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STERIC EFFECTS IN THE ENE REACTION.

THE REACTION OF BENZYNE WITH cis-AND trans-2-METHYLBUT-1-EN-1-YL ACETATES

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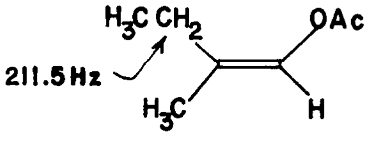
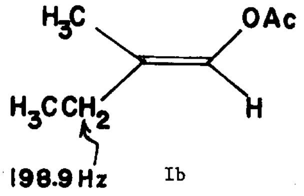
In previous studies on the stereochemistry of benzyne addition to enol ethers and acetates we observed both stereoselective 2+2 cycloaddition and ene reaction.[1] In each series, however, we found that the proportion of ene product relative to cycloaddition was significantly larger with the trans-isomer as compared to the cis, suggesting that steric effects may play a significant role in governing the favorability of the ene reaction. These results have led us to explore further reactions of benzyne with electron-rich olefinic systems. Our findings in the case of cis- and trans-2-methylbut-1-en-1-yl acetate (I) are reported below.

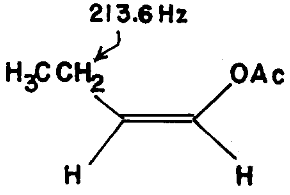
A mixture of cis- and trans-2-methylbut-1-en-1-yl acetates (Ia and Ib)[3] was prepared from 2-methylbutyraldehyde by the method of Meinwald.[2] The isomers were separated and collected by preparative vpc using a 20' x 3/4" column of 20% polyphenyl ether (6 ring) on Anaprep at 120°.



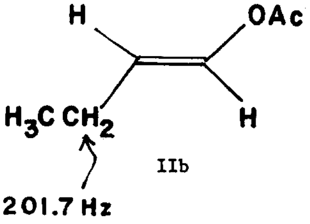
Ia



Ib



IIa



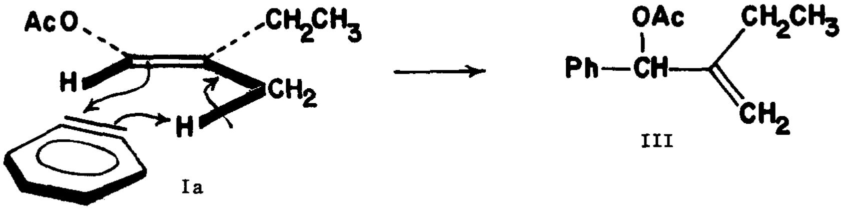
IIb

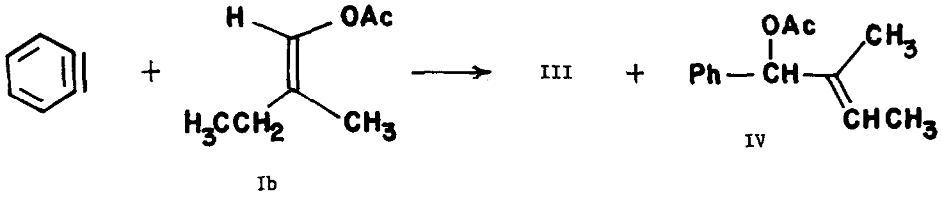
The pure cis and trans isomers were assigned stereochemistry based on their 100 MHz n.m.r. spectra.[4] It was possible to distinguish clearly between the two forms based on the deshielding effect of the acetoxy group on the methylene resonance of the cis-ethyl group. The signal for the methylene protons in the cis isomer (Ia) appears at 211.5 Hz (from TMS) while the corresponding absorption in the trans isomer (Ib) appears at 198.9 Hz. This downfield shift of 12.6 Hz is very similar to that observed for the corresponding protons in cis- and trans-but-1-en-1-yl acetates (IIa and IIb).[5] In the latter cis-trans pair, the deshielding effect is 11.9 Hz, with the corresponding resonances appearing at 213.6 Hz (from TMS) in the cis isomer and 201.7 Hz in the trans isomer.

The reaction of benzyne (generated from the decomposition of benzene-diazonium-2-carboxylate in refluxing methylene chloride[6]) with a 10% molar excess of pure cis-2-methylbut-1-en-1-yl acetate (Ia) afforded α-phenyl-β-ethylallyl acetate (III) as the sole product. Approximately half of the starting olefin was recovered intact, and conversion of the reacting substrate to this single product was 74%. Compound III was identified by independent synthesis from the reaction of but-1-en-2-ylmagnesium bromide with benzaldehyde in tetrahydrofuran followed by acetylation with acetic anhydride in pyridine.

On the other hand, reaction of benzyne with a 10% molar excess of pure trans-2-methylbut-1-en-1-yl acetate (Ib) afforded a mixture of III and α-phenyl-β-methylcrotonyl acetate (IV)[9] in equal amounts. In this case, conversion of starting material to products was 77% and examination of unreacted starting material indicated that no isomerization had occurred during the course of the reaction. The structure of compound IV was confirmed by comparison with an authentic sample synthesized independently from the addition of but-2-en-2-ylmagnesium bromide[9] to benzaldehyde in tetrahydrofuran followed by acetylation with acetic anhydride in pyridine.

Formation of the allylic acetate (III) in the reaction with Ia is in accord with an approach by the benzyne molecule at the least hindered side of the olefin,[7] leading to a transition state in which methyl group hydrogens are preferably abstracted. The same steric factors appear to be operative in the reaction of benzyne with butenyl acetate, Ib. In this case, each side of the double bond of Ib is substituted by a relatively large group (ethyl vs. acetoxy) and, accordingly, the direction of approach by the benzyne becomes less selective. Reaction at either side of the double bond becomes more equally favorable, and ene products are formed by hydrogen abstraction from both the methyl and ethyl groups.





The question as to whether the ene reaction is a concerted or a stepwise process has received recent attention.[8a-d] The experiment (Ia + benzyne) in which formation of III occurs to the total exclusion of IV clearly favors a concerted process in which bond rotation, allowing interconversion of the methyl and ethyl groups, does not take place. Studies by Crews and Beard serve to strengthen this interpretation.[8b]

It should also be noted that, in contrast to the results with the corresponding enol ethers, no 2+2 cycloaddition products were formed with benzyne from either of the isomeric acetates (Ia or Ib). This is in agreement with our findings that the ene reaction tends to predominate over 2+2 cycloaddition in olefinic systems as the electron density of the double bond is decreased.[1]

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References

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1. H.H. Wasserman, A.J. Solodar, and L.S. Keller, *Tetrahedron Lett.*, 5597 (1968).
2. J. Meinwald, J.W. Wheeler, A.A. Nimetz, and J.S. Liu, *J. Org. Chem.*, **30**, 1038 (1965).
3. Satisfactory C and H analyses were obtained for both isomers (Ia and Ib) and for all new products prepared in this work.
4. *cis*-2-Methylbut-1-en-1-yl acetate shows n.m.r. absorption at 671.8 Hz (from TMS)(broad singlet, olefinic proton, 1H); 211.5 Hz (quartet, -CH$_2$CH$_3$, J=7.6 Hz, 2H); 204.9 Hz (singlet, acetoxy group, 3H); 162.3 Hz (doublet, vinylic methyl, J=1.5 Hz, 3H); 98.5 Hz (triplet, -CH$_2$CH$_3$, J=7.6 Hz, 3H).

   trans-2-Methylbut-1-en-1-yl acetate shows peaks at 686.4 Hz (from TMS) (quintet, olefinic proton, J=1.5 Hz, 1H); 204.4 Hz (singlet, acetoxy group, 3H); 198.9 Hz (quartet, -CH$_2$CH$_3$, J=7.8 Hz, 2H); 166.0 Hz (doublet, vinylic methyl, J=1.5 Hz, 3H); 102.9 Hz (triplet, -CH$_2$CH$_3$, J=7.5 Hz, 3H).
5. *Cis*- and *trans*-but-1-en-1-yl acetates were prepared by the method of Meinwald[2], and separated by preparative vpc using a 20' x 3/8" column of 20% Carbowax on Anaprep. The stereochemistry was assigned on the basis of the coupling constants of the *cis* and *trans* olefinic protons.
6. The benzenediazonium-2-carboxylate was prepared by a modification of Stiles' original procedure. This variant avoids the use of Ag$_2$O in the work-up. cf. L. Friedman, *J. Amer. Chem. Soc.*, **89**, 3071 (1967).
7. Simmons has also suggested that the ene reaction is sterically inhibited by the interaction of bulky groups with benzyne. H.E. Simmons, *J. Amer. Chem. Soc.*, **83**, 1657 (1961).
8. See e.g., discussions in (a) H.M.R. Hoffman, *Angew. Chem., Int. Ed. Engl.*, **8**, 556 (1969); (b) P. Crews and J. Beard, *J. Org. Chem.*, **38**, 522 (1973); (c) I. Tabushi, K. Okazaki, and R. Oda, *Tetrahedron*, **25**, 4401 (1969); and (d) G. Ahlgren and B. Akermach, *Tetrahedron Lett.*, 3047 (1970).
9. A mixture of *cis*- and *trans*-isomers.