful silica gel chromatography of a mixture of *cis*- and *trans*-anethole obtained from triplet photosensitized photoequilibration.[4] The reactions with an excess of cyclopenta-1,3-diene were carried out at 0 °C in dry dichloromethane solutions for various times and in the presence of various concentrations of cyclopenta-1,3-diene. The results are given in Scheme 1. The reaction of *cis*-anethole



Scheme 1 Cation radical Diels–Alder cycloadditions of *cis*- and *trans*-anethole to cyclopenta-1,3-diene.

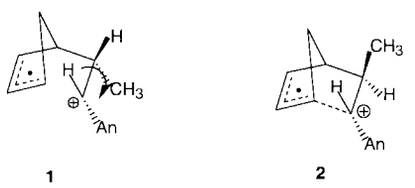
is non-stereospecific, yielding all four of the diastereoisomeric Diels–Alder adducts in rather comparable amounts in an overall yield of 80%. Each of the adducts was purified individually and identified by ^{1}NMR, COSY, and NOESY spectroscopy. The stability of each of the products under the reaction conditions (0 °C, 2 min) was established, ruling out the possibility of stereorandomization subsequent to their formation. Moreover, product ratios were reasonably constant from very early in the reaction (5 s) to completion (2 min). Under none of the above conditions was the *cis*-anethole isomerized to detectable amounts of the *trans* isomer. Further, the same reaction carried out under photosensitized electron transfer (PET) conditions gave rise to the same four products in very similar ratios, indicating that there is nothing special about the aminium salt method of ionizing *cis*-anethole which would tend to generate any of the *trans*-anethole cation radical. Unimolecular isomerization of the *cis*- to the *trans*-anethole cation radical in competition with cycloaddition was also ruled out by the

DOI: 10.1039/b001264p

observation that the product ratios remained constant when the concentration of cyclopentadiene was varied from a 5-fold to a 20-fold excess. If isomerization were occurring in competition with cycloaddition, the extent of isomerization would be inversely proportional to the diene concentration.

In rather sharp contrast, the reaction of *trans*-anethole yields only two adducts, the *trans*,*endo* and *trans*,*exo* isomers, the former predominating as is usual in cation radical Diels–Alder reactions. Neither of the *cis* isomers could be detected, and quantitative GC experiments established that 0.1% of a *cis* isomer could easily have been detected. Although the *trans* isomers are likely to be somewhat more stable thermodynamically than the *cis* isomers, it is at least somewhat surprising that essentially none of the latter was formed. In the reaction of the aryl *cis*- and *trans*-propenyl ethers with cyclopentadiene, for example, all four product diastereoisomers are formed in comparable amounts from both geometric isomers, as is also the case in the addition of *cis*-anethole.

The stereochemical results for *cis*-anethole are readily interpreted in terms of a stepwise mechanism in which bond rotations in the intermediate distonic cation radical (**1**; Scheme 2) occur at a rate comparable to cyclization, as in the



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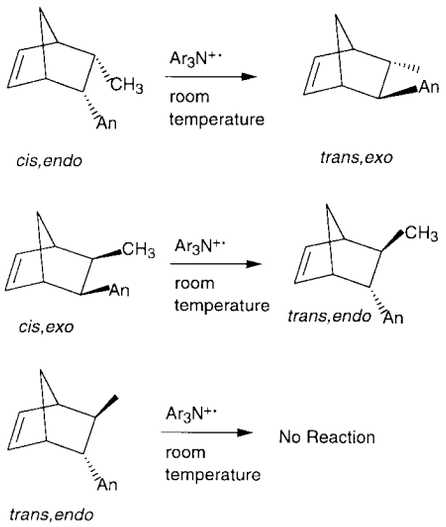
Scheme 2 Distonic cation radical intermediates in the cycloadditions of *cis*- and *trans*-anethole to cyclopenta-1,3-diene.

case of the previous additions of aryl propenyl ethers and *N*-vinylcarbazole. On the other hand, it appears that in the case of *trans*-anethole an analogous stepwise mechanism would be consistent with the stereochemical results only if cyclization is approximately three orders of magnitude faster than bond rotation. Although such a large disparity in relative rates of rotation and cyclization between *cis* and *trans* isomers is initially somewhat surprising, it is conceivable that the steric effect presented by the methyl substituent does slow the rotation of the anisyl group into cisoid conformations sufficiently to engender the observed predominance of cyclization. We propose that this effect is further assisted by a weak interaction between the carbocation and radical sites (**2**; Scheme 2). The presence of such a stabilizing interaction might also explain the strong preference for Diels–Alder cycloaddition over cyclobutanation in these reactions. Alternatively, the results for *trans*-anethole could be interpreted in terms of a concerted mechanism. However, in this case the highly unusual circumstance would prevail that *cis* and *trans* isomers undergo reaction by different mechanisms, *i.e.*, that there is a mechanistic crossover for these isomers, and we view this possibility as less likely. Nevertheless, in view of the pronounced preference for cyclization over rotation in the *trans*-anethole case, and the sharply contrasting results for aryl propenyl ethers and *N*-vinylcarbazole, it appears appropriate to regard the *trans*-anethole cycloaddition as occurring *via* a reaction path which, while not a true concerted addition, rather closely approaches this mechanistic type.

Although the four adducts were found to be stable for a few minutes at 0 °C under the aminium salt reaction conditions, it was found that the *cis* isomers do rearrange in the presence of the aminium salt at room temperature (Scheme 3). Interestingly, the *cis*,*endo* diastereoisomer rearranges exclusively to the *trans*,*exo* diastereoisomer as a 1 : 1 mixture of starting material (the *cis*,*endo* adduct) and the *trans*,*exo* adduct, and the *cis*,*exo* diastereoisomer rearranges to the *trans*,*endo* isomer (also as a



Scheme 3 Stereoselective rearrangement of the *cis* adducts in the presence of the aminium salt at room temperature.

mixture of the starting adduct and the single rearranged adduct). The *trans* adducts fail to undergo any detectable isomerization. These observations are consistent with the reversal of the cyclization step, in the case of the *cis* isomers, to give a distonic cation radical, followed by bond rotation and recyclization. The same distonic cation radical which is postulated for the cycloaddition is therefore implicated in the reverse reaction. There is no evidence for the formation of an analogous distonic cation radical from the *trans* adducts. These results also rule out a complete reversal of adduct formation to reform the anethole cation radicals, followed by re-addition to the diene, since the *cis* adducts would then rearrange to a mixture of all four adducts and the individual *trans* adducts would rearrange to a mixture of *endo* and *exo trans* isomers.

Conclusions

The cycloaddition of the *cis*-anethole cation radical to cyclopenta-1,3-diene at 0 °C proceeds in a stepwise manner, *via* a distonic cation radical intermediate, to form all four of the possible diastereoisomeric Diels–Alder adducts. Evidence for the same distonic cation radical is also implicit in the stereoselective rearrangement of the *cis*,*endo* adduct to the *trans*,*exo* adduct and the *cis*,*exo* adduct to the *trans*,*endo* adduct in the presence of the aminium salt at room temperature. In contrast, the cycloaddition of the *trans*-anethole cation radical to cyclopenta-1,3-diene yields only *trans* adducts, with the *trans*,*endo* diastereoisomer predominating. Since either of the *cis* adducts could have been detected in amounts even less than 0.1%, it is evident that if a distonic cation radical intermediate is involved in this reaction its cyclization is at least 1000 times as fast as rotation around the single bond which could produce stereorandomization. In sharp contrast, bond rotation and cyclization occur at approximately equal rates in the *cis* isomer. It is proposed that the *trans*-anethole cycloaddition also occurs *via* a stepwise mechanism in which, however, bond rotation is slowed by a combination of effects, including the steric effect of the methyl group and a weak interaction between the carbocation and radical sites of the intermediate distonic cation radical.

Experimental

Equipment

Proton NMR spectra were recorded on a Bruker AC250 or a Varian UNITY INOVA 500 spectrometer. Chemical shifts (δ)

are relative to tetramethylsilane, and coupling constants (J) are in Hz. Carbon spectra were recorded on the Bruker 250 instrument, and COSY and NOESY spectra on the Varian UNITY INOVA 500 spectrometer. High resolution mass spectra (HRMS) were recorded on a VGZAB-2E mass spectrometer. GC measurements were made using a Hewlett-Packard 6890 instrument with HP 6890 Series Integrator.

Chemicals and solvents

All 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.[5]

Diels–Alder reaction of *trans*-anethole with cyclopenta-1,3-diene

To a solution of 296 mg (2 mmol) of *trans*-anethole (>99.9% pure) and cyclopenta-1,3-diene (660 mg, 10 mmol) in 20 mL of anhydrous dichloromethane were added 164 mg (0.2 mmol) of the catalyst, tris(4-bromophenyl)aminium hexachloroantimonate, dissolved in 8 mL of dichloromethane. The reaction was quenched after 2 minutes by adding saturated potassium carbonate–methanol solution. Aqueous work-up and column chromatography on silica gel (hexanes–dichloromethane 15 : 1) gave 352 mg (82%) of the diastereoisomeric *trans* Diels–Alder adducts, with an *endo:exo* ratio of 85 : 15. Small samples of the pure diastereomers obtained by such chromatography yielded the following data. ^{1}H NMR for the *trans*,*endo* diastereoisomer (500 MHz, $CHCl_3$, positional assignments by COSY and NOESY spectroscopy): δ 1.19 (3H, d, J = 7.04, Me protons), 1.42 (1H, m, H7-*anti*), 1.66 (1H, m, H6), 1.67 (1H, m, H7-*syn*), 2.47 (1H, s, H1), 2.68 (1H, m, H5), 2.94 (1H, s, H4), 3.75 (3H, s, OMe), 5.87 (1H, dd, J = 5.63, 2.62, H2), 6.30 (1H, dd, J = 5.63, 3.02, H3), 6.75 (2H, d, J = 8.65), 7.06 (2H, d, J = 8.45). ^{13}C NMR (250 MHz, $CDCl_3$): δ 21.055, 41.354, 46.880, 49.219, 49.504, 52.491, 55.184, 113.199, 128.709, 133.568, 136.841, 138.007, 157.705. HRMS: Calc. for $C_{15}H_{19}O$ *m*/*z* 215.143590. Found 215.143576. ^{1}H NMR for the *trans*,*exo* isomer (500 MHz, $CDCl_3$): δ 0.93 (3H, d, J = 6.8), 1.49 (1H, m, H7-*anti*), 1.72 (1H, d, J = 8.4, H7-*syn*), 1.98 (1H, dd, J = 5.02, 1.3, H5), 2.05 (1H, m, H6), 2.72 (1H, s, H1), 2.76 (1H, d, J = 1.35, H4), 3.8 (3H, s, OMe), 6.09 (1H, dd, J = 5.65, 2.85, H2), 6.32 (1H, dd, J = 5.65, 3.15, H3), 6.82 (2H, d, J = 8.75), 7.17 (2H, d, J = 8.7). ^{13}C NMR (250 MHz, $CDCl_3$): δ 19.407, 42.341, 47.646, 47.889, 49.455, 51.724, 55.277, 113.715, 128.146, 134.434, 137.861, 138.458, 157.625. HRMS: Calc. for $C_{15}H_{19}O$ *m*/*z* 215.143590. Found 215.143609.

Separation of pure *cis*-anethole

A photostationary mixture of *cis*- and *trans*-anethole was prepared from *trans*-anethole, using cyclohexane as the solvent, benzophenone as the triplet sensitizer, and a 450 W Hanovia medium pressure lamp. The sample was irradiated in a Pyrex vessel for 3 h and then subjected to chromatography on silica gel (hexanes–dichloromethane 15 : 1), to yield samples of the *cis* isomer which were >99.9% pure (GC).

Diels–Alder reaction of *cis*-anethole with cyclopenta-1,3-diene

To a solution of 148 mg (1 mmol) of *cis*-anethole and cyclopenta-1,3-diene (330 mg, 5 mmol) in 9 mL of anhydrous dichloromethane was added a solution of 82 mg (0.1 mmol) of tris(4-bromophenyl)aminium hexachloroantimonate in 4 mL of dichloromethane. The reaction was quenched after 2 min with methanolic potassium carbonate solution. After aqueous work-up and chromatography on silica gel (hexanes–dichloromethane 15 : 1) a total of 172 mg (80% yield) of four diastereoisomeric Diels–Alder adducts was obtained. The first chromatography yielded pure samples of the *cis*,*endo* and *cis*,*exo* isomers. The remaining adduct mixture was re-chromatographed using the same eluent to obtain the pure *trans*,*endo* isomer and a highly enriched sample of the *trans*,*exo* isomer. ^{1}H NMR of the *cis*,*endo* isomer (500 MHz, $CDCl_3$): δ 0.52 (3H, d, J = 7.3), 1.49–1.50 (2H, m, H7-*syn*,*anti*), 2.56 (1H, m, H6), 2.8 (1H, s, H1), 3.0 (1H, s, H4), 3.38 (1H, dd, J = 9.95, 3.05, H5), 3.75 (3H, s, OMe), 6.22 (1H, dd, J = 5.75, 3.1, H2), 6.36 (1H, dd, J = 5.45, 2.95, H3), 6.74 (2H, d, J = 8.8), 7.04 (2H, d, J = 8.5). ^{13}C NMR (250 MHz, $CDCl_3$): δ 16.76, 39.39, 48.71, 49.03, 49.13, 50.38, 55.14, 112.96, 130.63, 134.78, 135.72, 136.14, 157.54. HRMS: Calc. for $C_{15}H_{19}O$ *m*/*z* 215.143590. Found 215.144275. ^{1}H NMR for the *cis*,*exo* isomer (500 MHz, $CDCl_3$): δ 0.54 (3H, d, J = 7.23), 1.49 (1H, m, H7-*anti*), 1.83 (1H, d, J = 8.63, H6), 1.87 (1H, m, H7-*syn*), 2.51 (1H, d, J = 0.6, H1), 2.69 (1H, dd, J = 8.84, 1.01, H5), 2.9 (1H, d, J = 1.41, H4), 3.8 (3H, s, MeO), 6.2 (1H, dd, J = 5.83, 3.02, H2), 6.26 (1H, dd, J = 5.62, 3.02, H3), 6.81 (2H, d, J = 8.7), 7.03 (2H, d, J = 8.6). ^{13}C NMR (250 MHz, $CDCl_3$): δ 18.985, 36.307, 43.699, 46.009, 47.094, 55.196, 113.251, 129.402, 135.599, 138.102, 138.504, 157.349. HRMS: Calc. for $C_{15}H_{19}O$ *m*/*z* 215.143590. Found 215.143766.

Control studies

In order to verify that the four adducts obtained from *cis*-anethole were primary products of the reaction and not secondary products resulting from isomerization subsequent to their formation, the products of the Diels–Alder reaction of *cis*-anethole with cyclopentadiene were studied at very early reaction times (5 and 10 s), at which times most of the *cis*-anethole was still unreacted. The same four products were formed and in approximately the same ratios as at times up to two minutes, at which point the reaction was complete. The product ratios varied slightly, and the percentage of products quoted in Scheme 1 are those obtained at the earliest time (5 s).

To exclude the possibility that the stereorandomization was occurring *via* the unimolecular isomerization of the *cis*-anethole cation radical, the same reactions were carried out with various concentrations of cyclopentadiene, from a 5-fold to a 20-fold excess. Again, the product ratios were essentially constant.

Finally, in order to exclude the possibility of isomerization during the ionization of *cis*-anethole by the aminium salt, the reaction was carried out under photosensitized electron transfer conditions, using 1,4-dicyanobenzene as the sensitizer and acetonitrile as the solvent, with cyclopentadiene in fivefold excess. Irradiations were carried out for 10 min, at which time no detectable amount of isomerization of *cis*- to *trans*-anethole had occurred. Again, the same four products were obtained and in similar ratios to those found in the aminium salt reaction: *cis*,*endo* (40.2%); *cis*,*exo* (18.1%); *trans*,*endo* (31.9%); *trans*,*exo* (9.7%).

Rearrangement of the *cis* Diels–Alder adducts at room temperature

Small (*ca*. 5–10 mg) samples of the pure adduct diastereoisomers were treated with the aminium salt in dichloromethane solution at room temperature for ten minutes. The rearrangement was followed by GC. The *cis*,*endo* isomer was observed to rearrange partially to an approximately 1 : 1 ratio of the starting material and the *trans*,*exo* isomer, while the *cis*,*exo* isomer was partially rearranged to the *trans*,*endo* isomer. No rearrangement was observed for the *trans*,*endo* isomer. The following is a typical procedure for these rearrangement reactions. To pure *cis*,*exo* adduct (20 mg, 0.093 mmol) in 6 mL of anhydrous dichloromethane at room temperature was added, all in one portion, a solution of 7.6 mg (0.093 mmol) of the aminium salt

in 1 mL of dichloromethane. After 10 minutes, the reaction was quenched with methanolic potassium carbonate and the crude product examined by GC. A 1 : 1 mixture of adducts was found, consisting only of the starting *cis*,*exo* isomer and the *trans*,*endo* isomer.

Acknowledgements

The authors thank the National Science Foundation (CHE-9610227) for support of this research.

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