

241. *Nucleophilic Reactivity. Part VI.¹ The Reaction between Triphenylphosphine and α -Halogenated Ketones.*

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The reactions between triphenylphosphine and several cyclic α -chloro- and α -bromo-ketones have been investigated and evidence is presented in support of a mechanism involving nucleophilic attack at the positive bromine atom. The nature of the reaction product formed from the intermediate ambident ion is shown to be determined by the frontier electron densities of the nucleophilic atoms concerned.

THE high reactivity of α -halogenated ketones towards nucleophilic reagents is well known,² and various mechanisms for substitution at the saturated carbon atom have been suggested.³ Recently, very hygroscopic quasi-phosphonium salts, analogous to the enol-phosphates formed from phosphite esters, have been isolated ⁴ as alternative products to the quaternary

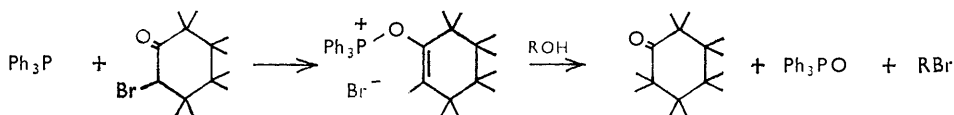
¹ Part V, *J.*, 1964, 3513.

² Tchoubar, *Bull. Soc. chim. France*, 1955, 1363.

³ Bartlett and Trachtenberg, *J. Amer. Chem. Soc.*, 1958, **80**, 5805.

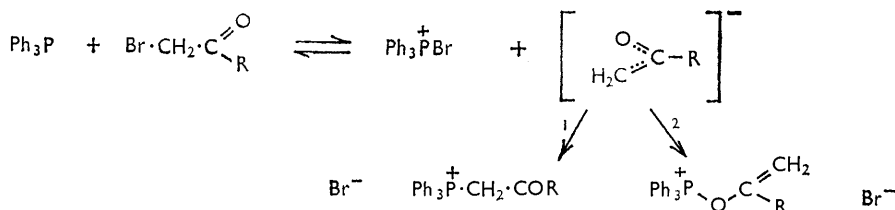
⁴ (a) Borowitz and Grossmann, *Tetrahedron Letters*, 1962, **11**, 471; (b) Trippett, *J.*, 1962, 2337; (c) Speziale and Partos, *J. Amer. Chem. Soc.*, 1963, **85**, 3313; (d) Hoffmann and Diehr, *Tetrahedron Letters*, 1962, **13**, 583.

phosphonium salts which are usually produced in the reactions between α -chloro- or α -bromo-ketones and tertiary phosphines, *e.g.*,



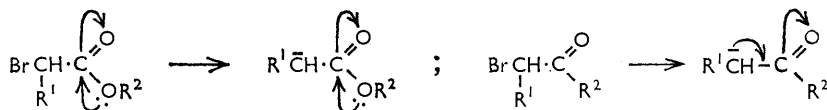
The salts are rapidly decomposed by water, alcohols, and other protolytic reagents, in contrast to the isomeric quaternary phosphonium salts.⁴

Borowitz and Virkhaus⁵ have shown that the reaction between triphenylphosphine and phenacyl bromide, which gives predominantly the quaternary phosphonium salt proceeds *via* the intermediate formation of a bromophosphonium-enolate ion-pair. The further attack may be either on the carbon or the oxygen atom of the ambident enolate ion, depending on the nature of R, leading to the following mechanism:



We find that α -bromo-cyclohexanone and -pentanone react almost instantaneously at 0° whereas the corresponding chlorides are inert in boiling benzene (24 hr.). This supports the contention that the quasi-phosphonium salt is formed by initial attack on bromine by path (2).

α -Bromo- γ -butyrolactone⁶ is considerably less reactive than the bromo-ketones, and several hours' boiling in benzene, tetrahydrofuran, or "monoglyme" gave the β -keto-phosphonium salt as the sole product. In the presence of alcohol (2 equiv.) no phosphonium salt was obtained, but the phosphine oxide and butyrolactone were isolated in good yield. A control experiment showed the bromolactone to be inert towards alcohol under the same conditions. These observations suggest that, as in the case of phenacyl bromide,⁵ the reaction proceeds by way of initial attack on bromine. On this assumption the rate of reaction is given by the change in conjugation on formation of the enolate ion, and the product composition by the charge distribution in the latter. Thus the low reactivity of the bromo-lactone is attributed to the ground-state conjugation which opposes conjugation in the enolate ion, and increases the relative charge on the carbon atom, as follows:



This is essentially a π -electron problem, which may therefore be treated by the Hückel L.C.A.O-M.O. method. Values of the change in resonance energy on reaction, ΔW , and of the frontier electron-densities * (f) of the carbon and oxygen atoms of several enolate ions, are given in Table I.

* The frontier electron-density of an atom is defined by Fukui⁷ as its charge density in the highest occupied molecular orbital. This index has enabled him to give a satisfactory interpretation of the product distribution in electrophilic aromatic substitution.

⁵ Borowitz and Virkhaus, *J. Amer. Chem. Soc.*, 1963, **85**, 2183.

⁶ Chopard and Salvadori, *Gazzetta*, 1963, **93**, 668; Fliszar, Hudson, and Salvadori, *Helv. Chim. Acta*, 1963, **46**, 1580.

⁷ Fukui, Yonezawa, and Shingu, *J. Chem. Phys.*, 1952, **20**, 722.

TABLE I.

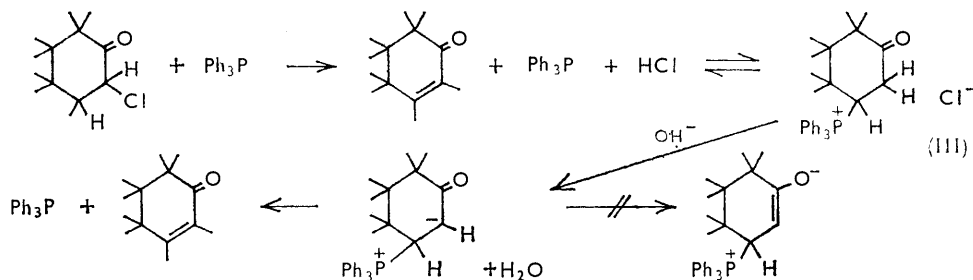
Reactant	ΔW (β -units)	Reactivity	Frontier electron density (f)		f_o/f_c	Position of reaction
			Oxygen	Carbon		
Reference *	1.186	Fast (0°)	0.187	0.650	0.288	Oxygen
Bromomalonate	1.911	Very fast (-40°)	0.143	0.559	0.259	Oxygen
Phenacyl bromide ...	1.1265	Slow (80°)	0.123	0.606	0.203	Carbon
Bromolactone	1.046	Very slow (80°)	0.116	0.680	0.170	Carbon

* *E.g.*, α -bromocyclohexanone and α -bromocyclopentanone.

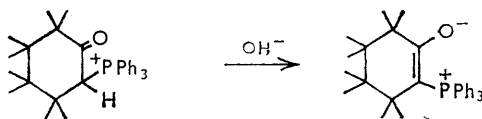
The reactivity increases with the increase in conjugation energy, ΔW (given in units of β). Moreover the ratio * of the frontier electron densities ⁷ for the oxygen and carbon atoms of the ambident enolate ions (taken as measures of the relative reactivity of these two centres) increases with the tendency for the quasi-phosphonium salt to form, *i.e.*, with the reaction on oxygen. No such correlation was obtained with the total charge densities.

Reactions between Triphenylphosphine and Chloro-ketones.— α -Chlorocyclopentanone gave a low yield of the α -ketophosphonium salt after reaction in "diglyme" at 90° for 15 hr., although α -chlorocyclohexanone failed to react under these conditions. The latter did react, however, in boiling dibutyl ether at 140° to give a mixture of the α - and β -ketophosphonium salts.

The β -derivative is probably formed by a β -elimination followed by a Michael addition of the phosphine to the activated double bond,⁸ as follows:



This reaction is frequently observed with tertiary amines, *e.g.*, α -bromo- γ -butyrolactone gives crotonolactone with triethylamine.⁹ The structure of (III) was confirmed by independent synthesis from cyclohexenone, triphenylphosphine, and hydrogen chloride. In alkaline solution, (III) does not form a non-conjugated betaine but regenerates the



β -unsaturated ketone. The α -derivative, which was identified by conversion into the corresponding betaine,¹⁰ may be formed in several ways, consistent with the low rate of formation.

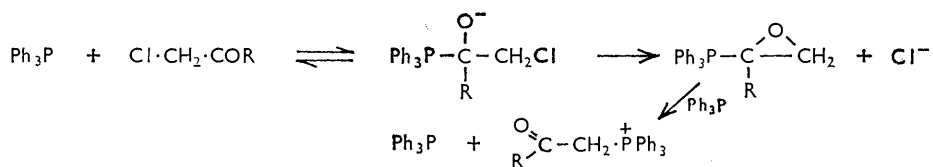
* It is pointed out that the choice of the parameters α and β (see p. 1385) will affect the values of f_c and f_o but not the order of their ratio.

⁸ Hoffmann, *Chem. Ber.*, 1961, **94**, 1331.

⁹ Judge and Price, *J. Polymer Sci.*, 1959, **41**, 437.

¹⁰ House and Babad, *J. Org. Chem.*, 1963, **28**, 90.

A mechanism involving preliminary attack on the carbonyl carbon atom has been suggested to explain the high reactivity of halogeno-ketones,³ viz.:



This mechanism is a very unlikely one for the cyclic chloro-ketones under consideration, as the chlorine atom is in the axial position.¹¹ The triphenylphosphine group thus



FIG. 1.

approaches the carbonyl group in the *trans*-position, owing to the strong steric interaction with the halogen atom. The carbonyl oxygen atom is therefore *cis* to the chlorine atom, and the second stage (which may be synchronous with the first) cannot proceed normally (see Fig. 1).

Steric hindrance at the secondary carbon atom would greatly reduce the rate of an S_N2 displacement with the bulky nucleophilic reagent, and moreover the additional steric effect in cyclohexanone owing to the β -hydrogen atoms is well known.¹² The very low reactivities of the cyclic chloro-ketones* are therefore in accord with a direct S_N2 displacement, as suggested by Borowitz and Virkhaus for phenacyl chloride.⁵ The extremely low reactivity, even when allowance is made for the steric effect, does raise the question of the extent to which the carbonyl group assists a direct S_N2 reaction of α -halogeno-ketones, and also the possibility of alternative mechanisms (*e.g.*, reaction of carbonyl or halogen) in the rapid reactions of the non-cyclic compounds.

In the reactions described above, the yields of α - and β -ketophosphonium salts were considerably reduced by reaction between triphenylphosphine and the solvent at high temperatures: the significance of this observation is discussed in the experimental section.

EXPERIMENTAL

Reaction of Triphenylphosphine with Cyclic α -Bromo-ketones.—Freshly distilled α -bromocyclohexanone (17.6 g.) was added drop by drop at 0° under a stream of nitrogen to a solution of triphenylphosphine (26.2 g.) in ether (150 ml.), producing a rapid precipitation of the quasi-phosphonium salt. One equivalent of ethanol was added to the mixture at room temperature, and after 24 hr. triphenylphosphine oxide (20 g., 70%), m. p. 153–155° was filtered off. The solvent was removed and the residue distilled giving a fraction, b. p. 45–90°, consisting mainly of cyclohexanone, and a fraction, b. p. 210–220°/0.01–0.02 mm. of triphenylphosphine oxide (5.2 g., 18%). Similar results were obtained from the corresponding reaction of α -bromocyclopentanone.

Reaction between Triphenylphosphine and α -Bromo- γ -butyrolactone.—(a) Triphenylphosphine (16 g., 0.061 mole) and α -bromo- γ -butyrolactone (10 g., 0.061 mole) were boiled in "monoglyme" (50 ml.) for 2 hr. to give γ -butyrolactonyl- α -triphenylphosphonyl bromide⁶ (13 g., 50%). After 16 hr., the crude phosphonium salt (22 g., 85%) was collected.

* We find, however, that trimethyl phosphite reacts rapidly with α -chlorocyclohexanone, a 50% yield of the corresponding vinyl ester being obtained after 2 hr. at room temperature; this indicates that the Perkow reaction proceeds by a different mechanism, which will be discussed in a further publication.

¹¹ Corey, *J. Amer. Chem. Soc.*, 1953, **75**, 2301; Reisse and Chuirdoglu, XIXth International Congress Pure Appl. Chem., London, 1963, A 3–35, p. 145.

¹² Fierens and Verschelden, *Bull. Soc. chim. belges*, 1952, **61**, 427.

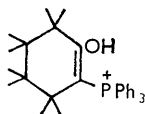
(b) The above procedure was repeated with a 4 : 1 mixture (50 ml.) of "monoglyme" and ethanol as solvent. After 2 hr. the solvent was removed, and the residue shaken repeatedly with ether to give triphenylphosphine oxide (12 g., 70%). The ethereal extracts gave a mixture (8.3 g.) of γ -butyrolactone and triphenylphosphine oxide, identified by infrared spectroscopy. Distillation of this residue gave γ -butyrolactone (2.2 g., 45%; b. p. 76—78°/13 mm.). In a control experiment, α -bromo- γ -butyrolactone (10 g.) was boiled for 2 hr. with a 4 : 1 mixture of "monoglyme" and ethanol (50 ml.) giving 7.05 g. (70%) of the starting material, which was separated by distillation.

Reaction of Triphenylphosphine with α -Chlorocyclopentanone.—A solution of triphenylphosphine (26.2 g., 0.1 mole) and α -chlorocyclopentanone (11.9 g., 1 equiv.) in "diglyme" (100 ml.) was heated at 90° for 15 hr. 2-Oxocyclopentyltriphenylphosphonium chloride (5 g., 13%), m. p. 257—260°, which separated from the cold liquid, was purified by dissolving in water, treatment with charcoal and recrystallisation of the residue, after evaporation of the solvent, from a mixture of propan-2-ol and ethyl acetate (Found: Cl, 9.0. Calc. for $C_{23}H_{22}ClOP$, Cl, 9.3%); $\nu_{C=O}$ 1750 cm^{-1} . When the reaction was carried out at 120—140°, triphenylmethylphosphonium chloride was the main product. A small quantity (0.8 g.) of the α -ketophosphonium salt in water (20 ml.) was treated with a solution of sodium carbonate. After a few min., 2-oxocyclopentylidetriphenylphosphorane¹⁰ (0.6 g., 80%), m. p. 243—245° ("monoglyme"), $\nu_{C=O}$ 1545 cm^{-1} , was obtained (Found: C, 79.8; H, 6.45; P, 8.8. Calc. for $C_{23}H_{21}OP$: C, 80.8; H, 6.15; P, 9.0%). The low analytical figures are probably due to incomplete combustion, frequently encountered with phosphorus compounds. The m. p. and $\nu_{C=O}$ are identical with those given by House and Babad.¹⁰

Reaction of Triphenylphosphine with 2-Chlorocyclohexanone.—(a) *In di-n-butyl ether.* A solution of triphenylphosphine (50 g., 0.19 mole) and 2-chlorocyclohexanone (25 g., 1 equiv.) in di-n-butyl ether was boiled under reflux for 15 hr. A solid (37 g.) separated from the cold mixture and on evaporation of the solvent, the unchanged phosphine (15.5 g.) was recovered. Fractional crystallisation of the solid from methylene chloride-ethyl acetate gave a 3 : 2 ratio of two isomeric phosphonium salts (A) and (B): (A) 3-oxocyclohexyltriphenylphosphonium chloride, m. p. 195—197°, was identified by direct preparation as follows. A slow stream of hydrogen chloride was passed through a solution of triphenylphosphine (8.2 g., 0.03 mole) and cyclohex-2-enone (3 g., 1 equiv.) in di-n-butyl ether (30 ml.) at 120—140° for 1 hr. The cold mixture was filtered to give 10 g. (90%) of 3-oxocyclohexylphosphonium chloride, m. p. 195—197° (Found: C, 72.3; H, 6.06; Cl, 9.6; P, 7.2. $C_{24}H_{24}ClOP$ requires C, 73.0; H, 6.1; Cl, 9.0; P, 7.9%). The low carbon and phosphorus analyses found in several cases are probably due to incomplete combustion of the phosphonium salts, although the presence of impurities cannot be ruled out in view of the difficulty of separating the mixture of phosphonium salts from the chloro-ketone and from the solvent. The suggested structure is supported by the n.m.r. spectra and by the formation of triphenylphosphine and cyclohexen-2-one by the action of alkali. The proton n.m.r. spectrum showed a complex band at τ 2.18, with a relative intensity of 15, and a large band of relative intensity 9 at *ca.* τ 7.6 in agreement with the structure. A solution of this salt (5 g.) in water (100 ml.) was treated with *n*-sodium hydroxide (20 ml.). Triphenylphosphine (2.9 g., 88%; m. p. 80—82°) was filtered off and the aqueous solution extracted with ether. Distillation of the dry extract ($MgSO_4$) gave cyclohexen-2-one (0.65 g., 55%) identified by comparison with an authentic sample.

(B) 2-Oxocyclohexyltriphenylphosphonium chloride, recrystallised from ethanol-ethyl acetate (19 : 1 v/v.), had m. p. 238—240° (Found: C, 73.2; H, 6.3; Cl, 9.4; P, 8.0. $C_{24}H_{24}ClOP$ requires C, 73.0; H, 6.1; Cl, 9.0; P, 7.9%).

The presence of a band at 2500 cm^{-1} (carboxylic OH) and of a carbonyl band at 1600 cm^{-1} in the i.r. spectrum indicates an important contribution from the enolic form shown below:



This structure is supported by a peak at τ 1.85 (characteristic of carboxylic acids) in the n.m.r. spectrum, a complex band of relative intensity 15 centred at τ 2.35 corresponding to the aromatic hydrogen atoms, and further complex band at τ 7.07, 7.54, and 8.22 for the 8 aliphatic hydrogen atoms.

The acid probably neutralises the alkoxide ion released from the ether, and hence suppresses the dominant back reaction. An α -chloro-ketone would also react irreversibly with the alkoxide ion, thus promoting the forward reaction.

Appendix.—The electronic levels of the π -systems of the molecules under consideration were calculated by the Hückel L.C.A.O.-M.O. method. The parameters used for the description of the carbonyl and ether groups were obtained in the following way.

The resonance integrals β_{C-O} are assumed to be equal to those of C-C bonds of equal length. The C=O and C-O distances are 1.22 and 1.42 Å, respectively, which lead¹³ to the values $\beta_{C=O} = 1.4 \beta$ and $\beta_{C-O} = 0.7 \beta$. For $\alpha_{O=}$ and α_{O-} the values of $E_0 + 1.8 \beta$ and $E_0 + 1.2 \beta$, suggested

TABLE 2.
Energy levels of the halogeno-ketones and enolate ions.

π -System of the halogeno-ketone	Energies of the bonding orbitals (β -units)	π -System of the ambient ion	Energies of the bonding orbitals (β -units)
	2.5643		{ 0.4989 0.6586
	1.2947 2.6484		{ 0.4098 1.3082 2.7480
	1.0000 1.08754 1.98204 2.70968		{ 0.4387 1.0000 1.11015 1.9829 2.8096
			{ 0.7580 2.5643 2.7618

TABLE 3.
Frontier electron densities of the atoms in the enolate ions.

Enolate ion	Frontier orbital energy (in β)	Frontier electron-density of atoms						
		1	2	3	4	5	6	7
	1.2947	0.1874	0.1619	0.6504				
	0.4098	0.1158	0.1142	0.6800	0.0896			
	0.4387	0.1235	0.1167	0.6063	0.0187	0.0405	0.0024	0.0494
	0.7580	0.1435	0.0795	0.5586	0.0795	0.1435	—	—

* In this case the frontier electron-densities are equal for atoms 6 and 8, and for 5 and 9.

by Mulliken,¹⁴ were adopted. The other coulomb and resonance integrals were equated to E_0 and β , respectively. These parameters have led to satisfactory interpretations of the u.v. spectra and polarographic behaviour of aromatic esters.¹⁵ The influence of non-conjugated atoms is neglected as the perturbations they produce are relatively small. The secular equations lower than the fourth degree were solved manually, and the others on an I.B.M. 1620 electronic computer.

¹³ Pullman and Pullman, "Les théories électroniques de la Chimie Organique," Masson, Paris, 1952, p. 200.

¹⁴ Mulliken, *Phys. Rev.*, 1948, **74**, 736.

¹⁵ Klopman and Nasielski, *Bull. Soc. chim. belges*, 1961, **70**, 490.

Values of k (where $E = E_0 + k\beta$) for all the bonding orbitals are given in Table 2, and the frontier electron-densities (electronic distribution in the highest orbital) are given in Table 3 for the various ambident enolate ions.

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