Figure 1. Stereoplot of the X-ray structure of dilithium tribenzylidene-methane-2TMEDA.

Figure 2. Schematic view of the structure in Figure 1. Important bond lengths in Å: C(8)-C(27) 1.460 (3), C(8)-C(17) 1.443 (3), C(8)-C(7) 1.434 (4), Li(4)-C(21) 2.667 (4), Li(4)-C(27) 2.234 (5), Li(4)-C(8) 2.287 (5), Li(4)-C(17) 2.304 (5), Li(3)-C(7) 2.297 (5), Li(3)-C(8) 2.337 (6), Li(3)-C(17) 2.626 (6), Li(3)-C(11) 2.784 (6), Li(3)-C(12) 2.673 (5), C(1)-C(2) 1.395 (4), C(2)-C(3) 1.372 (4), C(3)-C(4) 1.437 (3), C(4)-C(5) 1.369 (4), C(5)-C(6) 1.371 (4), C(1)-C(6) 1.462 (3). Lithium-nitrogen distances vary between 2.025 and 2.118 Å.

dianion\(^1\) and confirms this interpretation. The phenyl groups are twisted from the trimethylenemethane plane, as suggested by MNDO calculations on the dianion.\(^3\) The entire structure, with lithium atoms above and below the dianion plane in bridging positions between the carbon atoms with the highest negative charges, is electrostatically very favorable. The quinonoid distortions of the phenyl substituents (indicative of delocalization of the negative charge) are most pronounced for the ring bound to C(7), although the differences are not large. Finally, we note that the orientation of the TMEDA ligand coordinated to Li(4) is that expected from Stucky's orbital arguments,\(^1,12\) but that the orientation of the other diamine moiety is consistent with an interaction with C(7) and C(12).\(^13\)

The X-ray structure of a related Y-conjugated 1,3-acetone "dianion" derivative (dilithiated dibenzyl ketone) has just been reported.\(^14\) We have now been able to obtain the X-ray structure of another Y-conjugated system, dilithium dibenzylidene-thylene-2-tetramethylpropanediamine.\(^15\) The geometry resembles \(^5\) more closely than does \(^2\).

Acknowledgment. This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie. We thank G. Boche and J. Klein for related discussions.

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With the increasing power and sophistication of experimental and theoretical methods for assigning chemical structures, it seems almost incredible that the structure of any reasonably stable organic entity with a small number of carbons could remain enigmatic for very long. Nonetheless, this is true of C\(_7\)H\(_7^+\)—one of the first "nonclassical" cations to be discovered, which has some of the characteristics expected for a very rapidly equilibrating mixture of classical cyclopropylmethyl, cyclobutyl, and 3-butenyl cations and yet other characteristics which wholly belie any description that implies conventional charge distributions or geometries derived from structural representations using solid lines representing two-electron bonds.\(^2\)

\(1^3\) See Bushby et al. (Bushby, R. J.; Tytko, M. P. J. Organomet. Chem. 1984, 270, 265) for an electrostatic interpretation of lithiated -carbonium structures.

\(1^4\) (a) Supported by the National Science Foundation. (b) NSF Fellow, 1979-1980.
preparative gas chromatography.

Further evidence bearing on the nature of C4H7D+ in SbF5-SO2ClF-SO2F2 ("superacid") has been obtained from [13C, 1H, and 2H NMR spectroscopy] at temperatures ranging from -121 to -80 °C. Specifically, (2E)-, (2Z)-, (3E-cyclopropyl-2,2-d2)methanol (2) affords a long-lived, quite stereochemically stable C4H7D+ species (3a), while (cyclopropyl-2,2-d2)methan-d-01 (4) under the same conditions, produces 3a and its stereoisomeric species 3b. These stereoisomeric species, the likelihood of which was earlier recognized by Saunders and Siehl, will be here designated as endo (3a) and exo (3b), although it is abundantly clear from earlier studies that they are very rapidly equilibrating mixtures of C4H7D+.

Figure 1 shows the three nonequivalent methylene resonances of the 125.7-MHz 13C NMR spectrum of 3a at -95 °C, each of which can be identified by its 1J(C,H) splitting pattern. Smaller peaks were earlier recognized by Saunders and Siehl, will be here designated as endo (3a) and exo (3b), although it is abundantly clear from earlier studies that they are very rapidly equilibrating mixtures of C4H7D+.

Figure 1. Methylene-shift region of the proton-decoupled 125.7-MHz 13C FT NMR spectrum of endo-C4H7D+ (3a) at -95 °C in SbF5-SO2ClF-SO2F2 solution. (* corresponds to an unknown resonance.)

Table I. 13C Chemical Shifts (ppm/Me,Si) Assigned to C4H7D+ (3a and 3b) at -95 °C

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<td>3a</td>
<td>51.35</td>
<td>56.69</td>
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<td>109.81</td>
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<tr>
<td>3b</td>
<td>53.68</td>
<td>50.51</td>
<td>55.70</td>
<td>110.28</td>
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Figure 2. FT 500-MHz 1H NMR spectrum of 3a containing some 3b, at -121 °C in SbF5-SO2ClF-SO2F2 solution; the proton resonances assigned to cyclobutylxanion ion (5) are so labeled. The methylene proton resonances (in ppm): 3a, 4.49, 4.12, 3.83; 3b, 4.49, 4.44, 3.94. (Figure 1) arising from the stereoisomer 3b could be identified by comparison with the corresponding equimolar mixture of 3a and 3b prepared from 4. Still other peaks correspond to cyclobutylxanion ion (5). The pattern of 13C shift differences between 3a and 3b, as well as between these moieties and the shifts for C4H7+ (1) is quite striking. Relative to the corresponding 13C resonances of 1 as internal standard, the following are the 13C shifts, in ppm at -94 °C, of 3a and 3b, respectively: (CH3) -3.0, -0.7; (CHD) 2.2, -3.6; (CD2) -0.8, 1.0 (?); (CH) 0.0, 0.4. Whatever else can be said about these shifts, the influence of the endo-exo configuration at the CHD carbon is indeed significant (Table I).

In the 500-MHz 1H NMR spectrum of 3a (admixed with some 3b) shown in Figure 2, the endo-methylene protons (the protons trans to the methine) have chemical shifts more toward lower fields (4.64 ppm) than do the exo-methylene protons (4.21 ppm). This suggests different shift assignments than derived previously. Several 76.7-MHz 1H NMR spectra of C4H7D+ samples prepared from 2 and 4 were taken to assess the extent of deuterium migration from methylene to the methine position. Even after extended periods above -80 °C, no 2H resonance was observed in the methine region.

Conversion of 3a to 3b was not clearly observed at -90 °C in 4 h. The outside limit of reaction was about 12%, which would correspond to a lower limit for the free energy of activation of around 14 kcal/mol. This, then, must be the lower limit for the free energy of C4H7+, either for conversion to the planar cyclobutyl cation or for rotation about a methylene to methane carbon-carbon bond. This fact, along with the small isotopic perturbations of the 13C chemical shifts reported here and by Saunders and Siehl, provide compelling evidence that C4H7+ cannot be regarded as a rapidly equilibrating mixture of classical cations.

The remarkable difference in the direction of the isotope shifts in the 13C chemical shifts of 3a and 3b and the much larger isotopic perturbations of the exo-proton shifts compared to the endo-proton shifts (Figure 2) indicates that one or more of the equilibrating structures of C4H7+ must have an exo-methylene proton located in a unique environment compared to the other protons. If the


(4) Chemical shifts are relative to external tetramethylsilane and are accurate to ±0.01 ppm for carbon and ±0.001 ppm for deuterium and hydrogen. For complete experimental details, see: Brittain, W. J. Ph.D. Dissertation, California Institute of Technology, Pasadena, CA, 1982.


(6) Synthesized starting from prop-2-en-1-ol. Protection of the carbonyl, cyclopropanation with CD3N2, vacuum pyrolysis of pyrazolines, deprotection, and lithium aluminum deuteride reduction gave a mixture of deuterated 3-buty1 and cyclopropylmethyl alcohols which could easily be separated by preparative gas chromatography.


(8) Uncertain because of poor signal-to-noise ratio and overlap with the resonances of C4H7+, which was present in the solution as internal standard.
Estrogen Biosynthesis. Concerning the Obligatory Intermediacy of 20-Hydroxy-10β-formylcholesterol-4-ene-3,17-dione

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Received May 7, 1984

The transformation of an androgen (1) to an estrogen (5) by human placental aromatase was shown to involve three oxidative steps, each of which requires 1 mol of O2 and 1 mol of NADPH.1 The process is initiated by (2P-hydroxylation2s3 and then dehydrated with the loss of the “second” hydroxyl to give the 19-aldehyde 4. The aldehyde is subsequently aromatized with the consumption of a (third) mole of oxygen (e.g., l8O atom of the 2P-hydroxyl must be incorporated into the formic acid produced in the aromatization process. In contrast, in mechanism C, the aromatization process is nonenzymatic in nature. Even at pH 7 with the loss of the 10-hydrogen to give estrone and formic acid, the aromatization process is nonenzymatic in nature.

Fishman et al.10-13 proposed that the “third” mole of oxygen and of NADPH are utilized for the enzymatic 20-hydroxylation of 19-aldehyde intermediate to give, e.g., 20-hydroxy-10β-formylcholesterol-4-ene-3,17-dione (6b) (Scheme I). They proved that the 20-hydroxy-10β-formyl 6b collapses nonenzymatically even at pH 7 with the loss of the 10β-hydrogen to give estrone and formic acid. On the basis of these and other observations,10-13 they postulated that the last step of estrogen biosynthesis is the nonenzymatic aromatization of the presumably “not enzyme bound” 6b. Accordingly they showed “that there is no end-product inhibition of aromatization by estrogens”.

The collapse of the 20-hydroxy-10β-formyl 6b can be rationalized in terms of the mechanisms (A, B, C) outlined in Scheme II. Pathway A provides for a “stepwise” aromatization of 6b, while pathway B is a concerted process. It should be noted that according to mechanisms A and B, the oxygen atom of the 20-hydroxyl of 6b is incorporated into the formic acid produced in the aromatization process. In contrast, in mechanism C, the aromatization process is initiated by a hydroxyl group attack on the 10β-formyl moiety, and the oxygen of the 20-hydroxyl group is eliminated as water.

Akhtar et al.9 proved that the third mole of oxygen, required for completion of the aromatization process, is incorporated into the formic acid derived from C-19. It follows therefore that if 6b is an obligatory intermediate in estrogen biosynthesis, the oxygen (e.g., 16O) atom of the 20-hydroxyl must be incorporated into the extruded formic acid, a point that was recognized by Hahn and Fishman.15

To test the Fishman et al. hypothesis, we have prepared [20P,10β-18O]-10β-formylcholesterol-4-ene-3,17-dione 2-((tert-butyldimethylsilyl) ether 14 (6b). The mass spectrum showed

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4 University of Bayreuth.

Table I. Aromatization of [20P,10β,19-3H]-20-hydroxy-10β-formylcholesterol-4-ene-3,17-dione (6b): GC-MS Analyses of the Derived Benzyl Formates

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<td>(1) authentic, ref</td>
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<td>(2) enzymatic aromatization of 6b</td>
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<tr>
<td>(3) enzymatic aromatization of 6b</td>
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*See text for details.