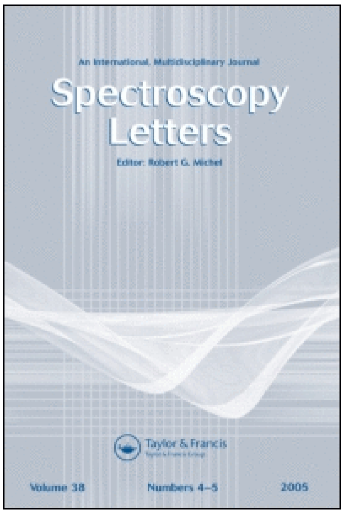

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NMR Determination of Molecular Stereochemistry of Hetero-Diels-Alder Reaction Products: Comparison with Calculation

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NMR DETERMINATION OF MOLECULAR STEREOCHEMISTRY OF HETERO-DIELS-ALDER REACTION PRODUCTS: COMPARISON WITH CALCULATION

Key Words: NMR, Molecular Stereochemistry, Diels-Alder reactions, ROSEY, TOCSY, NOESY, Molecular Simulation

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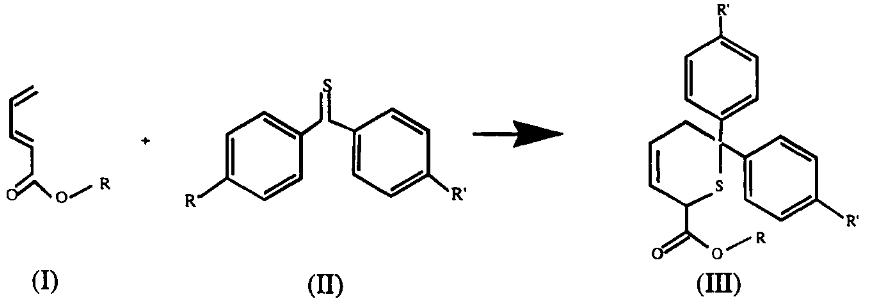
Abstract: An asymmetric hetero-Diels-Alder cycloadduct (III) is synthesized and isolated. The ^1H-^1H distance between a proton on the C_{12} chiral center and an ortho phenyl proton is measured by NMR spectral studies (ROSEY, NOESY, TOCSY) of the reaction product of 2,4-penanedienoic acid –(-)-menthol ester with 4,4'-dimethoxy-diphenythione. The experimentally determined value is compared to the distance computed by molecular modeling software (Sybyl). The agreement between experiment and computation is only fair indicating that the use of such measurements for small molecules of uncertain geometry must be approached with care. The results indicate that the distance of closest approach between two protons in a molecule is more consistent with the NMR determined distance than is the equilibrium, lowest energy form of the molecule.

Introduction: The Diels-Alder reaction of *trans*-2,4-pentanedienoic acid-(-)-menthol ester with 4,4'-dimethoxy-diphenylthione produces two stereoisomers in unequal amounts. It is known, that the reaction of similar, non asymmetric dienophiles react with diphenylthione with 100% regio selectivity to produce compound III as shown in scheme I, below.[1] Because the stereochemistry of C-S bond formation in hetero Diels-Alder



Scheme I

reactions are not well studied in comparison to the widely studied C-C bond formation, it is of interest to verify the utility of available stereochemical measurement methods.[2-6] Since the reaction studied here produces well characterized and understood products it can serve as a model for other C-S systems whose products are less certain. Therefore, the study reported here was undertaken to evaluate the reliability of the NMR methods for stereochemical evaluation. Since the product contains a chiral center fixed in a ring and a enantiomerically pure chiral group, two diastereomers are produced and the stereochemistry of the products can reliably be calculated by common computational methods which serve as "true" values for comparison with the experimental measurements.

Experimental: Preparation of *trans*-2,4-pentanedienoic acid –(-)-menthol ester: 6.1 g (0.06 mol) of *trans*-2,4-pentanedienoic acid was transferred by syringe into 40 mL of petroleum ether (90 –120 °C) (Na Dry) in a dry round bottom flask and heated to 60 °C. 6 mL of thionyl chloride was added to the hot solution over 10 minutes and the mixture stirred for 2 hours. Next 7 g (0.045 mol) of menthol dissolved in 10 mL of petroleum ether was added dropwise. A slight vacuum was maintained during the reaction period to remove the HCl produced. After 4 hours the reaction mixture was cooled to room temperature, shaken with saturated sodium carbonate (30 mL) and washed with water (30 mL). The organic phase was separated, dried over sodium sulphate and the solvent evaporated under reduced pressure. The residue was passed through a silica gel column and eluted with a petroleum ether:diethyl ether mixture (50:1) to yield 4.2 g (30%) of pure compound.

Reaction of *trans*-2,4-pentanedienoic acid-(-)-menthol ester with 4,4'-dimethoxy-diphenylthione: *trans*-2,4-pentanedienoic acid-(-)-menthol ester (0.1411 g, 0.598 mmol) and 4,4'-dimethoxy-diphenylthione (0.1378 g, 0.534 mmol) were dissolved in 1.0 mL of benzene. The dark blue solution was transferred into a 1.0 cm (o.d.) x 4.0 cm glass tube containing a small copper plate to prevent polymerization. Nitrogen gas was bubbled through the solution for at least 5 minutes prior to sealing the tube. The sealed tube was placed in a dark water bath and heated at various temperatures for 2 days. Following the reaction period, the mixture was cooled and placed on a silica gel column. The sample was eluted with benzene to give a mixture of diastereoisomers (0.16 g, 60%) as a white powder.

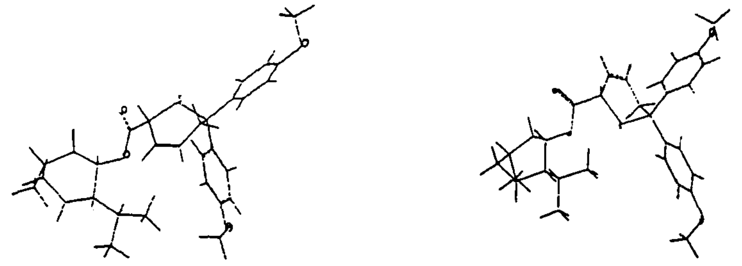
The mixture of diastereoisomers obtained from the reaction work-up was separated into its components by hplc elution through a C18 column with a mixed solvent of methanol:water (78:22). Two peaks of unequal intensity were obtained for the two isomers. The intensity ratio varied from 1.6:1 at a reaction temperature of 70 °C to 2.5:1 at a reaction temperature of 40 °C corresponding to enantiomeric excesses of 22 and 43% respectively and an activation energy difference of approximately 13 KJ/Mol. The smaller peak, due to the less stable isomer, was chosen for examination by NMR methods as it will have the smaller ^1H-^1H distances and, thus, will result in the largest through space effects.

Results and Discussion: Figure 1, below shows Structures IIIA and IIIB, the more and less stable isomers respectively for the reaction product. The numbering system is given in Figure 2, below. Examination of space filling models and molecular modeling calculations performed by the program Sybyl show that the ^1H-^1H distance between H_{12} and H_{18} is approximately 2.5 Å for the less stable isomer and about 4.4 Å for the more stable isomer. Thus, it should be possible to distinguish between these two isomers by ROESY or NOESY as the magnitude of cross peaks are proportional to $(1/r)^6$ where r is the ^1H-^1H distance.

In order to measure the interproton distance by these NMR procedures it is, of course, necessary to assign the NMR spectrum. The ^1H and ^{13}C spectra are given below.[7] While it is not required to assign every peak in the spectrum, it is necessary to determine which signals arise from H_{12} and which from H_{18} so that the correct cross peak can be identified. There are two potential assignments for H_{12} in the ^1H spectrum: 4.023 and 4.376 ppm.[7] The peak at 4.376 was shown to be a cyclohexane proton by a TOCSY experiment which showed long-range coupling of this peak to all of the menthyl cyclohexane protons, while the peak at 4.023 showed no coupling at all to the cyclohexane. Secondly, an HMQC experiment was performed to determine which of the deshielded protons is due to H_{18}. The result of this experiment was the assignment of the ^1H peak at 7.20 ppm to H_{18}. Thus the ROESY or NOESY cross peak at 4.023, 7.20 is sensitive to the H_{12}-H_{18} internuclear distance and its integrated intensity can be used to estimate the ^1H-^1H internuclear distance.

The interproton distance was estimated by volume integration of the ROESY cross peak between H_{12} and H_{18} and comparison to the volume integral of a cross peak of known interproton distance. The ROSEY cross peak for the methylene group comprised of H_{15A} and H_{15B} was chosen as the reference peak because its interproton distance is reliably known to be 1.773 Å and is unaffected by possible intramolecular flexibility. The H_{12}-H_{18} distance, r_{ij}, was then estimated from the standard relationship given in equation 1.

$$r_{ij} = r_{ref}(V_{ref}/V_{ij})^{1/6} \quad (1)$$



Stereoplot of the conformation of (-)-(R) D-A isomer.
IIIA

Stereoplot of the conformation of (-)-(S) D-A isomer.
IIIB

Figure 1: Structures of product diastereoisomers. The more stable isomer is IIIA.

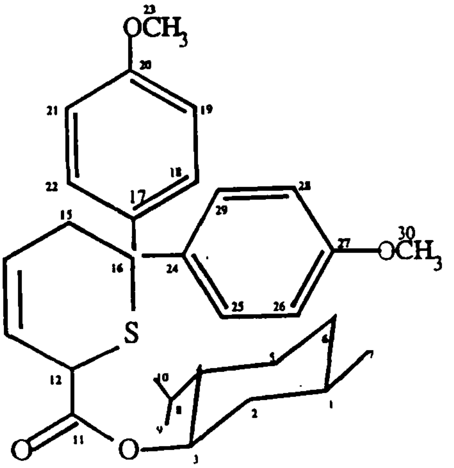


Figure 2: Compound Numbering System. Proton numbers are equal to the number of the carbon to which they are attached.

where r_{ref} is the reference interproton distance (1.773 Å in this case), V_{ref} is the volume integral for the reference cross peak and V_{ij} is the volume integral for the cross peak due to nuclei i and j.[8] In order to verify that equation 1 should be valid for the molecule and conditions employed, the volume integrals were measured over a range of mixing times from 100 to 600 msec. Both integrals were found to be linear functions of mixing time over this range. Thus, equation 1 can be used to estimate the interproton distance. The H_{12}-H_{18} distance obtained from the volume integrals, however, is only about 1.9 Å, a significant deviation from the 2.5 Å expected by the molecular structure.

The disagreement between the measured and computed internuclear distances can be explained by fact that the NOE is sensitive to the average internuclear distance while the computed value represents the lowest energy conformation. Because of the high power dependence on distance, the NOE is weighted in favor of those conformations with shorter H-H distances. For example, it has been shown that if two protons are 10% closer that the equilibrium distance for 10% of the time, then that conformation contributes as much as 90% to the relaxation.[9] CPK models of the two possible isomers were constructed and subjected to reasonable twists and bends to simulate higher energy forms which might reasonably be expected to be populated at room temperature. Examination of these twisted forms indicated that moderate deformation of the structure produced an H_{12}-H_{18} distance of about 2 Å for structure IIIB and of about 4 Å for structure IIIA. Thus, we note that the NOE derived distance is more appropriate to the distance of closest approach than to the lowest energy conformation.

In conclusion, the use of NOE measurements by either the ROESY or NOESY techniques can provide valuable structural information for determining the isomeric identity of a molecule. However, this work shows that significant discrepancies can arise if conformations having shorter H-H distances than the equilibrium, lowest energy form are populated in which case the NOE determined distance is better compared to the distance of closest approach than it is to the equilibrium lowest energy value.

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7. ^{1}H NMR Spectrum: 2.57 (1H, d, H_{15A}), 2.96 (1H, d, H_{15B}), 3.72 (3H, H_{23}), 3.74 (3H, H_{30}), 4.02 (1H,s, H_{12}), 4.38 (1H, m, H_3), 6.05 (2H, m, H_{13}, H_{14}), 6.72 (4H, d, H_{19}, H_{21}, H_{26}, H_{28}), 7.20 (4H, d, H_{18}, H_{22}, H_{25}, H_{29}).
^{13}C Spectrum: 16.13 (C_{10}), 20.82 (C_9), 21.87 (C_7), 23.14 (C_5), 25.94 (C_{15}), 26.05 (C_8), 31.10 (C1), 34.12 (C_6), 40.04 (C_2), 46.74 (C_4), 51.27 (C_{12}), 54.11 (C_{16}), 55.13 (C_{30}),

55.20 (C_{23}), 74.15 (C_3), 112.78 (C_{26}, C_{28}), 112.99 (C_{19}, C_{21}), 126.48 (C_{14}), 127.73 (C_{13}), 129.37 (C_{25}, C_{29}), 129.66 (C_{18}, C_{22}), 135.82 (C_{24}), 137.91 (C_{17}), 157.89 (C_{27}), 158.28 (C_{20}), 170.30 (C_{11}).

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9. Reference 8, p 110.

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