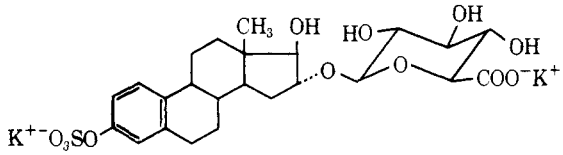
onic acid) in the form of its dipotassium salt I.[2] Increasing reference to this double conjugate, and related



I

conjugates, in significant amounts in human fluids suggests an important role for such species in estrogen endocrinology and metabolism.[3]

Estriol (II) in absolute ethanol was refluxed for 2 hr with benzyl chloride in the presence of potassium carbonate to provide 3-benzyloxyestra-1,3,5(10)-triene-16α,17β-diol (III), mp 124–125° (acetone–hexane), $[\alpha]$D +51°.[4] In benzene, III was coupled selectively at the C-16 position with methyl (tri-O-acetyl-α-D-glucopyranosyl bromide)uronate[5] in the presence of silver carbonate according to the procedure of Meystre and Miescher[6] to give methyl (3-benzyloxy-17β-hydroxyestra-1,3,5(10)-trien-16α-yl-2′,3′,4′-tri-O-acetyl-β-D-glucopyranosid)uronate (IV) (mp 245–246°, $[\alpha]$D +6°), isolated by direct crystallization in 27% yield.[7]

The important consequence of glucuronide coupling at C-16 was confirmed by oxidation of IV in acetone with chromic acid at 0–5° which gave methyl (3-benzyloxyestra-1,3,5(10)-trien-17-on-16α-yl-2′,3′,4′-tri-O-acetyl-β-D-glucopyranosid)uronate (VI), mp 217–218° (methylene chloride–methanol).[8] Acetylation of IV with acetic anhydride–pyridine afforded the 17-acetate VII, which sinters at 119°, melts at 180° (methanol), $[\alpha]$D −23°. Methyl (17β-acetoxy-3-hydroxyestra-1,3,5(10)-trien-16α-yl-2′,3′,4′-tri-O-acetyl-β-D-glucopyranosid)uronate (VIII), mp 213–215° (methylene chloride–methanol), $[\alpha]$D −30°, was obtained on hydrogen–palladium–charcoal debenzylation in glacial acetic acid of recrystallized VII, or from IV without purification of VII. Sulfation of VIII using triethylamine–sulfur trioxide[9] in pyridine at room temperature provided the completely blocked double conjugate, methyl (17β-acetoxy-3-sulfooxyestra-1,3,5(10)-trien-16α-yl-2′,3′,4′-tri-O-acetyl-β-D-glucopyranosid)uronate triethylammonium salt (IX), mp 212–213° (methanol), $[\alpha]$D − 28°. *Anal.* Calcd for $C_{39}H_{57}NO_{16}S$: C, 56.58; H, 6.93; N, 1.69; S, 3.87. Found: C, 56.79; H, 6.76; N, 1.68; S, 3.89. Saponification with 1 *N* potassium hydroxide–methanol at room temperature for 18 hr gave the desired sulfoglucuronide dipotassium salt I as a dihydrate in the form of fine needles (aqueous acetone); mp >250° with slow decomposition; $[\alpha]$D −5° (water). *Anal.* Calcd for $C_{24}H_{30}O_{12}SK_2 \cdot 2H_2O$: C, 43.88; H, 5.22; S, 4.88; K, 11.87; H_2O, 5.42. Found: C, 43.35, 43.80, 43.50; H, 5.07, 5.83, 5.56; S, 5.12; K, 11.87; H_2O, 6.0. The mixed conjugate I did not exhibit the diagnostic methylene blue test for sulfates;[10] this has also been observed for estradiol 3-sulfate 17-glucuronide.[1] However, the blocked mixed conjugate IX gave the typical positive color test with this reagent.

(2) M. Levitz, J. Katz, and G. H. Twombly, *Steriods*, **6**, 553 (1965), have presented compelling evidence for the successful biosynthesis of estriol 3-sulfate 16-glucuronide by incubation of estriol-16-glucuronide in a 100,000*g* supernatant of homogenized guinea pig liver in the presence of adenosine triphosphate and magnesium sulfate.

(3) (a) R. F. Straw, P. A. Katzman, and E. A. Doisy, *Endocrinology*, **57**, 87 (1955); (b) P. Troen, B. Nilsson, N. Wiqvist, and E. Diczfalusy, *Acta Endocrinol.*, **38**, 361 (1961); (c) J. C. Touchstone, J. W. Greene, Jr., R. C. McElroy, and T. Murawec, *Biochemistry*, **2**, 653 (1963); (d) R. Wilson, G. Ericksson, and E. Diczfalusy, *Acta Endrocrinol.*, **46**, 525 (1964); (e) E. Diczfalusy, M. Barr, and J. Lind, *ibid.*, **46**, 511 (1964); (f) M. Levitz, S. Shotsky, and G. H. Twombley, "Estrogen Assays in Clinical Medicine," C. A. Paulsen, Ed., University of Washington Press, Seattle, Wash., 1965, p 155; (g) O. W. Smith and D. D. Hagerman, *J. Clin. Endocrinol. Metab.*, **25**, 732 (1965); (h) M. Levitz, *ibid.*, **26**, 773 (1966); (i) U. Goebelsmann, G. Eriksson, E. Diczfalusy, M. Levitz, and G. P. Condon, *Acta Endocrinol.*, **53**, 391 (1966); (j) S. Emerman, G. H. Twombly, and M. Levitz, *J. Clin. Endrocrinol. Metab.*, **27**, 539 (1967); (k) E. R. Smith and A. E. Kellie, *Biochem. J.*, **104**, 83 (1967).

(4) The structure of all reported compounds was supported by spectral (ultraviolet, infrared, nmr) data and gave satisfactory elemental analyses. All compounds were shown to be homogeneous by tlc and, in the case of I and IX, by paper electrophoresis. All rotations are for chloroform solutions at 25°, unless otherwise indicated.

(5) G. N. Bollenbach, J. W. Long, D. G. Benjamin, and J. A. Lindquist, *J. Am. Chem. Soc.*, 77, 3310 (1955).

(6) Ch. Meystre and K. Miescher, *Helv. Chim. Acta*, **29**, 231 (1944).

(7) The utility of the 3-benzyloxy group in the synthesis of estrogen glucuronides has been demonstrated by J. S. Elce, J. G. D. Carpenter, and A. E. Kellie, *Biochem. J.*, **91**, 30P (1964).

(8) Compound VI was identical with an authentic sample synthesized by Dr. E. W. Cantrall in these laboratories and subsequently reported by J. C. Elce, J. G. D. Carpenter, and A. E. Kellie, *J. Chem. Soc., Sect. C*, 542 (1967).

(9) The use of this complex as a steroid sulfating agent will be discussed fully in forthcoming publications by J. P. Joseph, J. P. Dusza, and S. Bernstein.

(10) O. Crepy, and F. Rulleau-Meslin, *Rev. Franc. Études Clin. Biol.*, 5, 283 (1960).

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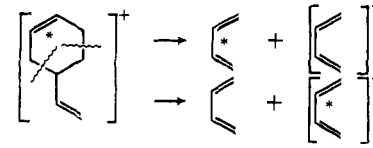
Mass Spectral Mechanisms. Preferential Association of Positive Charge with the Butadiene Fragment Containing the Vinyl Group of 4-Vinylcyclohexene in Competition with the Butadiene Fragment Arising from the Ring[1,2]

Sir:

The case is well documented that more stable cations are generally formed preferentially in mass spectra. We wish to report an experiment designed to answer the question whether two identical cations (along with two identical neutral species) originating from different environments within the same molecule are formed in equal or unequal abundances. We have found that in the mass spectrum of 4-vinylcyclohexene (dimer of butadiene) the retro-Diels–Alder reaction gives more of the budadiene fragment ion containing the vinyl group of the original molecule than of the butadiene fragment ion originating solely from the ring of the original molecule (eq 1).



(preferential) (1a)

(1b)

Deuterium-labeled 4-vinylcyclohexene,[3] labeled in

(1) Previous paper in this series: S. J. Weininger and E. R. Thornton, *J. Am. Chem. Soc.*, **89**, 2050 (1967).

(2) Supported by Public Health Service Grant 10693 from the National Institute of General Medical Sciences to the University of Pennsylvania.

(3) Prepared by allylic bromination of positions 3 and/or 6 of vinylcyclohexene with N-bromosuccinimide followed by treatment of the bromo derivative with zinc dust, sodium iodide, cupric chloride, and deuterium oxide in dioxane solution.[4] An average of ten nmr integrations showed that 1.00 ± 0.02 proton had shifted from the allylic region of 4-vinylcyclohexene to the region δ 5 in the bromo derivative, confirming that essentially all bromination had occurred at the 3 and/or 6 posi-

the 3 and/or 6 position, gave *m/e* 54 in the preferential process but *m/e* 55 in the less preferred process. The retro-Diels–Alder fragment is the most intense by a good deal in the mass spectrum of 4-vinylcyclohexene,[5] indicating that rearrangement of the molecular skeleton upon ionization is an extremely unlikely cause for the selectivity we have observed.

Numerically, the (*m/e* 54):(*m/e* 55) ratio (corrected for isotopes) is found to be 1.49 at 81.6 ev,[6] 1.36 at 25.6 ev, 1.85 at 20.6 ev, and 1.62 at 15.6 ev. It will be noted that the selectivity is a maximum at 20.6 ev; this interesting result is accompanied by a maximum in the per cent Σ_{24} arising from retro-Diels–Alder cleavage. Obviously, the selectivities are substantial and much greater than possible combined experimental and correction errors. Furthermore, the secondary isotope effect difference associated with only one deuterium atom must be far too small to be a major factor.

The idea that there may be selectivity in mass spectral fragmentation even though identical ions and neutral fragments are formed in two separate processes from the same molecular ion has therefore been confirmed. If the selectivity arises in quasi-equilibrium processes, there must be different activated complexes for paths 1a and 1b, both of which correspond to eventually breaking the same two bonds of the molecular ion. Several extremely interesting possibilities exist for the structures of these two activated complexes, ranging from "simple" explanations involving isomeric *molecular* ions (*e.g.*, *s-trans* and *s-cis* or cyclic and open chain), which seem unlikely for the present reaction and conditions, to "ground state" *and* (low-lying) electronically excited activated complexes or even electronic potential energy surface(s) involving two saddle points.

Investigation of such possibilities should prove to be very fruitful in understanding mass spectral fragmentation mechanisms. Study of cyclic adducts wherein no *s-cis* or *s-trans* possibility exists, as well as other experiments which suggest themselves, will further elucidate this new phenomenon.

tions and essentially none at the 4 (tertiary) position. Rearrangement during deuteration of the bromo derivative would give 3-vinylcyclohexene, which is excluded by absence of nmr absorption between δ 2 and 3 in the deuterated compound; the compound was purified by vpc three times. Therefore, the deuterium is present exclusively in the 3 and/or 6 positions; an average of ten nmr integrations indicated ~5% nondeuterated contaminant.

(4) D. Craig and R. B. Fowler, *J. Org. Chem.*, **26**, 713 (1961).

(5) For a discussion of retro-Diels–Alder fragmentations in mass spectra, see H. Budzikiewicz, J. I. Brauman, and C. Djerassi, *Tetrahedron*, **21**, 1855 (1965).

(6) The ionizing voltages reported have been very approximately corrected by adding 5.6 v to the observed value, as determined using argon as a standard.

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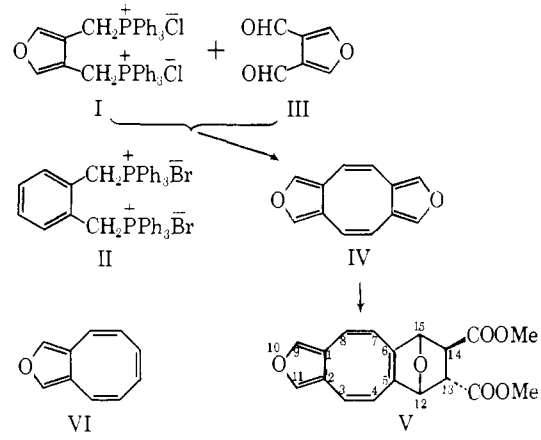
[1,2:5,6]Di[*c*]furocyclooctatetraene and [3,4-*c*]Furooctalene[1]

Sir:

We report the synthesis of [1,2:5,6]di[*c*]furocyclooctatetraene (IV) and [3,4-*c*]furooctalene (VIII), tricyclic systems containing a periphery of 16 π and 18 π electrons, respectively.

A key intermediate in the synthesis of both IV and VIII was furan-3,4-bis(methylenetriphenylphosphonium chloride) (I) (mp >250°),[2] readily obtained in quantitative yield from 3,4-bischloromethylfuran[3] by treatment with triphenylphosphine in boiling dimethylformamide. No triphenylphosphine could be detected when I was treated with base, in marked contrast to the behavior of the corresponding benzenoid compound, *o*-xylylenebis(triphenylphosphonium bromide) (II).[4] This difference is presumably due to the low bond order of the 3,4-furan bond and may account for the finding that I gives yields superior to those of II in the Wittig reaction.



Wittig reaction of I and furan-3,4-dicarboxaldehyde (III)[5] with lithium ethoxide in dimethylformamide at 90° yielded 44% [1,2:5,6]di[*c*]furocyclooctatetraene (IV), colorless plates, mp 131–133° dec; mass spectrum, molecular ion at *m/e* 184.055; λ_{max}^{EtOH} 239 mμ (ϵ 43,500), 246 (46,300), 296 sh (5600), 308 (6200), and 320 sh (4800). The nmr spectrum (all in CCl_4, 60 Mcps) showed 4 H singlets at τ 2.73 (furan ring protons) and 4.00 (eight-membered ring protons). The substance was unstable, the crystals rapidly becoming yellow and then orange on standing in air (appearance of infrared carbonyl bands at 1700 and 1670 cm^{-1}).

Treatment of IV with excess dimethyl fumarate in boiling benzene for 96 hr gave 77% of the monoadduct V, orange prisms, mp 110–111°; mass spectrum, molecular ion at *m/e* 328; λ_{max}^{EtOH} 206 mμ (ϵ 16,200), 247 sh (15,500), 256 (19,800), 265 (19,100), 276 (11,200), and 315 (3200). The nmr spectrum confirmed structure V, showing a 2 H singlet at τ 3.03 (H^9, H^{11}), a 4 H multiplet at 3.97–4.73 (H^3, H^4, H^7, H^8), a 2 H broad singlet at 5.24 (H^{12}, H^{15}), singlets (3 H each) at 6.27 and 6.36 (H^{Me}), and a 2 H quartet centered at 6.68 (H^{13}, H^{14}). The adduct V is a 5,6-disubstituted derivative of cyclo-

(1) Unsaturated Eight-Membered Ring Compounds. IV. The following papers are considered to belong to this series: part I: J. A. Elix, M. V. Sargent, and F. Sondheimer, *Chem. Commun.*, 508 (1966); part II: *ibid.*, 509 (1966); part III: *J. Am. Chem. Soc.*, **89**, 180 (1967).

(2) Satisfactory elemental analyses or high-resolution mass spectra were obtained for all new compounds.

(3) K. Y. Novitskii, Y. K. Yur'ev, V. N. Zhingareva, and E. F. Egorova, *Dokl. Akad. Nauk SSSR*, **148**, 856 (1963); *Chem. Abstr.*, **59**, 3859c (1963).

(4) J. A. Elix, K. Grohmann, M. V. Sargent, and F. Sondheimer, unpublished observations; see C. E. Griffin, K. R. Martin, and B. E. Douglas, *J. Org. Chem.*, **27**, 1627 (1962); C. E. Griffin and J. A. Peters, *ibid.*, **28**, 1715 (1963).

(5) Substance III (mp 75–76°) was obtained in 12% yield from 3,4-bishydroxymethylfuran[3] by oxidation with manganese dioxide in boiling chloroform.