The Mechanism of the Favorski Reaction.

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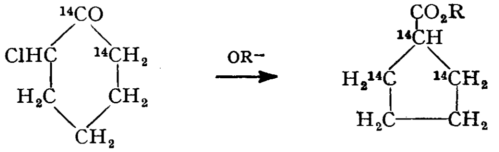
Molecular-orbital analysis of the various intermediates which have been proposed for the Favorski reaction indicates that the reaction proceeds by loss of halogen from the initial carbanion to give the zwitterion suggested by Aston and Newkirk. This structure collapses into the *cyclo*propanone intermediate proposed by Loftfield, and final products result from the further reactions of this intermediate. The LCAO–MO calculations indicate that the conversion of the initial carbanion into the zwitterion is accompanied by an increase in conjugation energy, and this increase undoubtedly provides the driving force for the reaction.

It has become apparent that in the Favorski reaction the two carbon atoms adjacent to the carbonyl group will, whenever possible, become equivalent. This was suggested by the discovery that two isomeric chloro-ketones gave the same rearranged product (McPhee and Klingsberg, *J. Amer. Chem. Soc.*, 1944, **66**, 1132) and has been unequivocally

$$Ph{\cdot}CH_2{\cdot}CO{\cdot}CH_2Cl \longrightarrow Ph{\cdot}CH_2{\cdot}CH_2{\cdot}CO_2R \longleftarrow Ph{\cdot}CHCl{\cdot}CO{\cdot}CH_3$$

demonstrated by Loftfield's finding (*ibid.*, 1950, **72**, 632; 1951, **73**, 4707) that [1 : 2-$^{14}C_2$]chloro*cyclo*hexanone yielded a *cyclo*pentanecarboxylic acid in which the isotope had



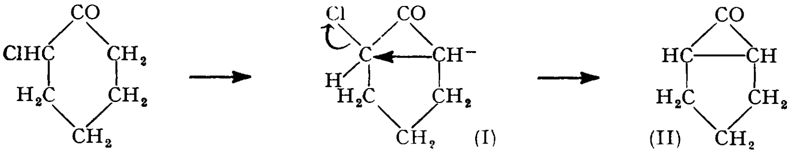
become equally distributed among the positions corresponding to the two α-carbon atoms of the chloro-ketone.

Two mechanisms have been advanced to explain this equivalence. Aston and Newkirk (*ibid.*, **1951**, **73**, 3900) proposed the formation of a zwitterion whose various contributing resonance structures will account for the products observed :

$$>\!\mathrm{CCl\cdot CO\cdot CH}\!< \xrightarrow[-\mathrm{Cl}^-]{-\mathrm{H}^+} >\!\overset{+}{\mathrm{C}}\cdot\mathrm{CO}\cdot\overset{-}{\mathrm{C}}\!< \longleftrightarrow >\!\overset{+}{\mathrm{C}}\cdot\mathrm{C(O^-){:}C}\!< \longleftrightarrow >\!\mathrm{C{:}C(O^-)}\cdot\overset{+}{\mathrm{C}}\!< \longleftrightarrow >\!\overset{-}{\mathrm{C}}\cdot\mathrm{CO}\cdot\overset{+}{\mathrm{C}}\!<$$

This seems at first sight inadequate as there is no obvious driving force to explain the removal of a chlorine ion from a molecule already containing one formal charge.

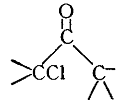
Loftfield suggested the formation of a *cyclo*propanone intermediate whose subsequent reactions also account for the equivalence of the two α-carbon atoms in the halogenoketone :



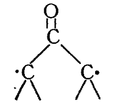
This mechanism also seems inadequate since in the preliminary ion (I) the negatively charged carbon atom is probably in a trigonal configuration coplanar with the carbonyl group, and the available π-electrons lie in *p*-orbitals perpendicular to that plane. The *p*-orbital of the negatively charged carbon atom thus cannot overlap significantly with orbitals of the carbon atom attached to chlorine, and so it is very difficult to see how any interaction between these carbon atoms could stabilize the S_N2 transition state for expulsion of the halogen with simultaneous formation of a three-membered ring.

Contrary to Loftfield's comment (*loc. cit.*) the zwitterions proposed by Aston and Newkirk are not resonance structures contributing to the stability of the *cyclo*propanone intermediate, since the two charged carbon atoms do not normally occupy the positions in space which they would have in the *cyclo*propanone structure and also since orbital symmetry thus required of the doubly charged structure would normally favour a system planar over five carbon atoms and the oxygen atom. This is impossible in (II).

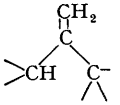
The first step in the reaction is undoubtedly the formation of a mesomeric carbanion (III). Aston and Newkirk's suggestion implies, in effect, that the intermediate (written as IV) has a much larger conjugation energy than (III), and that the conversion of (III) into (IV) is facilitated by the increase in conjugation energy.



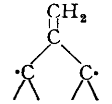
(III)



(IV)



(V)

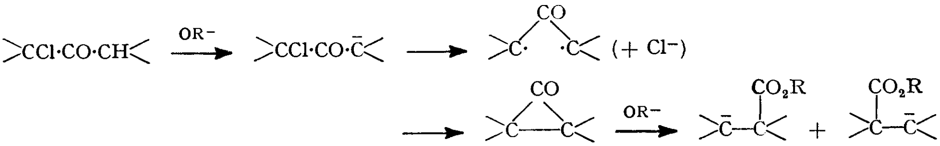


(VI)

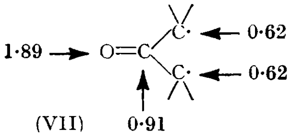
This possibility can be examined in two ways : First, one may compute the conjugation energies of (V) and (VI) which are isoconjugate with the ion (III) and the intermediate, (IV). The conjugation energies of these can be computed unambiguously by the standard LCAO–MO method and are 0·828β and 1·464β respectively, where β is the C–C resonance integral (with overlap neglected). Thus (VI) is more stable than (V) by 0·636β, and the difference between (III) and (IV) should be comparable. As an additional check, we have computed the total π-electron energies of (III) and (IV) by the same method, using reasonable values for the parameters (see Appendix). The energies found were 6·687β and 7·420β respectively, and the difference (0·733β) is of the same order of magnitude as that between the conjugation energies of (V) and (VI). The energy difference is indeed relatively insensitive to the parameters involved; thus, even in the limiting case where oxygen is considered infinitely electronegative, the energy difference changes only to 0·828β, (III) and (IV) degenerating effectively to vinyl and allyl.

The increase in conjugation energy on removal of chloride ion from (III) to give (IV) should therefore be very considerable (14 kcal. since β ~20 kcal.) and to this extent

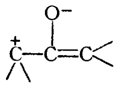
Aston and Newkirk's mechanism seems quite satisfactory. It is not immediately apparent how the intermediate (IV) could be converted into the observed final products. However, the calculated conjugation energy of (IV), although large (1·96β ~40 kcal.) is much less than the energy of formation of a C–C single bond (81 kcal.); therefore, even when allowance is made for the strain energy in a three-membered ring (30 kcal.), the conversion of (IV) into the isomeric *cyclo*propanone (II) should be exothermic. It seems reasonable to suppose that the intermediate (IV) is formed first and subsequently cyclizes to the Loftfield intermediate (II). Reaction of (II) with base then gives the observed final products. Our interpretation of the reaction is annexed.



In these calculations interactions between the non-bonded carbon atoms have been neglected. It is easily shown that such interactions should be bonding and should further stabilize the intermediate (IV) to some extent; the effect could not be large enough to make (IV) more stable than the isomeric *cyclo*propanone, although it should further facilitate the formation of (IV) from (III).



(VII)


(VIII)

The distribution of π-electrons in (IV) is of interest and is indicated in (VII). The structure approximates to one in which the oxygen atom carries a full formal negative charge, and each of the α-carbon atoms carries half a positive charge; in resonance terminology this would imply a major contribution from structures of the type (VIII).

APPENDIX

The calculations were carried out by the usual LCAO–MO method with neglect of overlap, and with the following parameters (cf. Bremmer and Bremmer, *J.*, 1950, 2335; Dewar, *Nature*, 1950, **166**, 790); $\alpha_0 = 2\beta$, $\beta_{C\cdot O} = \beta_{C\cdot C}\sqrt{2}$. No allowance was made for change in the coulomb integrals of carbon atoms adjacent to oxygen since such changes would not significantly affect calculations of relative energies.

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