Mechanism of the Triethyloxonium Ion Catalyzed Homologation of Ketones with Diazoacetic Esters[1a]

William L. Mock*[1b] and Marvis E. Hartman

Department of Chemistry, Carnegie-Mellon University, Pittsburgh, Pennsylvania 15213

Received April 20, 1976

In the homologation of cyclohexanone with ethyl diazoacetate catalyzed by triethyloxonium fluoroborate, the rate-determining step is O-alkylation of ketone by trialkyloxonium salt, as evidenced by an approximately linear dependency of rate on oxonium ion concentration, and by no systematic dependency upon diazoacetate concentration. The intermediate carboxonium ion has been independently prepared and shown to be kinetically and regiodirectively competent. The relative proportions of aryl and methyl migration in a series of substituted acetophenones was nearly invariant. From this the absence of a significant regiodirective inductive effect is inferred. Neither variation in steric demand in the 2 position of substituted cyclohexanones nor change in alkyl residue size in the catalyst could be experimentally directly implicated in determining regioselectivity. There is an apparent dependency on the size of the diazo reagent, with increasing bulk conferring specificity on the homologation product. Evidence is presented that the syn–anti ratio of the initially formed carboxonium ions influences the ultimate product distributions. It is concluded that the observed regioselectivity is in fact under conformational control, with a number of (partially offsetting) steric factors consistently combining to result in an only slightly varying pattern of limited steric discrimination.

The scope of the exceedingly useful conversion of ketones to β-keto esters with ethyl diazoacetate and triethyloxonium fluoroborate has been described.[2,3] In the present article we consider the mechanism of this reaction. While we are chiefly interested in the reaction as a synthetic tool, knowledge of its intermediate steps is a prerequisite to intelligent application. These are here elucidated by kinetic studies and by the testing of potential intermediates. We have focused particularly on the factors controlling the direction of insertion in the case of unsymmetrical ketones (eq 1), for which a peculiar pattern of

$$\mathrm{RCOR' + C_2H_5O_2CCHN_2} \xrightarrow{(C_2H_5)_3O^+BF_4^-} \mathrm{RCH(CO_2C_2H_5)COR' + RC(CO_2C_2H_5)OCHR'} \quad (1)$$

regioselectivity has been observed. The utility of the reaction would be greatly increased if it could be directed exclusively to the formation of one product or the other. This article does not describe attainment of the latter goal; however, the numerous homologations which are given allow reasonable predictions of product distributions on empirical grounds, as well as a theoretical model within the framework of conformational analysis for interpretation of the results.

Similar studies have been carried out by other authors on diazomethane expansions.[4] The mechanistic insight herein provided has applicability for these homologations and for related amino alcohol deaminations, as is briefly considered later.

Results

Rate-Determining Step. Semiquantitative kinetic studies of the reaction were carried out in order to determine the concentration dependency of the critical reactants. Rates were determined spectrophotometrically by measuring the accumulation of β-keto ester (as its $FeCl_3$ chelate, 583 nm) from cyclohexanone. The reaction proved to be approximately linearly dependent upon the concentration of catalyst triethyloxonium fluoroborate (over a 2.5-fold range). However, reaction velocity was *independent* (or perhaps even slightly inversely dependent) upon the concentration of ethyl diazoacetate. It follows that the rate-determining step involves reaction only between ketone and triethyloxonium salt, most probably by the scheme given in eq 2.

Intermediacy of Carboxonium Ion. The implication of eq 2 is that the ketone reactant undergoes O-alkylation by

$$\mathrm{R{-}\overset{\overset{O}{\|}}{C}{-}R + (C_2H_5)_3O^+ \xrightarrow{\text{slow}} R{-}\overset{\overset{OC_2H_5}{|}}{C^+}{-}R + (C_2H_5)_2O}$$

$$\xrightarrow[\text{fast}]{C_2H_5O_2CCHN_2} \left(\mathrm{\overset{C_2H_5O}{\underset{R_2C}{|}}{-}\overset{CO_2C_2H_5}{\underset{CHN_2^+}{|}}} \xrightarrow{-N_2} \mathrm{\overset{C_2H_5O}{\underset{RC^+}{|}}{-}\overset{CO_2C_2H_5}{\underset{CHR}{|}}} + N_2 \right)$$

$$\xrightarrow[\text{fast}]{(C_2H_5)_2O} \mathrm{\overset{\overset{O}{\|}}{RC}{-}\overset{CO_2C_2H_5}{\underset{CHR}{|}}} + (C_2H_5)_3O^+ \quad (2)$$

triethyloxonium fluoroborate to yield a carboxonium ion (alkoxycarbenium ion) in the rate-determining step. In fact this is an endothermic transformation with most ketones (contrary to literature inferences);[5] our NMR examination of reaction mixtures containing ordinary aliphatic ketones reveals insignificant transfer of ethyl residue from tertiary oxonium ion to carbonyl at equilibrium. This is in accord with a reasonable extrapolation from heats of protonation of ethers and ketones.[6] (It is for this reason that such massive amounts of catalyst are prescribed.)

However, acetophenone may be alkylated with the more potent reagent, *O,O'*-diethylformate hexachloroantimonate, to give the corresponding carboxonium salt, isolable as a crystalline solid (eq 3).[7] This material reacted very rapidly

$$\mathrm{C_6H_5COCH_3 + HC^+(OC_2H_5)_2\,SbCl_6^-} \rightarrow \mathrm{C_6H_5C^+(CH_3)OC_2H_5\,SbCl_6^- + HCO_2C_2H_5} \quad (3)$$

with ethyl diazoacetate to give, after hydrolysis–decarboxylation, a low yield of phenylacetone and propiophenone. The yield was substantially increased in the presence of diethyl ether, from which we hypothesize the necessity of an alkyl residue acceptor in the ultimate step of the homologation (eq 2). Significantly, even in the absence of ether, the product ratio (phenylacetone:propiophenone) was the *same* as in the standard homologation. Hence, independent evidence (regiodirective and kinetic[8]) is consistent with the formulation of the mechanism in eq 2.

It is a reasonable a priori anticipation that the intermediates **1** or **2** might accumulate (eq 4), explaining the lack of further

$$\mathrm{\underset{\mathbf{1}}{\overset{OC_2H_5}{|}\,RC^+CHRCO_2C_2H_5} \underset{?}{\overset{-H^+}{\rightleftharpoons}} \underset{\mathbf{2}}{\overset{OC_2H_5}{|}\,RC{=}CRCO_2C_2H_5}} \quad (4)$$

Table I. Homologation of Aryl Methyl Ketones

$$ArCOCH_3 + 1.7C_2H_5O_2CCHN_2 \xrightarrow[CH_2Cl_2,\ 3h,\ 24\ °C]{3.0(C_2H_5)_3O^+BF_4^-} ArCH(CO_2C_2H_5)COCH_3 + ArCOCH(CO_2C_2H_5)CH_3$$

Registry no.	Aryl substituent ($XC_6H_4COCH_3$)	Product keto esters total yield, %	Decarbethoxylation, ratio ($ArCH_2COCH_3$: $ArCOCH_2CH_3$)[a]
100-06-1	1. p-C_2H_5O	55[b]	>98:2
943-27-1	2. p-t-C_4H_9	77	90:10
122-00-9	3. p-CH_3	62	90:10
92-91-1	4. p-C_6H_5	79	90:10
98-86-2	5. H	78	90:10
99-91-2	6. p-Cl	68	90:10
99-90-1	7. p-Br	70[c]	89:11
2142-63-4	8. m-Br	82	90:10
1443-80-7	9. p-CN	80	84:16
121-89-1	10. m-NO_2	74	85:15
100-19-6	11. p-NO_2	81	81:19

[a] Ratio average of NMR and (where feasible) GLC determination after complete hydrolysis and decarboxylation. [b] Incomplete conversion (30% recovery of ethoxyacetophenone). [c] Incomplete conversion (15% recovery of bromoacetophenone).

homologation, etc. However this appears not to be the case. Precipitation of all oxonium salts in the reaction mixture (before workup) with CCl_4 yields only pure $(C_2H_5)_3O^+BF_4^-$ in nearly quantitative recovery (NMR analysis). Likewise, no evidence has ever been obtained for the presence of enol ethers (2) in the reaction mixture;[9] they should certainly survive the sodium bicarbonate workup conditions. Our supposition is that 1 undergoes prompt dealkylation (ethyl transfer to ether or another ketone) and the product is thereby protected (by the inductive effect of the carbethoxy group) from further homologation.

Arylalkyl Ketones. A conventional Hammett treatment was applied to a series of substituted acetophenones in order to evaluate the electronic effect on "migratory aptitudes" in unsymmetrical ketones. The results are summarized in Table I. It will be observed that there is indeed only a very slight substituent effect, with consistently 80–90% insertion into the carbonyl–aryl bond. In order to calculate a ρ value, the assumption was made that the rate of insertion into the carbonyl–methyl bond was constant; i.e., that the facility with which methyl migrates is independent of the nature of the aryl substituent. While evidence to support this hypothesis is lacking, it does allow a quantitative comparison of the rate of migration of the various aryl groups. In Figure 1 is plotted log k_{Ar}/k_{Me} vs. σ.[10] Upon the assumption that k_{Me} is invariant, this yields a ρ of −0.30 (root mean square error 0.066). However, this computation excludes p-ethoxyacetophenone, for which only a single product was detected (Table I). Since the point for the latter substance would fall well off Figure 1, a different mechanism (rate-determining step) perhaps applies. We regard the small ρ value recorded as a null result. The systematic errors embodied in the experimental design are sufficient to account for the deviation from $\rho = 0$. In any event, one should not lose sight of the fact that methyl migration in fact competes effectively with aryl participation in the product-determining step. We tentatively conclude that some other factor(s) than an inductive effect largely determines the position of insertion.

Analysis of Steric Factors. Since the preceding evidence failed to reveal a substantial inductive effect within the product-determining step, attention was directed to a systematic variation of steric factors. It was hoped that a limited

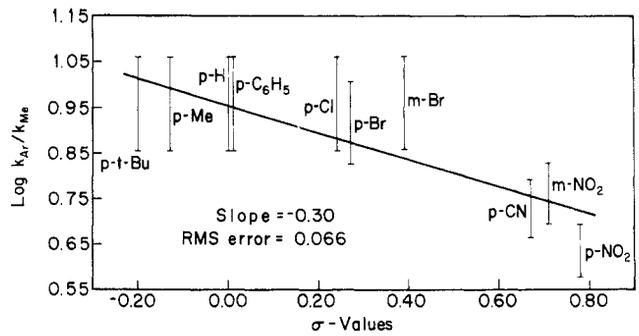


Figure 1. Log k_{Ar}/k_{Me} vs. σ for a series of substituted acetophenones.

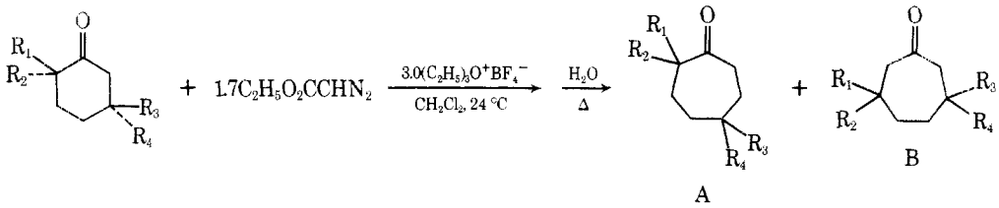
number of nonbonded interactions could be singled out as chiefly responsible for inducing the predominant direction of insertion. In order to facilitate interpretation, investigation was restricted to the conformationally well-defined cyclohexanone system.

A. Variation in the Vicinity of the Ketone. Product ratios (after hydrolysis and decarboxylation) from a series of 2-substituted cyclohexanones are recorded in Table II. The results are rather surprising, for the position of insertion is relatively insensitive to steric bulk adjacent to the carbonyl group. There is no obvious systematic variation within the series 2-methyl, 2-ethyl, 2-isopropyl, 2-*tert*-butyl, 2-phenyl, although in each case predominantly the $-CH_2-$ residue migrates. It might be hypothesized that the lack of a uniform transition among these examples should be attributed to variable amounts of axial substituent in the *reactive* conformation. However, 2,2-dimethylcyclohexanone (entry 6), in which both the axial and equatorial positions are occupied, did not give interpretationally different results. Furthermore, the isomers of menthone were examined. In the case of *trans*-2-isopropyl-5-methylcyclohexanone (entry 7), an equatorial isopropyl group may be assumed; the results are in accord with previous examples. With *cis*-2-isopropyl-5-methylcyclohexanone (entry 8), a substantial amount of the conformer with an axial isopropyl group has been postulated.[11] In this instance slightly less regioselectivity was noted, consistent with the hypothesis that an axial 2 substituent is sterically less significant than an equatorial one. However, the magnitude of the difference is scarcely convincing. Finally, in the case of norbornanone (entry 9, a particularly facile homologation, incidentally) no discrimination at all was noted between migration of CH_2C and CHC_2.

B. Variation in Catalyst. It seemed plausible that steric congestion involving the *O*-alkyl residue in the reactive intermediate carboxonium ion (eq 2) should contribute to product ratio determination. In Table III are the results of homologation of 2-methylcyclohexanone catalyzed by trimethyl-, triethyl-, and tripropyloxonium fluoroborates. It will be noted that no significant difference in the relative amounts of methylcycloheptanones is found. It should be observed that the steric requirements of these residues (methyl, ethyl, propyl) are likely too similar to allow an interpretation. Unfortunately, bulkier trialkyloxonium salts are unavailable. It can only be concluded that there is no evidence either indicating or disproving a substantial steric interaction at this site.

C. Variation in Diazo Ester. An equally plausible hypothesis is that nonbonded interactions between the *diazo ester* and various residues on the activated ketone are what determines product ratio. A strictly controlled variation in the steric requirements of the former moiety is not feasible. However, Table IV describes products obtained with 2-methylcyclohexanone and a series of diazo ester analogues,[3]

Table II. Products of Expansion of Substituted Cyclohexanones



Registry no.	Reactant[a] (R = H except as noted)	Reaction time, h	Intermediate keto esters total yield, %	Decarbethoxylation ratio (A:B)
583-60-8	1. $R_1 = CH_3$	4	72[b]	82:18
4423-94-3	2. $R_1 = C_2H_5$	14	94	80:20
1004-77-9	3. $R_1 = i\text{-}C_3H_7$	15	91	90:10
1728-46-7	4. $R_1 = t\text{-}C_4H_9$	19	~20[c]	73:27
1444-65-1	5. $R_1 = C_6H_5$	15	95	>95:5[d]
1193-47-1	6. $R_1 = CH_3$; $R_2 = CH_3$	19	39[c]	88:12
89-80-5	7. $R_1 = i\text{-}C_3H_7$; $R_4 = CH_3$	16	97	86:14
491-07-6	8. $R_1 = i\text{-}C_3H_7$; $R_3 = CH_3$	17	55	67:33
497-38-1	9. $R_1, R_3 = -CH_2-$ (norbornanone)	6[e]	92	51:49

[a] Standardized conditions (see Experimental Section). [b] Yield 96% at 0 °C (Table IV). [c] Incomplete conversion. [d] Only 2-phenylcycloheptanone detected. [e] Reaction temperature 0 °C instead of 24 °C.

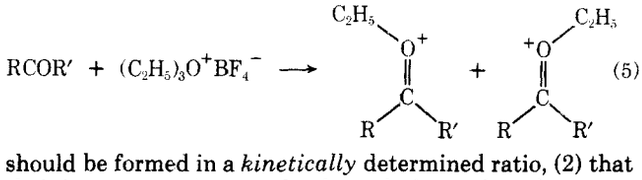
Table III. Expansion of 2-Methylcyclohexanone Catalyzed with Different Trialkyloxonium Salts

Catalyst[a]	Intermediate keto esters total yield, %	Decarbethoxylation ratio (2-CH_3:3-CH_3)[b]
1. $(CH_3)_3O^+BF_4^-$	96	83:17
2. $(C_2H_5)_3O^+BF_4^-$	96	85:15
3. $(n\text{-}C_3H_7)_3O^+BF_4^-$	97	81:19

[a] Conditions: 3.0 equiv of $R_3O^+BF_4^-$, 1.7 equiv of $C_2H_5O_2CCHN_2$, 0 °C, 3.5–4 h. [b] Cycloheptanone product.

listed in approximate order of their steric bulk. Diazoacetonitrile is a nearly symmetrical molecule (NNCHCN); perhaps significantly, it shows very little product discrimination. The probable increasing bulk in the series N_2CHCF_3, $N_2CHCO_2C_2H_5$, $N_2CHCO_2C(CH_3)_3$ results in progressively enhanced selectivity. Unfortunately, homologation of this ketone fails with dimethyl diazophosphonate, in which the substituent on the diazomethane reactant likely possesses greater steric requirements than in the latter three cases. While the evidence is less than convincing, an argument can be made that steric repulsions involving the carbethoxy group of ethyl diazoacetate (and corresponding group in analogues) are felt in the product-determining step of these homologations. This hypothesis will be developed in the Discussion.

D. Kinetic vs. Thermodynamic Control of Activation. Our deepest attempted divination of the mechanism of this reaction involves modification of the catalytic activation of the ketone. It has previously been established that the *rate-determining step* (as the homologation is normally conducted) is O-alkylation of the carbonyl group by triethyloxonum ion. In general, in the case of an unsymmetrical ketone this should result in a mixture of syn and anti intermediate carboxonium ion isomers (eq 5). We postulate (1) that these intermediates



should be formed in a *kinetically* determined ratio, (2) that their interconversion *may* be slow relative to the subsequent steps,[12] and (3) that the isomers *might* be expected to interact differently with ethyl diazoacetate in a *product-determining step* (to yield different diastereomer ratios; see Discussion). A test of these assumptions and their consequences has been devised.

We have also indicated that the intermediate carboxonium ions may be isolated in certain cases, using a more potent alkylating agent, and that they may subsequently be inserted into the reaction sequence. It is a reasonable proposition that if such an isolated carboxonium ion is allowed to equilibrate, it may form a *thermodynamic* distribution of syn and anti isomers, which differs from that obtained kinetically. Should the latter mixture (or perhaps single isomer) yield a different distribution of homologated products, then an inference may be drawn connecting the steric environment of the carboxonium ion with the product-determining step. Substances selected for such a test were acetophenone and norbornanone, which yield crystalline ions (e.g., upon alkylation with *O,O′*-dialkylformate hexachloroantimonate). The results are given in Table V. Comparison is drawn between the product ratios as the reaction is normally run, and ratios with independently generated (isolated) carboxonium ion. As previously indicated, with acetophenone no differences are noted between putative kinetically and thermodynamically controlled reactions. Likewise, in the case of norbornanone with O-ethylation yielding the reactive species, there is an insignificant shift in product isomer ratios ensuing from the manner of activation. It might be noted that these observations are independent of the counterion (BF_4^- or $SbCl_6^-$). The null results in these experiments neither confirm nor deny our postulates; i.e., the syn–anti ratios in the alkylation may be coincidentally invariant in the kinetic and thermodynamic instances, there may be rapid equilibration, etc.

However, in the third example (Table V) an experimentally significant difference is observed. With norbornanone and an *O-methyl* activating residue, a reversal in the major:minor isomer ratio is observed which is outside of error limits. We surmise the sought-after connection between syn–anti carboxonium ion ratio and homologation product. Steric interactions between diazoacetate and carboxonium ion in the bimolecular combination of these species (*following* the rate-determining step, O-alkylation), is product-*influencing* and may be exclusively product determining. In the Discussion we offer general speculations as to the details of these interactions. Even though the syn:anti ratio of an equilibrated solution of O-methylnorbornanone cation has been measured

Table IV. Expansions of 2-Methylcyclohexanone with Different Diazo Reagents, Yielding Substituted Methylcycloheptanones

Reactant[a]	Reaction time, h	Initial products,[b] total yield, %	Product isomer ratio (2-CH_3:3-CH_3)
1. N_2CHCN	5	89	53:47[c]
2. N_2CHCF_3	2.5	87	78:22[d]
3. $N_2CHCO_2C_2H_5$	4	96	85:15[d]
4. $N_2CHCO_2C(CH_3)_3$	4	92	88:12[d]
5. $N_2CHPO(OCH_3)_2$	>5	0[e]	

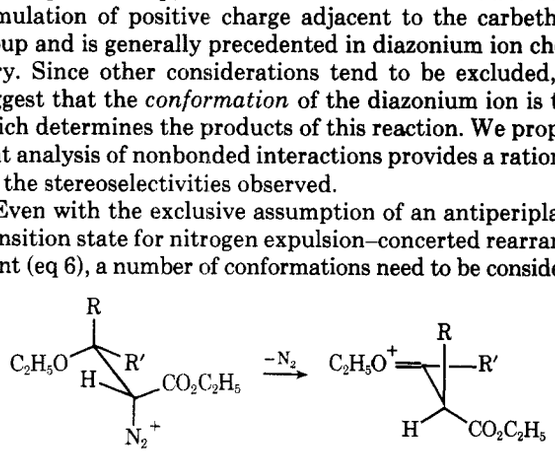
[a] Conditions: 1.7–2.5 equiv of N_2CHR, 3.0 equiv of $(C_2H_5)_3O^+BF_4^-$, 0 °C. [b] Homologated ketone, with CN, CF_3, etc. [c] Ratio of cyano ketones, determined directly (without hydrolysis and decarboxylation). [d] Ratio of methylcycloheptanones, after hydroysis and decarboxylation. [e] No keto phosphonate detected.

by NMR (FSO_3H solution, −68 °C, CH_3 syn to bridgehead is disfavored by 1:4;[13] SO_2 solution, 40 °C, ratio 1:3) there are too many variables to permit a justifiable fitting of the admittedly slight product differences to a particular model (for this single example—see Discussion, however). We are satisfied to claim, on the basis of present evidence, that a correlation probably exists between carboxonium ion stereochemistry and distribution of homologation products.

Discussion

In summary, our view of the mechanism of this homologation is as follows. A rate-determining O-alkylation of the ketone by triethyloxonium fluoroborate precedes a rapid coordination with ethyl diazoacetate. The diazonium ion thus formed probably loses nitrogen concertedly with alkyl or aryl migration to the incipient cationic site adjacent to the carbethoxy group. A new carbethoxycarboxonium ion is thus formed, which promptly yields an ethyl residue to some acceptor in the medium (eq 2). We should like to focus on the product-determining step, in an attempt to understand the unconventional distribution of homologation products in the cases of unsymmetrical ketones. It would appear that the position of insertion is not determined directly by the structure of the migrating group. Primary centers move in preference to secondary and tertiary centers in this cationic rearrangement, methyl competes effectively with phenyl, and the substituent effect in aryl migrations is small. These observations are consistent with a very early transition state for the rearrangement step, which is reasonable in that it avoids accumulation of positive charge adjacent to the carbethoxy group and is generally precedented in diazonium ion chemistry. Since other considerations tend to be excluded, we suggest that the *conformation* of the diazonium ion is that which determines the products of this reaction. We propose that analysis of nonbonded interactions provides a rationale for the stereoselectivities observed.

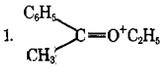
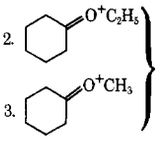
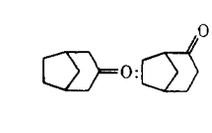
Even with the exclusive assumption of an antiperiplanar transition state for nitrogen expulsion–concerted rearrangement (eq 6), a number of conformations need to be considered



(6)

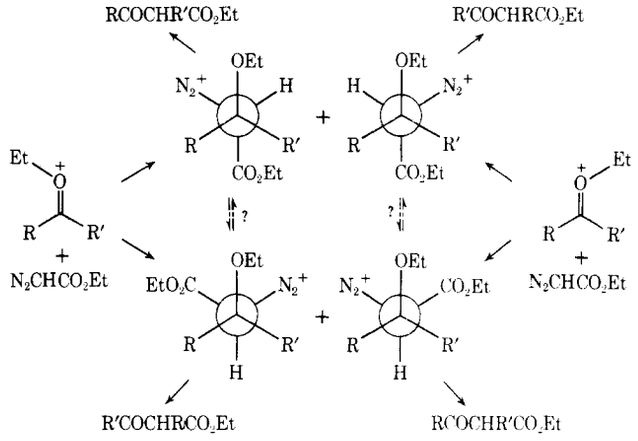
in the case of unsymmetrical ketones. As summarized in Scheme I, there should be syn and anti forms of the carboxonium ions, each of which may give rise to either of two diastereomeric diazonium ions, which individually may exist in either of two reactive conformations. The resulting four theoretically significant complexes may collapse to yield the observed two products as shown (Scheme I). Since either product may arise from either carboxonium ion via either

Table V. Ketone Homologation Ratios as a Function of Mode of Generation of Carboxonium Ion

Reactant (intermediate)	Decarbethoxylation product, ratio of homologated material (i) from isolated carboxonium ion[a] (ii) from in situ generated carboxonium ion[b]
1. 	 (i) 89:11, (ii) 89:11
2. 	 (i) 47:53, (ii) 49:51
3.	(i) 58:42, (ii) 46:54

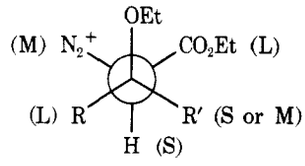
[a] Counterion: $SbCl_6^-$. [b] Counterion: BF_4^-.

Scheme I. Kinetically Significant Diazonium Ions



diastereomeric diazonium ion, the selection of a preferred reaction path to fit the observed product distribution may not be done unequivocally. However, the generalization may be made that partitioning between the diastereomeric diazonium ions (and hence population of the reactive conformations) *should* be a function of the syn–anti ratio of the original carboxonium ion. Therefore, the ultimate product distribution should in part be a function of the kinetically controlled alkylation of the ketone by triethyloxonium ion. Evidence consistent with this conclusion was cited in the Results section (*O*-methylnorbornanone cation).

It may then be further assumed that conformations which minimize gauche steric repulsions will be favored. Conventional small–medium–large (SML) analysis rationalizes preferred migration of the least bulky group. Of the four conformations in Scheme I, the least congested is **3**, which situates the largest substituents in an anti relationship. However, it should in general be accompanied by a diastereomer, for which



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a clear conformational preference cannot be specified (pair of conformers on left, Scheme I). On the assumption that *conformation* controls migration (i.e., intrinsic differences in the activation energies for migration of various groups are small and the free energies of the transition states therefore correlate with conformational stabilities[4q] or, alternatively, the internal rotational barrier is greater than that for rearrangement), the expectation should be for both possible products with a predominance of insertion into the less substituted bond (**3**, C–R′). In other words, the larger of the ketone substituents, being preferentially gauche to the departing diazonium moiety, migrates least.

In support of this steric interpretation we would chiefly cite the regioselectivity trend exhibited with the diazo ester analogues (Table IV). Diazoacetonitrile (similar bulk of –C≡N, –N≡N) was indiscriminant, whereas the trifluoromethyl and carboxylate reactions gave greater specificities. It is troublesome, however, that all substituted cyclohexanones gave similar product distributions (Table II). Increasing bulk adjacent to the carbonyl should likewise produce enhanced selectivity. A reasonable rationalization of this noneffect may be found in the kinetically controlled syn–anti O-alkylation yielding the initial carboxonium ions. We postulate that bulky equatorial substituents direct the O-alkylation preferentially to the anti position. Not unreasonably, this could produce an internal steric *compensation*, such that the diastereomeric diazonium ions (all conformers) are produced in a ratio that yields a *roughly constant product isomer distribution.*

The foregoing has been a speculative interpretation, built largely on inference. We justify such conjecturing on the grounds that the peculiar pattern of regioselectivity demands some explanation before the mechanism of this reaction may be taken to be established. Several minor considerations were glossed over, which at least require acknowledgment. The most obvious deviation from our steric explanation is the acetophenones (Table I), in which the major product consistently results from aryl migration (factor of 9:1). However, it should be noted that in more hindered phenyl ketones a reversal does occur. In isobutyrophenone aryl migration is the minor reaction path.[3] The apparent relative ease of insertion into the carbonyl–phenyl bond may be a consequence of an intrinsically lower activation energy for aryl participation, as is well documented for genuine cationic rearrangements.[14] Alternatively, unique dispersion (London) forces between the diazoacetate moiety and the aromatic ring may preferentially favor conformations of the intermediate diazonium ion leading to the observed products. In discussion of the substituted cyclohexanones, a distinction was not drawn between equatorial or axial attack by diazoacetate upon the (chair conformation) carboxonium ion. Upon the assumption of competing pathways of diazo ester approach,[4n,o,t] yet another parameter is added to explain the puzzling 2-substituent effects.[15] For reasons of brevity we have not considered relevant literature examples of *diazomethane* (CH_2N_2) homologations.[4] Such reactions are experimentally not so clean (corrections for multiple expansions and by-products have not always been made) and regioselectivities are generally reduced in comparison, but a similarity of ketone substituent effects is noted for the most part.[4b,d–g,i,l,n–q] Although our conformational explanation requires some modification and supplementary assumptions, it may be similarly applied to many of these cases, as has been done in specific instances.[4r,u] For example, altered regioselectivity of diazoethane compared with diazomethane conforms to our interpretation.[4q] However, the substantially smaller steric demands of diazomethane (which occasionally gives moderate regioselectivity[4]) suggest that we should duly note the reservation that additional factors than those we have considered could be operative in diazo ester homologations. Nevertheless, the reactions are sufficiently different that our interpretation may stand on its own.

In conclusion, this mechanistic investigation was undertaken with the hope of developing a technique for improving or controlling the regioselectivity of the homologation. This has not materialized. However, the numerous examples which we describe provide an empirical guide to the expected isomer ratios for most synthetic applications. While unquantitative steric-factor explanations are notorious as the last refuge of the perplexed organic chemist, it does appear that nonbonded interactions provide the most plausible rationalization for the peculiar product distributions observed in the present instances. We suggest that the elaborateness of this investigation should encourage further application of the conformational control concept to other reaction mechanisms involving diazonium ion intermediates.

Experimental Section

General directions for carrying out homologations are presented in an accompanying article.[3] Full details for many of the experiments which cannot be described here are to be found in the Ph.D. Thesis of M.E.H.[1a]

Kinetic Measurements. Standard homologation conditions for cyclohexanone[2,3] were approximated, except that all of the ethyl diazoacetate was added initially. Progress of reaction was monitored by withdrawal of aliquots followed by quenching with ethanolic ferric chloride solution, with subsequent spectroscopic (583 nm) determination of keto ester concentration. Appropriate calibrations and adjustments of concentrations were carried out. In one set of experiments the concentration of only triethyloxonium fluoroborate was varied systematically from 2.5 to 1.75 to 1.0 equiv (relative to cyclohexanone). In the first case reaction was practically instantaneous (over in a few minutes); in the last case the reaction took several hours for completion (half consummated at ca. 60 min). Although smooth time and concentration dependencies were observed, no attempt to fit a rate expression was made. In a second set of experiments the concentration of ethyl diazoacetate was varied, with other parameters held constant. Reaction with 1.0 equiv was actually slightly faster than with 1.25 equiv, which in turn was faster than with 1.75 equiv. However, total (ultimate) conversion to keto ester was greater in the latter instances; apparently side reactions consume diazo ester. Although extent of conversion varied smoothly with time in all cases, fitting to a rate expression was deemed impractical. Nevertheless, there is clearly an apparent small *inverse* rate dependency upon ethyl diazoacetate concentration, which is perhaps associated with a base or solvent effect.[16] This phenomenon was not further investigated. However, a practical conclusion ensues; preparatively it is preferable to slowly add the diazo ester during the course of the reaction.

Substituted Acetophenones. The homologations listed in Table I were carried out under standardized conditions (100 ml of methylene chloride, 25 mmol of ketone, 1.7 equiv of ethyl diazoacetate, 3 equiv of triethyloxonium fluoroborate, 24 °C, 3-h reaction duration). Since the purpose of this study was to examine relative proportions of aryl and methyl migration (and this could not be determined directly with the keto esters in general) great care was taken in ensuring that total hydrolysis and decarboxylation was induced (by checking that product ratios did not vary under increasingly severe conditions of hydrolysis).[3] Details of the individual experiments and product characterization (involving preparative GLC where necessary) may be found elsewhere.[1a]

Substituted Cyclohexanones. For homologations listed in Table II, the critical experimental parameters are incorporated in the table. For the individual substances, the following notes apply (all final products fully characterized spectroscopically). (1) 2-Methylcyclohexanone, experimental procedure given previously.[3] (2) 2-Ethylcyclohexanone gave a keto ester mixture, bp 121–135 °C (4.5 mm), yielding (after decarbethoxylation and preparative GLC) 2-ethylcycloheptanone, semicarbazone mp 139–140 °C,[17] and 3-ethylcycloheptanone, semicarbazone mp 175–176 °C.[18] (3) 2-Isopropylcyclo-

hexanone gave a keto ester mixture, bp 91–96 °C (0.2 mm), yielding (after decarbethoxylation and preparative GLC) 2-isopropylcycloheptanone, semicarbazone mp 174–175 °C,[19] and 3-isopropylcycloheptanone. (4) 2-*tert*-Butylcyclohexanone gave a keto ester mixture indicating only partial conversion, bp 92–105 °C (0.4 mm), yielding (after decarbethoxylation and preparative GLC) 2- and 3-*tert*-butylcycloheptanones, identified by NMR (comparison with earlier examples). (5) 2-Phenylcyclohexanone gave apparently a single keto ester, bp 131–145 °C (0.1 mm), yielding 2-phenylcycloheptanone only, identified from published spectra[4b] and by deuterium exchange experiments. (6) 2,2-Dimethylcyclohexanone gave a keto ester mixture indicating only partial conversion, bp 83–90 °C (0.3 mm), yielding (after decarbethoxylation and preparative GLC) 2,2- and 3,3-dimethylcycloheptanone, distinguished by their NMR spectra ($-CH_2CO-$ integral). (7) *trans*-2-Isopropyl-5-methylcyclohexanone (menthone) gave a keto ester mixture, bp 85–96 °C (0.25 mm), yielding (after decarbethoxylation and preparative GLC) 2-isopropyl-5-methylcycloheptanone, 2,4-DNP derivative mp 105–107 °C,[20] and 3-isopropyl-6-methylcycloheptanone, 2,4-DNP derivative mp 88–93 °C (minor amount).[21] (8) *cis*-2-Isopropyl-5-methylcyclohexanone (isomenthone, contaminated with 10% menthone) gave a keto ester mixture indicating only partial conversion, bp 86–110 °C (0.2 mm), yielding (after decarbethoxylation and preparative GLC) 2-isopropyl-5-methylcycloheptanone, 2,4-DNP derivative mp 91–92 °C, and 3-isopropyl-6-methylcycloheptanone, 2,4-DNP derivative (amorphous) mp 52–56 °C. The respective cycloheptanone isomers obtained from menthone and isomenthone were spectrally identical; the disparity in derivative melting points is attributed to differing optical purities (which were not examined), and/or to cis–trans isomerism (certainly in the case of the 3,6 isomer and possibly in the case of the 2,5 isomer, which is susceptible to epimerization during hydrolysis and decarboxylation). A correction for the contaminating menthone is not incorporated in Table II. (9) Bicyclo[2.2.1]heptanone (norbornanone) gave a keto ester mixture, bp 69–82 °C (0.1 mm), yielding (after decarbethoxylation and preparative GLC) bicyclo[3.2.1]-octan-3-one, semicarbazone mp 190–191 °C,[22] and bicyclo[3.2.1]-octan-2-one, semicarbazone mp 170–172 °C.[23]

Homologation with Trimethyl- and Tripropyloxonium Fluoroborates.[24] Expansions of methylcyclohexanone were carried out with pure homologues of triethyloxonium fluoroborate. Insofar as possible conditions for the reactions were kept invariant; however, the insolubility of the trimethyloxonium salt resulted in a heterogeneous reaction mixture. Results are recorded in Table III.

Homologations with Diazo Ester Analogues. For the methylcyclohexanone expansions listed in Table IV, reaction conditions were as given for cyclohexanone in the accompanying article.[3] It might be noted that yields were uniformly higher in these cases (excepting fifth entry). For the individual substances the following notes apply (all final products fully characterized spectroscopically). (1) Diazoacetonitrile gave a mixture of 2-cyano-3-methyl- and 2-cyano-6-methylcycloheptanone, bp 67–71 °C (0.2 mm), directly separated by preparative GLC (ratio 47:53). (2) 2,2,2-Trifluorodiazoethane gave a mixture of expansion products (plus contaminants), bp 86–108 °C (55–60 mm), which could not be separated by GLC. Basic hydrolysis yielded the methylcycloheptanones as previously described.[3] (3) Ethyl diazoacetate, note that discrepancy from Table II is a consequence of reaction temperature. (4) *tert*-Butyl diazoacetate gave a mixture of keto esters, bp 73–76 °C (0.2 mm), yielding the corresponding methylcycloheptanones upon acid treatment ($CH_3C_6H_4SO_3H$, C_6H_6, 80 °C, 12 h).

Carboxonium Ion Isolation and Reaction. The O-alkylation products of acetophenone and norbornanone have been described.[7,13] As given under Results, a solution of *O*-ethylacetophenone hexachloroantimonate[7] in methylene chloride at 0 °C was treated dropwise with 5 equiv of ethyl diazoacetate. After 0.5 h, aqueous sodium bicarbonate workup yielded a much contaminated product which was submitted to acidic hydrolysis–decarboxylation directly. A mixture (19%) of phenylacetone and propiophenone (89:11) plus acetophenone was obtained.

An experimentally more convenient procedure was applied for preparation of the cations from norbornanone, as will be exemplified for O-methylation. A solution of 4.0 g (0.025 mol) of 2,2-dimethoxynorbornane in 15 ml of methylene chloride was cooled to −78 °C in a dry flask protected with a drying tube under a nitrogen atmosphere. To the magnetically stirred solution, 15 g (0.05 mol) of antimony pentachloride was added. After a few minutes, the dark reaction mixture was allowed to warm to room temperature and the precipitate (CH_3OSbCl_4?) which formed during the reaction was removed by filtration. The precipitate was discarded and 150 ml of carbon tetrachloride was added to the filtrate. Another precipitate was formed which was collected on a rigorously dried sintered glass funnel in a stream of dry nitrogen. The brownish solid was dried by passing dry nitrogen through the filter. The solid was identified from its NMR spectrum as *O*-methylnorbornanone hexachloroantimonate: NMR (SO_2) δ ca. 1.4 (m, 6), ca. 2.3 (m, 3), ca. 3.3 (m, 1), and 4.3 ppm (s, 3). The resonance at 4.3 ppm may be resolved into two singlets occurring in a ratio of ca. 3:1. A peak at slightly higher chemical shift is the predominant signal. In addition to the signals given, small (i.e., less than one proton) resonances were observed at 4.7 and 8.4 ppm, attributed to an unidentified impurity.

The hexachloroantimonate of *O*-methylnorbornanone was added to 100 ml of methylene chloride cooled to 0 °C in a dry flask protected with a drying tube under a nitrogen atmosphere. A solution of 5.2 g of ethyl diazoacetate in 5 ml of diethyl ether was rapidly added dropwise to the magnetically stirred solution. Nitrogen was rapidly evolved. After a total reaction period of 5 min, the reaction was quenched with 150 ml of saturated sodium bicarbonate. The precipitated antimony salt was removed and the aqueous layer was separated and washed twice with 25 ml of methylene chloride. The combined methylene chloride extract was dried over anhydrous magnesium sulfate, solvent was removed, and the residue was distilled at reduced pressure. After a forerun of 0.7 g of an unidentified product mixture, 1.0 g (20%, from the ketal) of keto ester was obtained, bp 75–87 °C (0.1 mm). The product was decarbethoxylated in the usual way; GLC analysis revealed bicyclo[3.2.1]octan-3-one and bicyclo[3.2.1]octan-2-one, ratio 58:42. The hydrolysis procedure also produced a small amount of white, acid-soluble material, which was not identified.

Homologation in the normal manner using trimethyloxonium fluoroborate gave a keto ester mixture (68%) yielding the same products in the ratio 46:54 (Table V). An analogous set of experiments involving O-ethylation yielded an essentially invariant product ratio (48:52 ± 1, see Tables II and V). In this case separate NMR signals from isomeric carboxonium ions were unobservable.

Acknowledgment. This work was partially funded through the National Science Foundation. Particular thanks are given to PPG Industries for financial support (to M.E.H.) and to the A. P. Sloan Foundation for a fellowship (to W.L.M.).

Registry No.—Ethyl diazoacetate, 623-73-4; triethyloxonium fluoroborate, 368-39-8; 2-isopropyl-5-methylcycloheptanone 2,4-DNP, 60705-58-0; 3-isopropyl-6-methylcycloheptanone 2,4-DNP, 60705-59-1; trimethyloxonium fluoroborate, 420-37-1; tripropyloxonium fluoroborate, 621-67-0; diazoacetonitrile, 13138-21-1; 2,2,2-trifluorodiazoethane, 371-67-5; *tert*-butyl diazoacetate, 35059-50-8; 2,2-dimethoxynorbornane, 10395-51-4; antimony pentachloride, 7647-18-9; *O*-methylnorbornanone hexachloroantimonate, 60705-61-5.

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The Mechanism of Amine-Catalyzed Halohydrin Formation from α-Chloro Ketones and Phosphonate Diesters

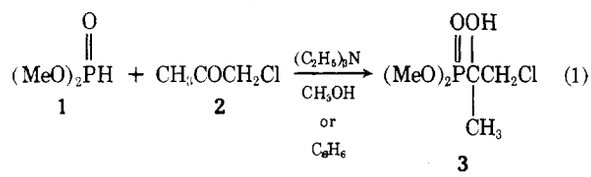
Bleecker Springs and Paul Haake*

Department of Chemistry, Wesleyan University, Middletown, Connecticut 06457

Received November 3, 1975

The formation of halohydrin in the triethylamine-catalyzed reaction of dimethyl phosphonate and chloroacetone was followed by NMR. In benzene the kinetics appear to be complex due to solvent effects and aggregation, and the results cannot be summarized by any simple rate law. The reaction in methanol is approximately first order in phosphonate and first order in triethylamine. The results suggest a rate-determining, tautomeric conversion of the phosphonate to the corresponding phosphite with rate law $v = 1.42 \times 10^{-2}\ M^{-1}\ s^{-1}$ [phosphonate][triethylamine].

The chemistry of bond formation between phosphorus and carbon is a significant problem; it underlies the synthesis of new structures which may be used to extend our knowledge of the chemistry of phosphorus, to furnish useful reagents for new synthetic methods, to investigate biologically important reactions through isosteric similarity to phosphates, and to provide medically useful drugs such as the antibiotic fosfomycin.[1-4] As part of our study on epoxyphosphonate synthesis, we have investigated the kinetics of formation of halohydrin phosphonates which are intermediates in some synthetic sequences.[1,5] The halohydrin **3** is formed by the base-catalyzed reaction of dimethyl phosphonate (**1**) and chloroacetone (**2**). This reaction (eq 1) was studied in methanol and



(1)

benzene by observation of the changes in the C–CH_3 signals in ^1H NMR spectra which were taken as the reaction proceeded.

Experimental Section

Kinetics. *In solutions of methanol,* the appropriate concentration of dimethyl phosphonate and chloroacetone was prepared in a 5-ml volumetric flask. A 0.5-ml aliquot was injected into an NMR tube and spun in the probe for 5 min to bring it to constant temperature. To the NMR tube was then added the appropriate amount of triethylamine or buffer stock solution in methanol. The concentrations were corrected for total volume. The reaction was followed by the disappearance of the methyl singlet of chloroacetone, **2**, at τ 7.75 and the appearance of a doublet for the C–CH_3 in **3** (J_{PCCH} = 15 Hz) at τ 8.48.[5] The reaction was followed with a 50 Hz sweep width of the singlet and one peak of the doublet. The area under each peak was determined by multiplying the peak height by the width at half the height. The area of the singlet over the sum of the area of the singlet and two times the area of one doublet peak gives the fraction of chloroacetone remaining at that time.

For experiments in benzene, triethylamine was added neat. The rate was determined by relative *integrations* of the methyl peaks using a Varian A-60A spectrometer. The average result of three integrations was used with the time recorded in the middle of the second integration. For some runs the reaction was also followed by a 50 Hz sweep width and the above described calculation of area. Results from the two methods were in good agreement. All reactions appeared to proceed to completion based on NMR spectra.

Results

Treatment of Rates. Since we followed the concentration of chloroacetone (**2**), it was necessary to express the rate law in terms of **2**. In all reactions the concentration of chloroacetone was less than or equal to that of phosphonate, so the stoichiometry demands that

$$-d[2]/dt = k[2]^a([2] + \Delta)^b[(C_2H_5)_3N]^c \quad (2)$$

where $\Delta = ([1] - [2])$. The concentration of triethylamine remains constant because it is a catalyst. In methanol as solvent we found that when the rate law was reduced to

$$v = -d[2]/dt = k'([2] + \Delta) \quad (3)$$

and integrated to give

$$\ln([2] + \Delta) = -k't + \text{constant} \quad (4)$$

we could fit the observed data and we obtained the first-order rate constants in Table I. Therefore, in methanol the reaction is first order in phosphite and zero order in chloroacetone (Table I). Dividing the k' values in Table I by $[(C_2H_5)_3N]$ gave a constant value for a second-order rate constant (eq 5, 6)