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STEREOCHEMISTRY OF THE ALDOL CONDENSATION OF BENZALDEHYDES WITH ALPHA-CHLORO ESTERS

AN EXAMPLE OF THE GAUCHE EFFECT OF ADJACENT POLAR BONDS*

M.-C. ROUX-SCHMITT and J. SEYDEN-PENNE
Groupe de Recherches No 12, CNRS 2 à 8 rue H. Dunant, 94-Thiais, France

and

S. WOLFE
Department of Chemistry, Queen's University, Kingston, Ontario, Canada

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Abstract—Under irreversible conditions, the stereochemical course of the aldol condensation of benzaldehydes with esters $R^1CHClCO_2R$ (R^1 = H or Me) in the presence of NaH, NaOR or KOR depends only on the nature of R. Solvent and temperature have negligible effects. The reaction has been performed with eight *ortho*- or *para*-substituted benzaldehydes; only in the case of *o*-methoxybenzaldehyde has a different stereochemical result been obtained. Possible transition states for the Darzens reaction are discussed and it is shown that all of the data are consistent with a mechanism involving addition of a pyramidal carbanion to the aldehyde CO group via the rotameric forms predicted on the basis of the *gauche* effect.

THE Darzens reaction, the base-induced addition of a compound bearing halogen and an electron-withdrawing substituent on the same C atom to an aldehyde or ketone, provides a general route to glycidic acid derivatives. The generally accepted mechanism of this reaction involves the following three steps: (a) proton abstraction from the carbon which carries the halogen substituent; (b) addition of the resulting carbanion to the aldehyde or ketone; (c) intramolecular nucleophilic displacement of halide ion.

Scheme 1 illustrates these steps for the reaction of benzaldehyde with ethyl chloroacetate.[1] In this case the addition step leads to the two diastereomeric anions **1** and **2**, which then cyclize, respectively, to *trans* **3** and *cis*-ethyl 3-phenylglycidate **4**. Our earlier study of the effect of solvent upon this reaction revealed that the overall stereochemical result depends upon the medium. However, it was not possible in all cases to interpret, in a meaningful way, the stereoselectivity of the aldolization step, because this reaction is not always irreversible. In hexamethylphosphoric triamide (HMPT) this step is irreversible so that in this case the ratio **3**/**4** of the glycidic esters depends only on k_E/k_T. However, in benzene and ether, the formation of **1** is irreversible but the formation of **2** is not; consequently, in these solvents the overall stereochemical result depends upon k_E, k_T, k_{-T} and k_T^1.

It seemed desirable to investigate in more detail the effects of solvent and chloroester upon the stereoselectivity of the aldolization reaction in weakly polar media and with appropriate modification of the reaction conditions so as to suppress

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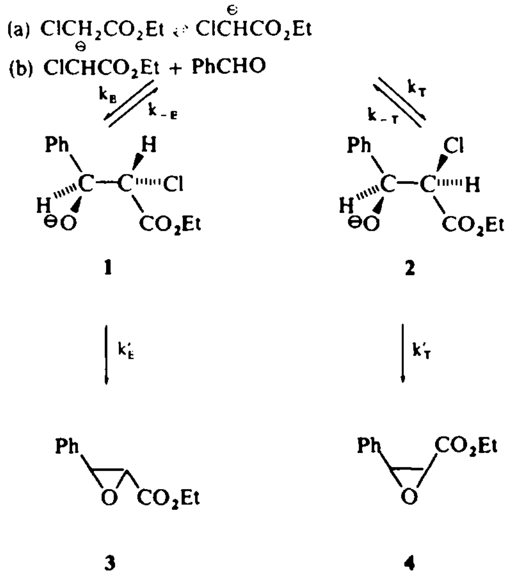
* Part IV in the series: Effet de Solvant sur la Stéréochimie de la Réaction de Darzens. For parts I-III, see refs 1-3.

SCHEME 1.

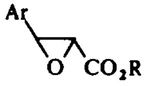


reversibility in this step. The present paper describes the results of such a study. In this work the stereochemistry of the reaction of several alkyl chloroacetates and α-chloropropionates with benzaldehyde and a number of substituted benzaldehydes has been determined in: HMPT containing sodium hydride; ether containing sodium hydride, sodium alkoxide or potassium alkoxide; and a 1:1 mixture of ether and t-butanol in the presence of sodium or potassium t-butoxide.

Methods. It was necessary first to establish the conditions under which the aldolization step is irreversible. In HMPT this condition is reached at ambient temperature, but in ether and t-butanol–ether the reaction is still more or less reversible at temperatures above −40°. Consequently, in these two solvent systems, it was necessary to operate at lower temperatures. Similar observations have been made by Villieras and Combret,[4] in the course of a study of the condensation of isobutyraldehyde with alkyl chloroacetates in the same media.

Identification of products. Two types of product were obtained following aqueous work-up of the reaction mixtures, *viz*, epoxides and halohydrins. Either one or the other or both were formed depending on the specific reaction conditions.

From alkyl chloro*acetates* were obtained the epoxyesters **5** and **6**, whose physical and spectroscopic properties were in accord with the literature values;[1,5] and the *RS*, *RS* **7** and *RS*, *SR* **8** alkyl 2-chloro-3-aryl-3-hydroxypropionates. These latter compounds had been obtained previously by Martynov and Titov,[6] for R = Et, but without determination of their stereochemistry. In the present work the chlorohydrins were separated and identified either by comparison with authentic samples obtained by esterification of the *RS*, *RS* acid corresponding to **7**[7] (Ar = Ph; R = Me and i-Pr) or by cyclization with sodium hydride in HMPT. In this way **7** (Ar = Ph; R = t-Bu) gave **5** (Ar = Ph; R = t-Bu) and **8** (Ar = Ph; R = Me, i-Pr, t-Bu) gave **6** (Ar = Ph; R = Me, i-Pr, t-Bu).



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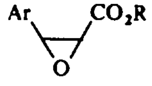

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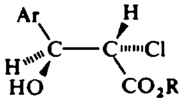

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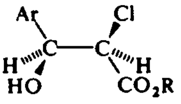

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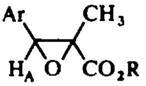
From alkyl α-chloro*propionates* were obtained the epoxyesters **9** and **10**, characterized by microanalysis and by their physical and spectroscopic properties. In the NMR spectra (CCl_4), H_A and the protons of the ester group of **9** appear at lower field than the corresponding protons of **10**, and the reverse is observed for the Me protons[8–10].



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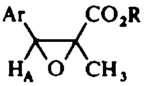

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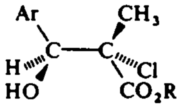
The *RS*, *RS* **11** and *RS*, *SR* **12** alkyl 2-chloro-2-methyl-3-hydroxy-3-phenyl-propionates were separated and identified by cyclization with sodium hydride in HMPT. Chlorohydrin **11** afforded **9** stereospecifically and **12** afforded **10**. The esters **11** (Ar = Ph; R = Me, Et, i-Pr) were also obtained by esterification of the corresponding acid, prepared by the literature* method.[11]



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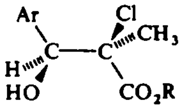

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Analysis of the reaction mixtures. The proportions of the various products were determined by NMR and by GLC. It was established that, with the exceptions indicated in the Tables, the products are stable under the conditions of the reaction and of the analytical method. At the temperatures employed for reactions conducted in t-BuOH solvent, transesterification, retroaldolization, or epimerization of epoxides or halohydrins did not occur. At ambient temperatures[8, 10] transesterification does occur. In contrast, at ambient temperature in HMPT, in the presence of sodium hydride or alkali t-butoxides, the isopropyl and t-butyl esters afforded glycidic acids†.

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* Addition of hypochlorous acid to α-methylcinnamic acid[11] leads to a mixture containing 80% of *RS*, *RS* 2-chloro-2-methyl-3-hydroxy-3-phenyl-propionic acid and 20% of the *RS*, *SR* isomer.

† This reaction proceeds by β-elimination: GLC analysis of t-butyl ester mixtures showed the presence of isobutylene.

In this process compounds **5** and **9** reacted more rapidly than **6** and **10**. The possibility that this reaction could lead to erroneous interpretation of the product ratios was, however, minimized by isolation of the products within 1 hr and only in the case of Run 8 was elimination then sufficiently rapid to give ambiguous results.

It was also noted that under certain conditions the *RS, RS* halohydrins **7** and **11** cyclize quantitatively to the corresponding epoxides. In these cases the mixtures consisted of epoxide **5** and halohydrin **8** or epoxide **9** and halohydrin **12**. The molar ratios **5/8** and **9/12** were determined by NMR following a verification that mixtures of **7** + **8** or **11** + **12** afforded **5** + **8** or **9** + **12** having the same molar ratios.

TABLE 1. CONDENSATION OF BENZALDEHYDE WITH $R^1CHClCO_2R$ AT 20°C IN HMPT CONTAINING NaH

Run	R	R^1	**5/6** or **9/10**
1	Me	H	50/50
2	Et	H	50/50
3	i-Pr	H	45/55
4	t-Bu	H	40/60
5[a]	t-Bu	H	34/66[b]
6	Me	Me	50/50
7	i-Pr	Me	40/60
8	t-Bu	Me	45/55[c]

[a] Experiment performed at −40° in a 1:1 (v/v) mixture of HMPT and ether

[b] A mixture of **5/6** + **8** in the proportions 34:48:18 (by NMR)

[c] Estimated ratio

TABLE 2. CONDENSATION OF BENZALDEHYDE WITH $R^1CHClCO_2R$ AT LOW TEMPERATURES

Run	R	R^1	Procedure[a]	**7/8** or **11/12**
9	Me	H	A	50/50
10	Me	H	B	50/50
11	Me	H	C	50/50
12	Et	H	A	50/50
13	Et	H	B	50/50[b]
14	Et	H	C	50/50
15	i-Pr	H	A	30/70
16	i-Pr	H	B	30/70[b]
17	i-Pr	H	C	30/70
18	t-Bu	H	A	30/70
19	t-Bu	H	B	45/55[c]
20	t-Bu	H	C	30/70[b]
21	Me	Me	B	50/50[b]
22	Et	Me	C	50/50[b]
23	i-Pr	Me	B	33/67[b]

[a] Method A: at −40° in ether containing NaOR or KOR;
Method B: at −40° in a 1:1 (v/v) mixture of t-BuOH-ether containing t-BuOK or t-BuONa;
Method C: at −80° in the same medium as B

[b] Mixture of **5/8** or **9/12** (by NMR)

[c] Mixture of **5/6** + **8**; retroaldolization was observed in this case

TABLE 3. CONDENSATION OF ArCHO WITH $R^1CHClCO_2R$

Run	Ar	R	R^1	Procedure	**5/6 or 9/10**
24	o-Cl-C_6H_4	Et	H	D[a]	50/50
25	p-Cl-C_6H_4	Et	H	D	50/50
26	o-CH_3-C_6H_4	Et	H	D	50/50
27	o-CH_3-C_6H_4	Me	Me	D	50/50
28	o-CH_3O-C_6H_4	Et	H	D	65/35
29	o-CH_3O-C_6H_4	Me	Me	D	67/33
30	o-CH_3O-C_6H_4	Et	H	E[b]	67/33
31	p-CH_3O-C_6H_4	Et	H	D	50/50
32	m-Cl-C_6H_4	Et	H	D	50/50

[a] Method D: at 20° in HMPT containing NaH

[b] Method E: at −40° in ether containing NaOEt: **7** and **8** were obtained in the ratios shown

RESULTS

Table 1 summarizes the observations made in experiments conducted with benzaldehyde in HMPT in the presence of sodium hydride. Table 2 contains the data obtained for reactions of benzaldehyde at low temperature in ether containing sodium hydride or in t-butanol-ether containing sodium or potassium t-butoxide (identical results were obtained in both solvent systems.*). The results obtained with substituted benzaldehydes are shown in Table 3.

The following points may be noted: (i) only epoxides are obtained in HMPT at room temperature; (ii) only halohydrins are obtained in ether at −40° and in t-BuOH–ether at −80°, with the exception of Run 20 (R^1 = t-Bu), in which some cyclization was observed; (iii) in t-BuOH–ether at −40°, one of the halohydrins cyclizes so that an epoxide and the other halohydrin are obtained; (iv) at −40° in t-BuOH–ether, chlorohydrin formation is reversible for R = t-Bu (Run 19); (v) the reaction is not stereoselective with the Me and Et esters; (vi) with the i-Pr and t-Bu esters the *RS, SR* chlorohydrin or the corresponding epoxide predominates under all conditions.

DISCUSSION

A. *Effect of solvent and of the ester group.* For the Darzens reaction in t-BuOH, Bachelor and Bansal[5] obtained stereochemical results different from those which we had observed in our earlier study,[1] conducted in HMPT. These differences must now be attributed to differences in the degree of reversibility of the aldolization step leading to different product-determining stages in the two solvents. When irreversible aldolization is ensured, essentially the same results are obtained in HMPT, in ether, and in t-BuOH–ether.

In contrast, a change in the nature of the ester group does lead to a different stereochemical result. For a given ester group the stereochemical result is the same with the chloroacetates and the α-chloropropionates; but, in both series, the *RS, SR* isomer (**8** or **12**) is progressively favoured by a progressive increase in the size of the ester group.

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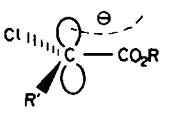
* This is also the case at 20°,[5] a temperature at which interpretation of the results is more ambiguous, for reasons already given.

B. *Effect of the aldehyde.* Electron-withdrawing or releasing substituents in the *meta* or *para* positions have no effect upon the stereoselectivity of the reaction of the ethyl esters in HMPT (Runs 25, 31, 32). There is also no effect by an *ortho* chloro or methyl substituent in condensations with ethyl chloroacetate or methyl α-chloropropionate (Runs 24, 26, 27). However, when *o*-methoxybenzaldehyde is employed, the proportion of epoxy ester **5** or **9** (Runs 28, 29) or of the *RS*, *RS* halohydrin **7** (Run 30) increases significantly.

C. *Transition state of the aldol condensation.* Several kinds of transition states may be envisaged for the addition step of the Darzens reaction according to whether addition to the CO group is made by a carbanion, a chloroketene or a carbene. However, the chloroketene route is ruled out because transesterification is not observed in the reactions of the Me, Et and i-Pr esters, and because addition of chloroketene to the electrophilic CO group of chloral occurs only at elevated temperatures.[12] A carbene route has also been ruled out.[13]



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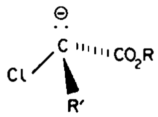

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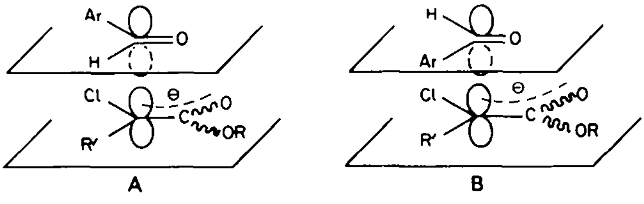
For the addition of a carbanion to the CO group, several possibilities still remain according to whether the carbanion is considered to have a planar (**13**) or pyramidal (**14**) configuration.[14] For attack by a planar carbanion, overlap of the CO π-orbital with the p-orbital of the carbanion may occur via *syn* approach[15] (Scheme 2) or *anti* approach[16, 17] (Scheme 3).

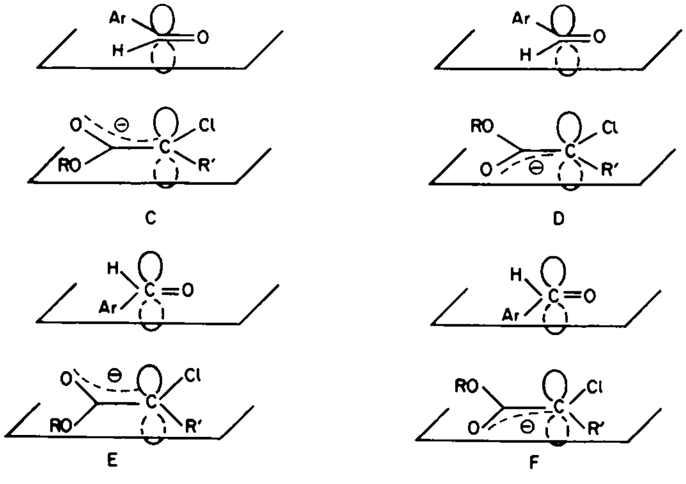
SCHEME 2.
syn-Approach of a planar carbanion



syn-Approach via transition state A would lead to the *RS*, *SR* chlorohydrin; the epimeric *RS*, *RS* chlorohydrin would then result from transition state B. However, this kind of transition state would predict that the proportion of the *RS*, *RS* isomer would decrease as R^1 is changed from H to CH_3, and that a change in the size of the R group should not affect the proportions of the two isomers. Neither of these predictions is correct.

anti-Approach via transition states C and D would lead to the *RS*, *RS* chlorohydrin; the epimeric *RS*, *RS* chlorohydrin would then result from E and F. This kind of geometry has been suggested by Dubois and Dubois[16] to explain the stereochemistry of aldolization in a dissociating medium or in the presence of a large cation, and by Kurtev and Kratchanov[17] for the Perkin reaction. The basis for these proposals is the assumed repulsive electrostatic interaction between the negatively charged O atom of the enolate anion and the CO oxygen. These transition states would predict that, although an increase in the size of R should cause D and F to become disfavoured, the proportions of C and E would be unaffected. Further, an *increase* in the *RS*, *RS* isomer is now predicted as R^1 is changed from H to Me. Again, neither of these predictions is correct. Moreover, the assumption that the geometry of the transition state should depend more on electrostatic repulsion than on nuclear-electron attraction is not compatible with theoretical analyses of the *gauche* effect.[18a,b]

SCHEME 3.
anti-Approach of a planar carbanion

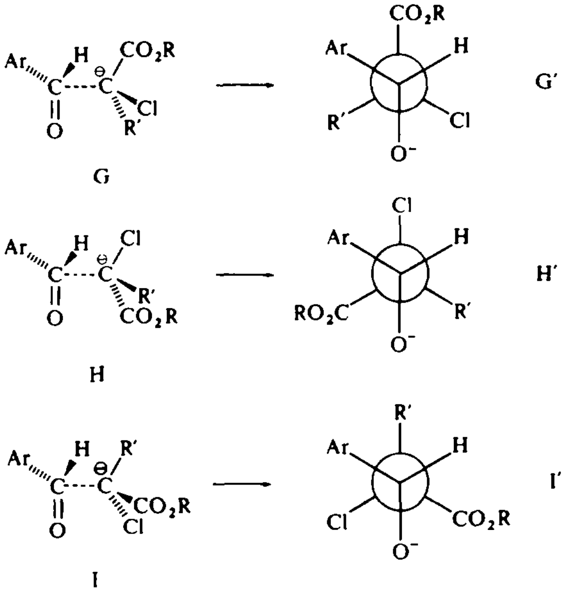


Thus a mechanism which involves the addition of a planar carbanion to the CO group is not consistent with the experimental observations. The alternative, pyramidal, geometry of the carbanion is acceptable on both theoretical and experimental grounds. For example, methylcarbanion,[19] like ammonia,[14c] has a pyramidal ground state and it is well established that, for pyramidal inversion at nitrogen[14a,b] and phosphorous,[20] electron-withdrawing substituents cause an increase in the barrier to inversion because of a relative stabilization of the pyramidal structure. Thus, the barrier to pyramidal inversion in fluoramine[21] is higher by 15 kcal/mole than that in ammonia. In the case of carbon, evidence for the pyramidal structure in a carbanion stabilized by two electron-withdrawing sulfonium substituents has been presented recently.[22] More striking evidence for the effect of electron-withdrawing substituents upon the barrier to inversion at carbon has been provided by the work of Hargreaves.[23] In the present case, the electron-withdrawing chlorine substituent should therefore increase the barrier relative to that in methylcarbanion (>5 kcal/mole[19]); this effect should be sufficient to offset any conjugative effect (as opposed to a purely inductive, electron-withdrawing, effect) of the alkoxycarbonyl substituent.* It should be noted that a pyramidal carbanionic intermediate alpha to an ester function has been proposed previously for the Reformatsky reaction.[24]

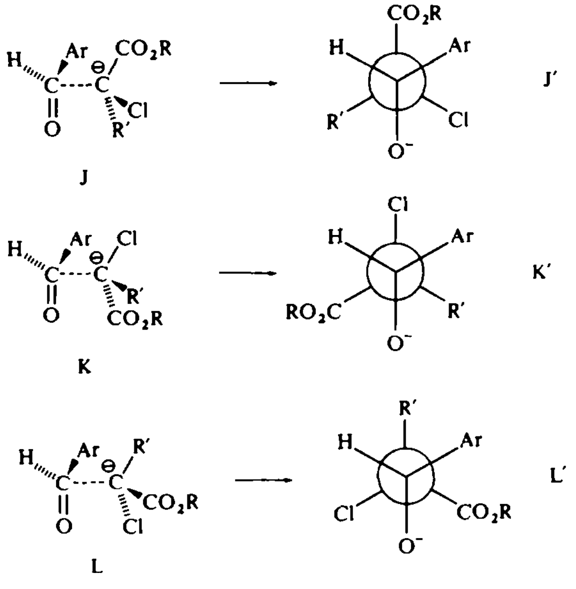
* We hope that experiments in progress will provide more direct evidence concerning the configuration at carbon in carbanions of the type $Cl\text{-}^{-}CH\text{-}CO_2R$.

For the addition of a pyramidal carbanion to a CO group, the three transition states shown in Scheme 4 (or their mirror images) would lead to the *RS*, *SR* (*threo*) isomer, and the three transition states shown in Scheme 5 (or their mirror images) would lead to the *RS*, *RS* (*erythro*) isomer.

SCHEME 4.
Formation of *RS*, *SR* (*threo*) chlorohydrin via attack by a pyramidal carbanion

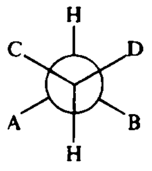


SCHEME 5.
Formation of *RS*, *RS* (*erythro*) chlorohydrin via attack by a pyramidal carbanion



It is reasonable to assume that the relative energies of G, H, I and of J, K, L should be proportional to the relative energies of the three staggered conformations (G^1, H^1, I^1 and J^1, K^1, L^1) of the *RS*, *SR* and *RS*, *RS* isomers, respectively.

Intuitively, it would be reasonable to consider conformations of type **15** and **16**, which have a smaller number of *gauche* interactions of the substituents A, B, C, D (Ar, Cl, CO_2R, O^-) to be more stable than conformations of type **17**–**20**, which have the maximum number of *gauche* interactions.



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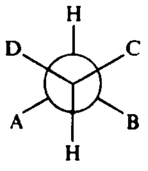

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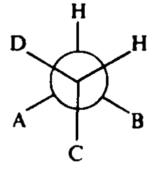

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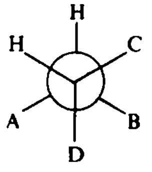

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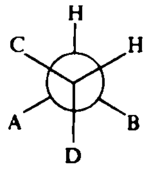

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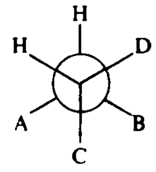

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This consideration would then lead to the prediction that G and K (and their mirror images) should be the preferred transition states leading to the *RS*, *SR* and *RS*, *RS* isomers, respectively. *However, this assumption cannot be correct, for two reasons.* To account for the observations it would be necessary to add the additional, unreasonable, assumption that G and K have equal energies. Even if this assumption were accepted, an increase in the size of R should now have destabilized G and caused formation of an excess of the *RS*, *RS* isomer; this does not agree with the experimental result.

We have recently introduced the term "the *gauche* effect"[18c] to describe the experimental finding that molecules or reactive intermediates which contain polar bonds on adjacent atoms preferentially adopt that conformation containing the maximum number of *gauche* interactions of these bonds. For the case of a $1, 1^1, 2, 2^1$-tetrasubstituted ethane there are no exceptions to this statement, i.e., conformations of type **15** and **16** have never been observed, either in the gas phase or in solvents of differing polarity. Thus the ruling out of transition states G and K on the basis of the present experimental evidence has ample precedent.

Of the remaining transition states, I and L alone permit a consistent interpretation of all of the experimental facts, viz., a change in the size of R^1 does not change the product ratio, but an increase in the size of R decreases the proportion of the *RS*, *RS* isomer (i.e., L is disfavoured). It is noteworthy that I and L differ from H and K, respectively, in having the gauche arrangement of chlorine and oxygen. There is considerable precedent for this.[18a,c]

D. *Effect of reversibility on the stereochemical course of the Darzens reaction.* As has been shown, under irreversible conditions the Darzens reaction can be made partially selective in favour of the *RS, SR* isomer by an increase in the size of the ester group. A change in the opposite direction can be achieved by a change in the degree of reversibility of the aldolization step. In practice, this condition can be met if the rate of retroaldolization of the *RS, SR* isomer cannot be decreased sufficiently. In our first report[1] we attributed the reversibility observed in the reaction of benzaldehyde with ethyl chloroacetate in a weakly polar medium to this latter factor: for the *RS, SR* isomer the rate of retroaldolization is higher than the cyclization rate. This interpretation is now confirmed by the present results. The *RS, RS* halohydrins (**7** or **11**) always cyclize more rapidly than the *RS, SR* isomers (**8** or **12**) (Runs 13, 16, 20–23). Also, in HMPT-ether at −40°, **7** cyclizes completely and **8** only in part (Run 5); in the other solvents **8** does not cyclize at low temperatures. The rate of cyclization of the halohydrins also depends on the nature of the ester; at −40°, in t-BuOH–ether the methyl ester **7** (Ar = Ph, R = Me) does not cyclize, but the Et and i-Pr esters do. The t-Bu ester cyclizes even at −80°.

The difference between our results and those of Bachelor and Bansal[5] can be understood by considering that these workers underestimated the reversibility factor of the reaction (k_{-T}/k_T^1). At 20° in t-BuOH or t-BuOH–ether, a net stereoselectivity in favour of epoxides **5** (Ar = Ph) for R = Me (80:20), Et (75:25) and i-Pr (67:33) was observed, and almost no selectivity for R = t-Bu (46:54). If, as Bachelor and Bansal proposed, these effects were due solely to variations in the stereoselectivity of aldolization, at low temperatures we should have observed isomer **7** as the principal product in the first three cases (Runs 11, 14, 17). However, the stereoselectivity of aldolization is affected neither by solvent nor by temperature. Consequently, the results of Bachelor and Bansal must have been caused by a different amount of reversibility with each ester.

E. *Polar bond effects on diastereomer stabilities.* Discussions of diastereomer equilibria which are based on substituent steric effects usually conclude with the predictions that *erythro* and *meso* isomers will be more stable than their *threo* and *dl* forms, respectively.[25] However, the *gauche* effect of adjacent polar bonds may now be expected to cause a reversal of these stabilities. For a compound $R_1CHXCHXR_2$ a *gauche* orientation of the X substituents would cause R_1 and R_2 to be *gauche* in the *erythro* isomer, but in the *threo* isomer these groups would be *anti*. The latter would then contain the best balance of steric and electronic interactions, and a reversal of the isomer stabilities should result. The available data are in agreement with this view. The *meso-dl* equilibria for the 2,3-dimethyl-2,3-diphenylsuccinonitriles[26] and the 2,3-dichlorobutanes[27] favour the *dl*-form; and the *threo* form of 2,3-dichloropentane[27] is favoured at equilibrium.

The present analysis of the Darzens reaction suggests that, when proper experimental controls are imposed, similar considerations may be applicable to other reactions in which *erythro-threo* mixtures are formed. For example, analogous discussions can be provided for the Wittig and related olefin syntheses. Experimental studies related to these reactions will be presented in a forthcoming paper.

CONCLUSIONS

The present work has considered the factors which affect the observed stereochemistry of the Darzens reaction and it has been shown that the gauche effect can be applied to aldolization reactions of this sort.

With alkyl chloroacetates and α-chloropropionates the stereoselectivity of the aldolization step is almost independent of the solvent. Therefore, the differences observed in benzene, ether, t-BuOH or HMPT reflect the influence of the medium upon the degree of reversibility of the aldolization step. The faster the cyclization of an *RS*, *SR* oxyanion (**2** or its homologues) the greater the relationship between the overall stereochemical result and the stereochemistry of the aldolization step.

EXPERIMENTAL

The NMR spectra were obtained on a Varian A60-D spectrometer and are reported as ppm downfield from TMS. We thank M. Chauffaille for his assistance.

GLC was performed on Girdel 75A or Aerograph 1400 equipment. Two-meter columns of 15% ethylene succinate on Chromosorb were employed, with N_2 as the carrier gas. The usual operating temps were: injector and detector, 180°; column, 160°. The order of elution is epoxyester **6**, epoxyester **5**, halohydrin **8**, halohydrin **7**; epoxyester **10**, epoxyester **9**, halohydrin **12**, halohydrin **11** for R = Me. For R = Et, i-Pr and t-Bu the halohydrins **11** and **12** could not be separated by GLC, and their ratios were determined by NMR in C_6D_6 (the peaks were less well separated in CCl_4).

When the GLC method was employed the ratios of epoxyesters and of chlorohydrins was determined by triangulation. When the mixture contained both halohydrins and epoxyesters the ratios were determined by NMR in CCl_4 or in C_6D_6.

Solvents were purified by distillation: ether from $CaCl_2$ followed by Cu powder; THF from LAH; t-BuOH from $CaSO_4$; and HMPT from CaH_2, under N_2 and reduced pressure.

Reaction of the aldehydes with the chloroesters in HMPT. A suspension of NaH (55–60% in mineral oil; 1·44 g; Fluka) was washed twice with hexane, twice with HMPT, and was then added to HMPT (25 ml). Then, with magnetic stirring under N_2, a soln of the aldehyde (0·03 mole) and the chloroester (0·03 mole) in HMPT (25 ml) was added, and the mixture was stirred. At the appropriate time the reaction was stopped by pouring onto ice, and the products were isolated by extraction with benzene, washing with sat NaCl aq., drying and evaporation. Analysis was performed on this residue.

Reaction of benzaldehyde with alkyl chloroacetates in t-BuOH-Ether at ambient temperature. To a soln of benzaldehyde (0·02 mole) and alkyl chloroacetate (0·02 mole), in 20 ml of a 1:1 (v/v) mixture of t-BuOH and ether, was added t-BuOH (0·02 mole: Merck) in t-BuOH-ether (15 ml). The mixture was stirred under N_2 for 1·25 hr and was then poured onto ice and extracted with ether. The ether extract was dried over $NaSO_4$ and evaporated. The ratio of **5** and **6** (Ar = Ph) was determined by GLC. For R = Et: **5**/**6** = 80/20 (lit[5]: 74/26); R = *t*-Bu: 49/51 (lit[5]: 46/54).

Reversibility of the reaction in t-BuOH-ether at ambient temperature. To 0·002 mole of a 30/70 mixture of halohydrins **7**/**8** (Ar = Ph; R = Et) and 0·002 mole of *m*-chlorobenzaldehyde, in 1:1 (v/v) t-BuOH-ether (6 ml), was added t-BuOk (0·002 mole), dissolved in the same solvent (4 ml). The mixture was stirred under N_2 for 1·25 hr and the product then isolated as already described. Analysis of the mixture by GLC revealed the presence of benzaldehyde, *m*-chlorobenzaldehyde, a small amount of epoxide **6** (Ar = Ph; R = Et), epoxide **5** (Ar = Ph; R = Et), epoxide **5** (Ar = *m*-ClC_6H_4; R = Et) and a small amount of **8**.

Reaction of benzaldehyde with chloroesters in ether (Method A). To 0·05 mole of aldehyde and 0·05 mole of chloroester, dissolved in ether (75 ml) was added, under N_2 and with stirring, 0·05 mole of sodium or potassium alkoxide. After an appropriate time, a few drops of ethereal HCl and 30 ml of water were added. The ether layer was separated, washed with water, dried over $NaSO_4$, and analyzed.

Reaction of benzaldehyde with the chloroesters in a t-BuOH-ether mixture (Methods B and C). The reaction was performed as in Method A, but with sodium or potassium t-butoxide in a 1:1 (v/v) mixture of t-BuOH and ether, at −40° or −80°.

Identification of the epoxyesters. The physical and spectroscopic properties of the various compounds summarised in Table 4. This Table also gives the microanalytical data obtained for pure epoxides; where these data do not appear, a mixture of isomers was obtained.

TABLE 4. EPOXYESTERS

Compound	Ar	R	R′	B.p.	Epoxide protons	Ester protons	Other peaks
6	Ph	H	Me	5			
5	Ph	H	Me	5			
6	Ph	H	i-Pr	5	3·57, 4·05 (4·5Hz)	0·92 (6H)	
5	Ph	H	i-Pr	5	3·27, 3·93 (1·8Hz)	1·28 (6H)	
6	o-ClC$_6$H$_4$	H	Et		3·74, 4·27 (4·5Hz)	3·93 (2H), 0·99 (3H)	
5	o-ClC$_6$H$_4$	H	Et		3·19, 4·29 (1·8Hz)	4·14 (2H), 1·32 (3H)	
6	p-ClC$_6$H$_4$	H	Et		3·64, 4·10 (4·5Hz)	3·96 (2H), 1·12 (3H)	
5	p-ClC$_6$H$_4$	H	Et		3·27, 3·98 (1·8Hz)	4·12 (2H), 1·31 (3H)	
6	o-CH$_3$C$_6$H$_4$	H	Et		3·69 and in the envelope (4·5Hz)	3·83 (2H), 0·86 (2H)	2·38 (3H)
5	o-CH$_3$C$_6$H$_4$	H	Et		3·19, 4·12 (1·8Hz)	4·12 (2H), 1·31 (3H)	2·32 (3H)
6	o-CH$_3$OC$_6$H$_4$	H	Et		3·64, 3·96 (4·5Hz)	0·85 (3H)	3·83 (3H)
5	o-CH$_3$OC$_6$H$_4$	H	Et		3·28, 4·27 (1·8Hz)	4·15 (2H), 1·3 (3H)	3·83 (3H)
6	p-CH$_3$OC$_6$H$_4$	H	Et		3·59, 4·14 (4·5 Hz)	3·90 (2H), 1·0 (3H)	3·74 (3H)
5	p-CH$_3$OC$_6$H$_4$	H	Et		3·28, 3·90 (1·8Hz)	4·18 (2H), 1·18 (3H)	3·74 (3H)
10	Ph	Me	Me	85/0·1 torr	3·85	3·70	1·65 (3H)
9	Ph	Me	Me	85/0·1	4·20	3·34	1·24 (3H)
10	Ph	Me	i Pr	76/0·1	3·84	0·88 (6H)	1·63 (3H)
9	Ph	Me	i Pr	76/0·1	4·18	1·29 (6H)	1·24 (3H)
10	Ph	Me	t Bu	107/0·1	3·82	1·10	1·61 (3H)
9	Ph	Me	t Bu	107/1·0	4·14	1·50	1·19 (3H)
10	o-CH$_3$C$_6$H$_4$	Me	Me		3·84	3·28	1·69 (3H), 2·19 (3H)
9	o-CH$_3$C$_6$H$_4$	Me	Me		4·16	3·73	1·16 (3H), 2·20 (3H)
10	o-CH$_3$OC$_6$H$_4$	Me	Me		4·00	3·33	1·65 (3H), 3·77 (3H)
9	o-CH$_3$OC$_6$H$_4$	Me	Me		4·30	3·70	1·20 (3H), 3·77 (3H)

Identification of the halohydrins. Halohydrins **7** (Ar = Ph; R = Me and i-Pr) were obtained from the corresponding acids by esterification with the appropriate alcohol in the presence of dry HCl.[7] They were isolated by distillation following neutralization, extraction with ether and washing with water. Halohydrins **11** (Ar = Ph; R = Me, Et, i-Pr) were prepared in the same manner from the corresponding acid.[11] Identification was made following cyclization by one equivalent of NaH in HMPT at room temp for 2 hr. Treatment with water, extraction with benzene and washing with a sat NaCl aq led to **9**, identified by GLC and NMR. In some cases the resulting epoxides were contaminated with small amounts of **12**. Halohydrins **7** and **11** (Ar = Ph; R = t-Bu) were not obtained in pure form but admixed with the isomers **8** and **12** (Ar = Ph; R = t-Bu). Their NMR spectra were deduced from the spectra of the mixtures, since **8** and **12** had already been obtained and characterized in pure form. Halohydrins **8** and **12** (Ar = Ph) were isolated, by column of preparative layer chromatography on silica gel (hexane: ether 90:10), from mixtures which contained epoxides **5** or **9** in addition to **8** or **12** (Methods B and C). Treatment with NaH in HMPT converted these chlorohydrins to **6** and **10**.

Methyl 2-chloro-3-hydroxy-3-phenylpropionate (RS, RS; **7**, R = Me): m.p. 58° (hexane); NMR (CCl_4): 4·92 (1H, d, 8Hz), 4·19 (1H. d, 8Hz), 3·75 (s, 3H).

Methyl 2-chloro-3-hydroxy-4-phenylpropionate (RS, SR; **8**, R = Me): NMR (CCl_4): 5·05 (1H, d, 5·5Hz), 4·35 (1H. d, 5·5Hz), 3·57 (3H, s).

Isopropyl 2-chloro-3-hydroxy-3-phenylpropionate (RS, RS; **7**, R = i-Pr): b.p. 135–140°/0·1 torr; NMR (CCl_4): 4·94 and 4·24 (AB quartet, J = 8·5Hz), 5·0 (1H, m), 1·26 and 1·10 (2 doublets, 6H).

Isopropyl 2-chloro-3-hydroxy-3-phenylpropionate (RS, SR; **8**, R = i-Pr): NMR (C_6D_6): 4·99 (1H, d, 7Hz), 4·33 (1H, d, 7Hz), 4·75 (1H, m), 0·87 and 0·74 (6H, two doublets). (Found: C, 59·11; H, 5·99; Cl, 14·75. Calcd. for $C_{12}H_{15}C10_3$: C, 59·3; H, 6·18; Cl, 14·6%).

t-Butyl 2-chloro-3-hydroxy-3-phenylpropionate (RS, RS; **7**, R = t-Bu): b.p. 140–145°/0·1 torr: NMR (C_6D_6): 5·0 (1H, d, 7Hz), 4·31 (1H, d, 7Hz), 1·31 (9H, s).

t-Butyl 2-chloro-3-hydroxy-3-phenylpropionate (RS, SR; **8**, R = t-Bu: NMR (C_6D_6): 5·0 (1H, d, 7Hz), 4·28 (1H, d, 7Hz), 1·14 (9H, s). (Found: C, 60·80; H, 5·78; Cl, 13·97. Calcd. for $C_{13}H_{17}ClO_3$; C, 60·81; H, 6·62; Cl, 13·84%).

Methyl 2-chloro-2-methyl-3-hydroxy-3-phenylproprionate (RS, RS, **11**, R = Me): b.p. 135°/0·1 torr, NMR (C_6D_6): 5·2 (1H, s, CHOH), 3·30 (3H, s), 1·64 (3H, s). (Found: C, 57·84; H, 5·51; Cl, 15·52. Calcd. for $C_{11}H_{13}ClO_3$: C, 57·7; H. 5·69: Cl. 15·5%)

Methyl 2-chloro-2-methyl-3-hydroxy-3-phenylpropionate (RS, SR; **12**, R = Me): NMR (C_6D_6): 5·14 (1H, s), 3·22 (3H, s), 1·53 (3H, s). (Found: C, 57·79; H, 5·64; Cl, 15·68. Calcd. for $C_{11}H_{13}ClO_3$: C, 57·7; H, 5·69; Cl, 15·5%).

Ethyl 2-chloro-2-methyl-3-hydroxy-3-phenylpropionate (RS, RS, **11**, R = Et): b.p. 158–160°/5 torr[28]; NMR (C_6D_6): 5·28 (1H, s), 4·1 (2H, q, 7Hz), 1·66 (3H, s), 0·96 (3H, t, 7Hz). (Found: C, 59·60; H, 6·26; Cl, 14.57. Calcd. for $C_{12}H_{15}ClO_3$: C, 59·3; H, 6, 18; Cl, 14·60%).

Ethyl 2-chloro-2-methyl-3-hydroxy-3-phenylpropionate (RS, SR, **12**, R = Et): NMR (C_6D_6): 5·20 (1H, s), 4·03 (2H, q, 7Hz), 1·55 (3H, s), 0·92 (3H, t, 7Hz).

Isopropyl 2-chloro-2-methyl-3-hydroxy-3-phenylpropionate (RS, RS; **11**, R = i-Pr): b.p. 130–133°/0·1 torr; NMR (C_6D_6): 5·28 (1H, s), 4·94 (1H, m), 1·66 (3H, s), 0·95, 1·00 (6H, 2 doublets). (Found: C, 60·59; H, 6·67; Cl, 13·59 Calcd. for $C_{13}H_{17}ClO_3$: C, 60·80; H, 6·7; C., 13·8%).

Isopropyl 2-chloro-2-methyl-3-hydroxy-3-phenylpropionate (RS, SR; **12**, R = i-Pr): NMR (C_6D_6): 5·24 (1H, s), 4·90 (1H, m), 1·58 (3H, s), 1·00 and 0·95 (6H, d of d).

t-Butyl 2-chloro-2-methyl-3-hydroxy-3-phenylpropionate (RS, RS; **11**, R = t-Bu): NMR (C_6D_6): 5·15 (1H, s), 1·53 (3H, s), 1·29 (9H, s). (Found: C, 61·96; H, 6·86; Cl, 13·26. Calcd. for $C_{14}H_{19}ClO_3$: C, 62·10; H, 7·02; Cl, 13·1%).

t-Butyl 2-chloro-2-methyl-3-hydroxy-3-phenylpropoinate (RS, SR; **12**, R = t-Bu): NMR (C_6D_6): 5·2 (1H, s), 1·64 (3H, s), 1·33 (9H, s).

Behaviour of the halohydrins under the reaction conditions. Only one example is presented in detail. All others were checked in the same way, starting with pure products or with variable mixtures of halohydrins.

To 425 mg of a 53/47 mixture of **11** and **12** (Ar = Ph; R = Me), in t-BuOH-ether (1:1, v/v, 4 ml) were added, at −40 , p-chlorobenzaldehyde (351 mg) in t-BuOH-ether (2 ml) and t-BuOk (224 mg) in t-BuOH-ether (8 ml). The mixture was stirred under N_2 for 1 hr. Then ethereal HCl (5 ml) and water (5 ml) were added. The organic layer was separated, washed with water and subjected to GLC. Epoxide **9** (Ar = Ph) and **12** (Ar = Ph) were detected but there was no trace of a *p*-chlorophenyl epoxide. The ratio of **9**/**12**, determined by NMR, was 54/46.

In this way it was verified that, except for the conditions of Run 19, there was no retroaldolization or change in the molar ratio of the different isomers. At higher temps, however, *p*-chlorophenyl epoxides were obtained.

Behaviour of the epoxides in the presence of excess base. Only one example is presented in detail. All others were checked in the same way.

Epoxide **9** (245 mg; Ar = Ph; R = t-Bu) and epoxide **10** (200 mg; Ar = Ph; R = t-Bu) were dissolved in HMPT (8 ml). This soln was divided into two parts and to one part (Solution B) was added NaH (41 mg) in hexane. Both were then stirred at room temp under N_2 for 3 hr. Then to each was added *trans*-stilbene (50 mg) and each was poured onto water (30 ml) and extracted 4 times with 25 ml portions ether. The ether extracts were washed with water, dried over $NaSO_4$, and analyzed by GLC. In the case of Solution A (no base added) the ratio **9**:**10**: stilbene was found to be 66:56:49. For solution B the ratio was 26:66:53, i.e., the proportion of **9** had decreased, and the gas chromatogram also showed the presence of isobutylene.

A similar treatment except that the reaction time was decreased to 0·5 hr gave, from Solution A, **9**:**10**: stilbene 60:48:50, and from Solution B, 54:49:48.

Analogous results were obtained with the isopropyl esters; with the methyl and ethyl esters Solutions A and B showed the same ratio of epoxides.

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