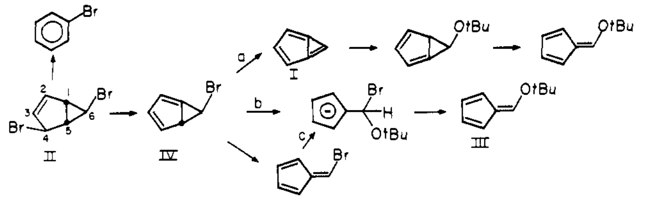
Scheme I



electrocyclic ring opening converting the diene into the product triene. IV would also be the precursor of the 6-*tert*-butoxyfulvene III. As shown in Scheme I, path a, the transformation could entail a second HBr elimination generating the triene I followed by addition of *t*-BuOH and then a similar electrocyclic opening. Several alternative pathways would convert IV to III without necessitating further loss of HBr. Grohmann had suggested nucleophilic attack of *tert*-butoxide at C_6 with concomitant ring opening and loss of bromide (path b).[2] Addition–elimination to 6-bromofulvene would also form III (path c).

Invoking Scheme I, one can predict the result of replacement of a bridgehead hydrogen with deuterium. For example, the primary isotope effect of a deuterium at C_1 would enhance formation of bromobenzene at the expense of both fulvenes. However, if the deuterium were at C_5, IV deuterated at C_5 should be formed at a rate comparable to the undeuterated material. The partitioning of IV between 6-bromo and 6-*tert*-butoxyfulvene should be unchanged if both were the result of only one HBr elimination. However, if III arose via I, the amount of 6-*tert*-butoxyfulvene should decrease due to the primary isotope effect.

To test this analysis, we prepared the monodeuterated dibromide II, containing one deuterium equally distributed between the bridgehead carbons, from 6-deuterio-1,4-dioxa-6-spiro[4.4]nonene (V) which was prepared by bromination, dehydrobromination, and Na/*t*-BuOD reduction of 1,4-dioxa-6-spiro[4.4]nonene. V was converted to I by sequential reactions with $CH_2Br_2/LiN(SiMe_3)_2$, H_3O^+, SeO_2, AlH_3, and HBr.[3] Under conditions identical with those employed for the undeuterated dibromide, bridgehead deuterated II was converted in poor yield to 6-*tert*-butoxyfulvene; the major products were bromobenzene and 6-bromofulvene. These results demonstrate that the loss of both bridgehead hydrogens was required for the formation of the 6-*tert*-butoxyfulvene. This observation is consistent with a mechanism entailing the intermediacy of bicyclo[3.1.0]hexatriene I and not a pathway entailing only one HBr elimination.

The following procedure was used to analyze for deuterium content and location. The standard conditions for the transformation of deuterated II to 6-dimethylaminofulvene (VI) were as follows: 1 mM of II in 1 ml of THF was added under argon over 30 min to 3 ml of THF at −75 °C containing 6 mM of KO-*t*-Bu and 8 mM of $HNMe_2$. After stirring for 1 h at −75 °C, the solution was quenched by H_2O. To prevent any possibility of exchange, the aqueous washes were kept neutral or alkaline.[4] The deuterium content of the product aminofulvene VI was determined by mass spectral analysis after conversion to 6-phenylfulvene.[5,6] To ascertain the location of the deuterium, we utilized the observation that the hydrogens at C_1 and C_4 of VI are easily exchanged by mild acid catalysis.[7] Moreover, under more vigorous conditions, exchange will even occur at C_2 and C_3. Typically, the product VI was split into two portions: only one of which was exchanged. Both samples were then converted to the 6-phenylfulvene. Comparison of the deuterium content of each established the location of the label as being distributed at one or more of the three distinct sets of positions: C_6, C_1 and C_4, and C_2 and C_3. We could not distinguish between C_1 and C_4 or between C_2 and C_3 by this method. Consistent with formation of I, the mixture of bridgehead monodeuterated dibromides was converted in poor yield to VI containing a total of 0.09 D (0.03 D at C_2 and C_3 and 0.06 D at C_1 and C_4).

To exclude the possibility of hidden skeletal rearrangements, we prepared II deuterated at C_3 and at C_6. II deuterated at C_3 was prepared by acid catalyzed exchange of the α-methylene protons of 6-bromo-2-bicyclo[3.1.0]hexanone followed by the procedure stated above. The dibromide II containing 0.5 D at C_3 was converted in excellent yield to VI containing 0.32 D at C_2 and C_3 and 0.06 D at C_1 and C_4.

To label C_6, II was prepared from deuterated benzvalene.[8] The labeled dibromide contained 1.5 total D of which 0.75 was at C_6, 0.22 at C_2 and C_4, respectively, and 0.15 at C_1 and C_5, respectively. Upon conversion in high yield to the aminofulvene VI, followed by exchange, 0.7 D remained in the molecule. By ^1H NMR, all the deuterium was at C_6.

From these two labeling studies it is apparent that no skeletal rearrangements occurred. Moreover, deuterium at C_3 or C_6, or as will be seen at C_2 or C_4, had no effect on the reaction course.[9] Only deuterium at either bridgehead position adversely affected the formation of 6-*tert*-butoxy or 6-dimethylaminofulvene. These results are consistent only with the formation of bicyclo[3.1.0]hexatriene, the chemistry of which is described in the following communication.[9]

Acknowledgments. We thank Research Corporation for financial support.

References and Notes

(1) W. Washburn, *J. Am. Chem. Soc.*, **97**, 1615 (1975).
(2) A. H. Amaro and K. Grohmann, *J. Am. Chem. Soc.*, **97**, 5946 (1975).
(3) The 3:1 exo/endo mixture of epimers of C_6 was separated as the enones.
(4) Separate control experiments with VI dideuterated at C_1 and C_4 and C_2 and C_3 confirmed that no deuterium loss occurred either under the reaction or workup conditions.
(5) Mass spectral analysis of VI to ascertain deuterium content was unreliable since controls revealed appreciable loss of deuterium from the ring carbons.
(6) 6-Phenylfulvenes were prepared by addition of phenyllithium to VI followed by dilute acetic acid. Control experiments established that deuterium could not be washed in or out under these conditions.
(7) A. Mannschreck and U. Kolle, *Chem. Ber.*, **102**, 243 (1969).
(8) T. J. Katz and N. Acton, *J. Am. Chem. Soc.*, **95**, 2738 (1973).
(9) W. Washburn and R. Zahler, *J. Am. Chem. Soc.*, following paper in this issue.

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Received May 21, 1976

Chemistry of Bicyclo[3.1.0]hexatriene

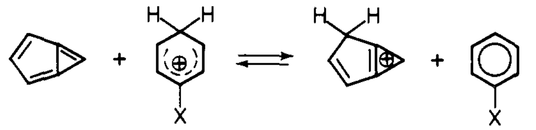
Sir:

This paper focuses on two aspects of the chemistry of bicyclo[3.1.0]hexatriene (I): (1) the acidity of I and (2) the transformation of I to fulvenes.

The complex nature of the latter was revealed by the examination of the products arising from a mixture of 2- and 4-deuterio-*exo,exo*-4,6-dibromobicyclo[3.1.0]hexenes (II) prepared by alane-d_3 reduction of 6-bromo-2-bicyclo[3.1.0]-hexenone followed by exposure to HBr. By ^1H NMR the sole deuterium was equally divided between C_2 and C_4. Under the standard conditions previously outlined,[1] this labeled dibromide was converted to 6-dimethylaminofulvene (III) containing 0.3 D distributed between C_1 and C_4.[2] The amount of deuterium washed out varied between 0.6 and 0.8 D, depending on the reaction conditions. The S_N2' products isolated from the reaction had not lost deuterium as judged by ^1H NMR, thus precluding prior exchange of II.

In contrast, when a 1:1 mixture of [2-^{13}C]- and [4-^{13}C]-4,6-dibromobicyclo[3.1.0]hexene, prepared from [1-^{13}C]cyclopentanone as previously described,[1] was converted to III, the ^{13}C label was equally distributed over all four carbons: C_1, C_2, C_3, and C_4.

The apparent incompatability of these two results prompted computational investigations using GAUSSIAN 70[4] in conjunction with the STO-3G[5] basis set. The isodesmic reaction (eq 1) was employed to estimate the basicity of the centers of high electron density, i.e., C_2 and C_4, by combining our calculations with respect to I with similar studies entailing the protonation of substituted benzene.[6] I was predicted to be more basic than *N,N*-dimethylaniline. In view of the basicity of C_2 and C_4 we suggest that the initial addition of $HNMe_2$ to I occurs via nucleophilic attack at C_6 accompanied by simultaneous proton delivery to either site to form 6-dimethylaminobicyclo[3.1.0]hexa-1^{1,5},2-diene (IV). A [1,5] hydrogen shift would convert IV to 6-dimethylaminobicyclo[3.1.0]hexa-1,3-diene (V) which would be transformed to the product fulvene by a disrotatory electrocyclic opening.

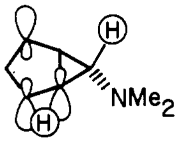


(1)

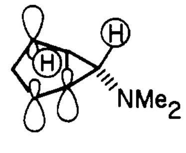
(2)

To explore whether the two possible [1,5] transition states were of similar energy, we compared the SCF energy for each transition state with the hydrogen midway between the two carbons involved. We found a substantial preference (12 kcal) for the migration of the hydrogen cis to the nitrogen. To our knowledge this is the first instance of σ asymmetry so perturbing a symmetrical system that only one of two otherwise equivalent [1,5]sigmatropic hydrogen migrations would be expected to occur.

One rationale for this event is as follows. Of the two σ bonds at C_6 the carbon-hydrogen bond is of higher energy and thus should mix preferentially with the π system. Applying Frontier orbital concepts invoking orbital distortion, one would predict higher electron density at C_1 and C_5 on the molecular face anti to this carbon-hydrogen σ bond.[7,8] From examination of the interaction of this π system with the two hydrogen atoms (A and B), preferential migration of the hydrogen which can maintain maximum bonding in the transition state (A) is not surprising.



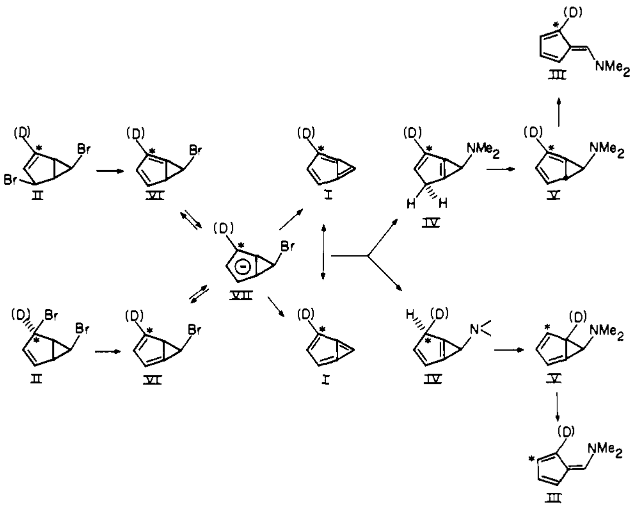
A



B

Applying these considerations to the two products expected from nucleophilic addition of $HNMe_2$ to the resonance stabilized C_2 labeled triene 1 leads to the following predictions (Scheme I): For ^{13}C labeled I, protonation at C_2 followed by [1,5] migration and ring opening would result in the label appearing at C_2 of the product fulvene. In contrast, protonation at C_4 would ultimately generate a C_4 labeled fulvene. The nucleophilic medium interconverts C_1 and C_4 and C_2 and C_3 by addition/elimination to C_6 of III.[9] Thus the ^{13}C label should appear at all ring carbons α and β to the exocyclic methylene as was observed. For the C_2 deuterated triene, proton delivery to C_4 would result in formation of 4-deuterio-6-dimethylaminofulvene. Delivery of the proton to C_2 of the deuterated triene would generate a 4-deuterio-6-dimethylaminobicyclo[3.1.0]-hexa-1^{1,5},2-diene which must be eventually transformed to a 2-deuteriodimethylaminofulvene. For this to occur, the deuterium must have exclusively migrated since failure of the deuterium to migrate would have resulted in its appearance at C_3 of the product fulvene.

Scheme I



In this instance, the electronic stabilization of the transition state should more than compensate for the unfavorable k_H/k_D isotope effect.[10] Furthermore, since the σ asymmetry at C_6 enhances only the migratory apptitude of the atom cis to the nitrogen, the deuterium must be cis, implying a trans addition of dimethylamine to the triene I.

In view of the π electron polarization of I, one might expect the C_6 hydrogen to be even more acidic than cyclopropene. We sought evidence, both theoretical and experimental, for the enhanced acidity of I. Streitwieser and McKelvey[12,13] had found a linear relationship between experimental pK_a's of a hydrogen bound to an sp^2 carbon and the energy difference between the hydrocarbons and the corresponding anion obtained by GAUSSIAN 70 calculations. From consideration of the isodesmic reaction (eq 2) where RH was benzene, ethylene, and cyclopropene, we predict that I should be more acidic than any of the above.[13] Given a pK_a of 43 for benzene,[14] the theoretically estimated pK_a of I is ~40-41.

When II was converted to III as previously described, except that 15 equiv of $DNMe_2$ was present, 0.2 D was incorporated at C_6 and ~0.03 D on the ring of III.[15] The amount of exchange at C_6 could be increased to 0.7 D by adding 1 equiv of 18-crown-6-ether to the reaction medium. No effect was observed on deuterium incorporation of the ring. Moreover, due to the increased base strength, a second reaction pathway producing bromobenzene became competitive. Analysis of *exo,exo*-2-dimethylamino-6-bromobicyclo[3.1.0]hexene formed by competitive S_N2' attack on II confirmed that prior exchange of II had not occurred at C_6 under these conditions. Likewise, controls established that the C_6 hydrogen of 111 was not labile.

We cannot exclude the possibility of exchange occurring from the product resulting from an initial 1,4 elimination of HBr, i.e., *exo*-6-bromobicyclo[3.1.0]hexa-1,3-diene (VI). However, we found that the amount of deuterium incorporation at C_6 under identical conditions was 0.4 D for II and 0.43 D for the isomeric *exo,endo*-2,6-dibromobicyclo[3.1.0]hex-2-ene. Since the overlap of the π system with the σ bond of the syn and anti hydrogens differs substantially, one would have expected more of an effect if exchange had occurred at this point.

The failure to observe substantial amounts of deuterium in the five-membered ring of III would indicate that the *t*-BuOH involved in the nucleophilic addition to I must contain one of the original bridgehead protons. A substantial primary isotope effect in conjunction with a solvent cage during the protonation of I would account for preferential hydrogen incorporation into III. To date, we cannot completely factor the contribution due to solvent cage and isotope effects. However, the net result is that very little of the bulk deuterium of the solvent appears in III.

The fact that varying amounts of exchange of deuterium originally present at C_2 and C_3 of II occurred suggests that the eliminations are not concerted. Presumably, the intermediate cyclopentadienyl anion VII leading from VI to I can be reversably protonated on carbons other than the bridgehead, thus providing a mechanism for deuterium loss. Once again, a primary isotope effect would account for the failure to observe appreciable deuterium incorporation. Cram has commented on a similar experience in which deuterium was lost more easily to a protio solvent pool than a hydrogen to a deuterio one involving the base promoted isomerization of 1-protio- and 1-deuterio-1-methyl-3-*tert*-butylindenes.[16]

The conversion of II to III is summarized in Scheme I. Since labeling studies revealed loss of deuterium from C_2 and C_3, the anion VII must be reversably protonated at all ring positions. However, to maintain the stereochemical integrity discussed above, I once formed is converted to III in concerted reactions. If an anion of IV or V were formed, nonspecific protonation would obligate the C_2 deuterated triene to be converted to III which would contain deuterium at all four ring carbons. Moreover, the rearrangement of IV to V entails an unique instance of the σ asymmetry at C_6 distinguishing between two otherwise equivalent electrocyclic reactions.

Acknowledgment. We thank Research Corporation for financial support. We thank Dr. John McKelvey for assistance with the estimates of the acidity of I.

References and Notes

(1) W. Washburn and R. Zahler, *J. Amer. Chem. Soc.*, preceding paper in this issue.
(2) By 100-MHz ^{1}H NMR in CH_3CN^3 deuterium appeared to be both at C_1 and C_4. However, the low amount of label and partial overlap of the C_4 and C_3 protons precluded rigorous assignment of amounts at each carbon.
(3) For ^{1}H NMR assignment of the ring protons of III see A. Mannschreck and U. Kolle, *Chem. Ber.*, **102**, 243 (1969).
(4) W. J. Hehre, W. A. Lathan, R. Ditchfield, M. D. Newton, and J. A. Pople, Quantum Chemistry Program Exchange, University of Indiana, Bloomington, Ind., Program No. 236.
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(6) J. M. McKelvey, S. Alexandratos, A. Streitwieser, J. M. Abboud, and W. J. Hehre, *J. Am. Chem. Soc.*, **98**, 244 (1976).
(7) K. Fukui, *Acc. Chem. Res.*, **4**, 57 (1971).
(8) C. L. Liotta, *Tetrahedron Lett.*, 519, 523 (1975).
(9) This process proceeded at a measurable rate for *tert*-butyl-ring substituted 6-dimethylaminofulvene but would be expected to be much faster for III since the alkyl inductive effect would destabilize the intermediate anion. For example the pK_a of *tert*-butylcyclopentadiene is ~19 compared to a pK_a of 16 for unsubstituted cyclopentadiene. (R. Zahler unpublished work.)
(10) At 25 °C typical values are 1–1.4 kcal.[11]
(11) C. W. Spangler, *Chem. Rev.*, **76**, 187 (1976).
(12) A. Streitwieser and J. M. McKelvey, unpublished work.
(13) The STO-3G basis set was employed for all calculations.
(14) A. Streitwieser, P. J. Scannon, and H. M. Niemeyer, *J. Am. Chem. Soc.*, **94**, 7936 (1972).
(15) As discussed previously,[1] a significant loss of deuterium did not occur in the conversion of C_6 deuterated dibromide II to the aminofulvene III reflecting a primary isotope effect. In the presence of 18-crown-6-ether 70% deuterium loss was observed.
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Received May 21, 1976

Use of Circular Dichroism Measurements to Determine the Formation Constant of the Complex between an Optically Active Benzo-15-crown-5 and Sodium Ion

Sir:

Circular dichroism (CD) provides a powerful tool with which to study the conformation of molecules in solution.[1] An obviously essential condition is that the substrate under study be optically active. To facilitate interpretation of the CD data, the structure of the compound should be as simple as possible, and incorporate at least one chromophore which absorbs in an accessible region of the electronic spectrum, thereby exhibiting a measurable Cotton effect. Although conformational freedom makes unambiguous interpretation of CD data difficult in most cases, the number of possible conformers is conveniently restricted in the case of cyclic molecules. One subset of these, the cyclic polydentate molecules,[2] is especially interesting in that additional restrictions are imposed on the conformation of the molecule when it binds a cation. Blout[3] has recently reviewed much of the research on the cyclic peptide ionophores in this connection.

In our laboratory attention has been directed toward those macrocyclic polyethers termed "crowns" by their discoverer Pedersen.[4] They possess the advantage of a high degree of solvolytic stability due to the inertness of the ether bond, and can readily be designed with considerable symmetry, and to incorporate at least one aromatic ring. This in turn provides two useful absorption bands in the ultraviolet, each potentially leading to a Cotton effect in optically active derivatives. It is also helpful that the literature provides information about the preparation and characterization of a number of the parent (achiral) compounds.[5] In this communication we wish to report the synthesis of an optically active "15-crown-5", specifically (8*S*,12*S*)-8,12-dimethyl-5,6,8,9,11,12,14,15-octahydro[*b*]benzo-1,4,7,10,13-pentaoxacyclopentadecin (VII), and the use of circular dichroism measurements to calculate the equilibrium constant governing the formation of its complex with sodium ion (as the perchlorate) in spectrograde methanol at ambient temperature.

The polyether VII was synthesized as described in Scheme 1; compound V is commercially available,[6] while the synthesis of I has been previously reported.[7] The elemental analysis of VII, its proton NMR, IR, and UV spectra were all consistent with the assigned structure. Its mass spectrum exhibited a strong parent ion peak at 296 mass units.

Figure 1 shows the CD spectra of a 1.51×10^{-4} M solution of VII in methanol, alone and in the presence of a 2000-fold molar (formal) excess of $NaClO_4$. (There were no significant differences between the latter curve, and those obtained with

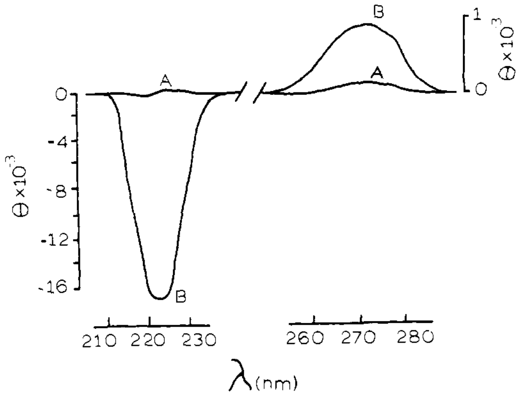

Figure 1. (A) CD spectrum of a 1.51×10^{-4} M solution of VII in anhydrous methanol, ambient temperature; JASCO ORD/CD/5, SS-20 modification. (B) Same as A except with addition of 250- to 2000-fold excess $NaClO_4$.