is approximately 1×10^6 sec.$^{-1}$. If k_3 is assumed to be of the same order of magnitude, then it can be shown using

$$k_1 = (kT/h)e^{\Delta S^{\ddagger}/R}e^{-\Delta H_1^{\ddagger}/RT} \quad (8)$$

that in order for k_1 to be greater than k_3, $\Delta H_1^{\ddagger}$ could be approximately 8 kcal., or less (assuming a reasonable value for $\Delta S^{\ddagger}$). In the alkaline hydrolysis of ethyl benzoate[2] which has an activation energy of 14.56 kcal., there could be an energy barrier of approximately 8 kcal. for the unstable intermediate and k_1 could still be greater than k_3.

Thus it is very possible that the life of the unstable intermediate is too short for the two oxygen atoms to become completely equivalent by proton transfer.

An explanation for equation 3 might be found in the effect of chain length upon the amplitude of the –C–OR bond vibrations or upon the probability that the bond will obtain the requisite energy for the reaction. Theimer[15] has shown, for example, that the relative intensities of the terminal modes in straight chain *n*-paraffins decrease with increasing chain length, *i.e.*, a linear relationship is obtained when the relative intensities, $I(\nu)$, are plotted against $1/N$ where N is the number of carbon atoms.

Morino and co-workers[16] have shown that the potential energy of both bonded and non-bonded atom pairs is related directly to the reciprocal of the reduced mass of the atoms.

The rates of hydrolysis of the aryl trifluoroacetates are qualitatively dependent upon the basicity of the ArO–group.

It was found, at least qualitatively, that the rate of hydrolysis of phenyl trifluoroacetate was very dependent upon the water concentration. This suggests that a possible mechanism for the non-catalyzed hydrolysis of this ester might be

$$CF_3CO_2C_6H_5 + H_2O \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} CF_3C(O^{\ominus})(\overset{\oplus}{O}H_2)C_6H_5 \xrightarrow{k_1} \text{products}$$

and thereby k_{-2} could be greater than or approximately the same as k_1; thus, the effect of the ionization step, k_1, could be felt in the over-all rate constant.

(15) O. Theimer, *J. Chem. Phys.*, **27**, 1041 (1957).

(16) Y. Morino, *et al.*, *ibid.*, **21**, 1927 (1953).

LAFAYETTE, IND.

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF NORTHWESTERN UNIVERSITY]

Overlap Control of Carbanionoid Reactions. II.[1] The Stereochemistry of the Perkin Reaction and Related Condensation Reactions

BY HOWARD E. ZIMMERMAN AND LEO AHRAMJIAN

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The Perkin reaction of aromatic aldehydes with phenylacetic acids has been known for quite some time to afford preferentially the α-phenylcinnamic acid stereoisomer with *cis*-phenyl groups but an unhindered carboxyl group. The nature of the stereochemical driving force has now been elucidated. Evidence is presented that the initial condensation step is not reversible and that the reaction stereochemistry is eliminatively controlled. The role of overlap control in affording condensation products with unhindered electron delocalizing groups is discussed.

It has been known for some time that the Perkin condensation of aromatic aldehydes with phenylacetic acids affords the α-phenylcinnamic acid stereoisomer with *cis*-phenyl groups.

$$C_6H_5CHO + C_6H_5CH_2COOH \xrightarrow{Ac_2O,\ base} \underset{H}{\overset{C_6H_5}{\diagdown}}C{=}C\underset{COOH}{\overset{C_6H_5}{\diagup}} \quad (1)$$

This knowledge derives mainly from the work of Stoermer and co-workers[2] and Bakunin.[3]

Recently, Crawford and Moore[4] have emphasized the generality of this reaction stereochemistry[5] and commented on the enigma of a reaction which leads preferentially to a product with *cis*-phenyl groups. To account for the observed reaction course a mechanism was proposed which involved preferential formation of the *erythro*[9]-3-hydroxy-2,3-diphenylpropionic acid anhydride intermediate[10] (Ib, R = Ac) followed by *trans* elimination of acetic acid

(1) For paper I in this series see H. E. Zimmerman, L. Singer and B. S. Thyagarajan, THIS JOURNAL, **81**, 108 (1959).

(2) R. Stoermer, *Ann.*, **409**, 15 (1915); R. Stoermer and L. Prigge, *ibid.*, **409**, 20 (1915); R. Stoermer and G. Voht, *ibid.*, **409**, 36 (1915).

(3) M. Bakunin, *Gazz. chim. ital.*, **27**, II, 34 (1897); *Chem. Zentr.*, **68**, II, 662 (1897).

(4) M. Crawford and G. W. Moore, *J. Chem. Soc.*, 3445 (1955).

(5) The configurations of the various α-phenylcinnamic acids are firmly established. The evidence includes the stereospecific decarboxylation to the stilbene of the same configuration (ref. 1), the much greater rate of esterification of α-phenyl-*trans*-cinnamic than of α-phenyl-*cis*-cinnamic acid (ref. 6) as would be expected from the less hindered carboxyl group of the former, the ready cyclization of only the α-phenyl-*cis*-cinnamic acid to the corresponding indone (ref. 7), the similar cyclization of the related nitrile stereoisomer to the indone contrasted with the non-reactivity of the α-phenyl-*trans*-cinnamonitrile (ref. 8), the Pschorr reaction of α-phenyl-*trans*-o-aminocinnamic acid compared with the formation of 3-phenylcoumarin from α-phenyl-*cis*-o-aminocinnamic acid on diazotization (ref. 2).

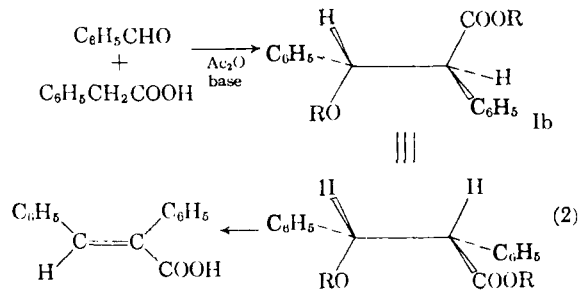
(6) J. J. Sudborough and L. L. Loyd, *J. Chem. Soc.*, 81 (1898); J. J. Sudborough and D. J. Roberts, *ibid.*, 1851 (1905).

(7) M. Bakunin, *Gazz. chim. ital.*, **30**, II, 340 (1900); *cf. Chem. Zentr.*, **71**, II, 1276 (1900).

(8) P. Pfeiffer, H. Kübler and H. Rüping, *J. prakt. Chem.*, [2] **121**, 85 (1929).

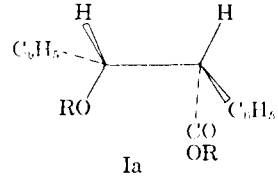
(9) It is convenient to assign the *erythro* and *threo* designations on the basis of similarity of relative size of groups rather than similarity of functionality. On this basis the *erythro* diastereomer will be the more stable one, since as has been pointed out by both D. J. Cram, F. D. Greene and C. H. DePuy, THIS JOURNAL, **78**, 790 (1956), and D. H. R. Barton and R. C. Cookson, *Quart. Rev.*, **10**, 48 (1956), it has available to it a low energy conformation in which not only the large groups (L and L′,) have an *S-trans* arrangement but also the medium groups (M and M′,).

(10) The suggestion that the stereochemistry of condensation reactions is controlled by preferential formation of the more stable *erythro*



(2)

However, this interpretation seemed inconsistent with our findings[14,15] that the condensation of benzaldehyde with either the magnesium or the sodium[15] enolate of phenylacetic acid led in the Ivanov reaction preferentially to *threo*-3-hydroxy-2,3-diphenylpropionic acid (Ia, R = H) rather than



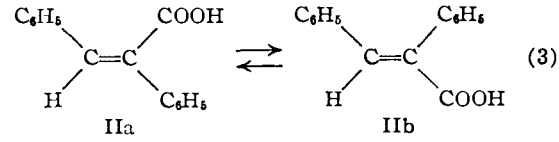
Ia

the proposed intermediate Ib (R = H).[16] With the intent of resolving this difficulty and elucidating the mechanism of the Perkin condensation, the present investigation was begun.

Since both diastereomers (Ia and Ib) of the 3-hydroxy-2,3-diphenylpropionic acid intermediate were available from the Ivanov reaction, a study of the behavior of each of these under Perkin conditions was undertaken. For this investigation a procedure for analyzing mixtures of the α-phenylcinnamic acid products (IIa and IIb) first had to be devised; and secondly, knowledge of the conditions under which these stereoisomers interconverted was needed. It was desirable to select reaction conditions for the mechanistic study mild enough such that product equilibration would not be a serious complication and yet conditions severe enough that the Perkin reaction would proceed essentially to completion.

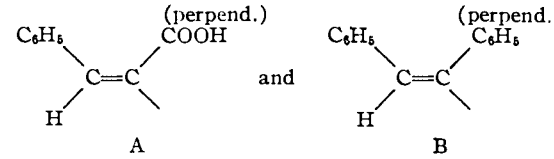
The first requisite was fulfilled by using an infrared technique devised earlier,[17] which allowed determination of the percentage of each isomer in a mixture with a maximum expected error of ±2 percentage units. The details are described in the Experimental section, and calibration data and analyses of known compounds are given in Table III.

The second requirement preliminary to the main investigation was information bearing on the interconvertibility and relative stabilities of the α-phenylcinnamic acid products. The early work of Stoermer[2] indicated that α-phenyl-*trans*-cinnamic acid (IIb) is the stable isomer. Moreover, recently Curtin[18] has reported the equilibrium constant for formation of IIb from IIa as 6. In agreement with the literature indications it was found in the present study that by refluxing for 22 hours in a dilute solution of acetic anhydride–triethylamine, α-phenyl-*cis*-cinnamic acid (IIa) was converted to an equilibrium mixture containing 81% of α-phenyl-*trans*-cinnamic acid (IIb) and 19% IIa. With only 35 minutes of refluxing IIa was converted to the extent of only 21% to IIb.



IIa IIb (3)

The greater stability of the isomer (IIb) having *cis*-phenyl groups is unusual and requires comment.[19,20] It is clear from inspection of models that in each stereoisomer only the *trans* related groups may approach coplanarity with the double bond with consequent resonance interaction. Thus the carboxyl group in IIa and the α-phenyl group in IIb are forced out of the molecular plane.[20a] Being electronically insulated from the rest of the molecule, these groups cannot influence resonance stabilization. Furthermore, since each of these groups is perpendicular to the molecular plane, and since the half-width thickness of a carboxyl group should not differ appreciably from that of a phenyl group, it may be concluded that the van der Waals repulsive forces due to the perpendicular carboxyl in IIa do not differ from those engendered by the perpendicular α-phenyl group in IIb. Thus from both an electronic and a steric viewpoint the systems



A B

as occurring in IIa and IIb are essentially the same, and therefore the observed energy difference must be attributed to the remaining portion of the system (*i.e.*, the *trans*-α-phenyl group in IIa and the *trans*-carboxyl group in IIb).

diastereomer has been put forth by several other groups as well. Thus it has been postulated by N. H. Cromwell and R. A. Setterquist (ref. 11), H. Kwart and L. Kirt (ref. 12) and H. Dahn and L. Loewe (ref. 13) that the condensation step of the Darzens reaction leads preferentially to the more stable *erythro* diastereomer.

(11) N. H. Cromwell and R. A. Setterquist, THIS JOURNAL, **76**, 5752 (1954).

(12) H. Kwart and L. Kirt, *J. Org. Chem.*, **22**, 116 (1957).

(13) H. Dahn and L. Loewe, *Chimia*, 11, 98 (1957).

(14) H. E. Zimmerman and M. D. Traxler, THIS JOURNAL, **79**, 1920 (1957). These findings were presented at the Sixth Reaction Mechanism Conference, held at Swarthmore, Pa., September, 1956.

(15) H. E. Zimmerman, L. Ahramjian and M. D. Traxler, Abstracts of the Organic Division, ACS Meeting, Miami, Fla., April, 1957, p. 45-O.

(16) The extrapolation of the Ivanov stereochemistry to the Perkin reaction is imperfect due to a solvent difference and the fact that the Ivanov reaction involves a dienolate while only a monoenolate occurs in the Perkin reaction.

(17) H. E. Zimmerman and T. W. Cutshall, THIS JOURNAL, **80**, 2893 (1958), and earlier papers cited therein.

(18) D. Y. Curtin, Abstracts of the Thirteenth Organic Symposium of the A.C.S., Ann Arbor, Mich., 1953, p. 40.

(19) It was erroneously assumed by Crawford and Moore (ref. 4) that α-phenyl-*cis*-cinnamic acid is the stable isomer.

(20) It should be noted that in the present case the isomerization involved is actually that between the mixed acetic α-phenylcinnamic acid anhydride stereoisomers, the equilibrium mixture being converted to the corresponding mixture of IIa and IIb during work-up.

(20a) The non-coplanarity of the carboxyl in IIa is evidenced by its shorter infrared carbonyl absorption wave length (5.87μ in CS_2 *vs.* 5.93 for IIb).

Although the literature suggests[21] greater resonance stabilization should be available from introduction of a coplanar phenyl group to system A than addition of a coplanar carboxyl group to system B, the carboxyl group, because of its smaller steric requirements and lesser van der Waals interaction with the perpendicular group, finds it easier to assume the planar conformation required for maximum resonance stabilization. Thus, the observed stability order can be attributed to ineffective resonance interaction by the α-phenyl group in IIa due to difficulty in attaining a planar conformation.

The next step in the present research was investigation of the behavior of each of the diastereomeric 3-hydroxy-2,3-diphenylpropionic acids under Perkin conditions.

Each of the diastereomers (Ia and Ib) was treated with refluxing 1:1 acetic anhydride–triethylamine for 35 minutes, under which conditions the interconversion of stereoisomers had been demonstrated to be only a minor complication.[22] Infrared analysis of the reaction mixture (note Table I)

TABLE I

Run	Reactants	Conditions	α-Phenyl-*trans*-cinnamic acid, %
1	*threo*-3-Hydroxy-2,3-diphenylpropionic acid	1:1 Ac_2O Et_3N 35 min. reflux	99
2	*erythro*-3-Hydroxy-2,3-diphenylpropionic acid	1:1 Ac_2O Et_3N 35 min. reflux	100
3	Phenylacetic acid and benzaldehyde	1:1 Ac_2O Et_3N 35 min. reflux	96
4	α-Phenyl-*cis*-cinnamic acid	1:1 Ac_2O Et_3N 35 min. reflux	21
5	α-Phenyl-*cis*-cinnamic acid	2:1 Ac_2O Et_3N 5.5 hr. reflux	75
6	α-Phenyl-*cis*-cinnamic acid	1:1 Ac_2O Et_3N 22 hr. reflux	81

indicated this to consist in each case of 99 ± 2% α-phenyl-*trans*-cinnamic acid (IIa). This result is striking for at least two reasons. First of all, it negates the mechanism proposed by Crawford and Moore,[4] for the elimination is not stereospecific as was presumed by these authors. Secondly, despite the lack of stereospecificity, the elimination is highly stereoselective[23]; thus, much more of the stable isomer IIb results than accountable on a thermodynamic basis.

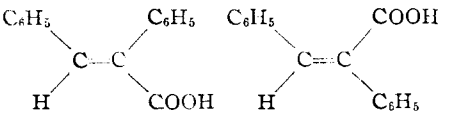
The observation having been made that under mild conditions 99% of α-phenyl-*trans*-cinnamic acid was formed starting with the β-hydroxy acid intermediates, the product distribution afforded by the Perkin reaction itself was of interest. Under the same mild conditions the condensation of benzaldehyde and phenylacetic acid led to product analyzing for 96% α-phenyl-*trans*-cinnamic acid (IIb). Thus both the Perkin reaction itself and the β-hydroxy acid intermediates afford 98 ± 2% of IIb (note Table I).

The product distribution obtained under the present conditions contrasts with the observation of Fieser[24] that an appreciable amount of α-phenyl-*cis*-cinnamic acid accompanies the major α-phenyl-*trans*-cinnamic acid product. Repetition of Fieser's procedure,[24] which involves a 35-minute reaction period with a more concentrated solution of the reactants in 1:1 acetic anhydride–triethylamine than employed in the present study, afforded in agreement with Fieser 21.6% of α-phenyl-*cis*-cinnamic acid in addition to the major α-phenyl-*trans*-cinnamic acid product. It is clear that the very high stereoselectivity of the Perkin reaction under the mild conditions is a kinetic consequence while the decreased selectivity under the more drastic conditions is due to an approach to the thermodynamic distribution by equilibration.

Of the two questions still requiring clarification, the nature of the non-stereospecific elimination and the reason for its high selectivity, the former was considered first. One possible explanation would be a rapidly established and reversible equilibrium between reactants and the β-hydroxy acid intermediates followed by a rate-determining and preferential *trans* elimination of acetylated *erythro*-3-hydroxy-2,3-diphenylpropionic acid.

$$C_6H_5CH_2COOH + C_6H_5CHO \underset{\text{fast}}{\rightleftharpoons} \textit{erythro}\ C_6H_5CHOHCH(C_6H_5)COOH + \textit{threo}\ \text{isomer} \quad (4)$$

slow ↓ rate-determining ↓ very slow



In order to test this possibility each of the elimination experiments, one beginning with *threo*-3-hydroxy-2,3-diphenylpropionic acid (Ia) and one with *erythro*-3-hydroxy-2,3-diphenylpropionic acid (Ib), was repeated in the presence of excess *m*-nitrobenzaldehyde. From each run there was obtained by chromatographic separation: unreacted *m*-nitrobenzaldehyde, *m*-nitrocinnamic acid arising from reaction of the acetic anhydride solvent and α-phenyl-*trans*-cinnamic acid. Had the condensation step been reversible, the highly reactive *m*-nitrobenzaldehyde would have competed with benzaldehyde for phenylacetic acid affording at least some α-phenyl-*m*-nitrocinnamic acid; however, none was isolated and the material balance indicated this was not formed.

In order to provide further evidence on this point, the elimination of *threo*-3-hydroxy-2,3-diphenyl-

(21) The data of R. B. Williams, THIS JOURNAL, **64**, 1395 (1942), indicate a decrease of 8.0 kcal./mole in heat of hydrogenation and hence 8.0 kcal./mole increase in resonance energy in introducing a *trans*-phenyl group into styrene. This contrasts with only a 3.9 kcal./mole effect obtained by introducing a *trans*-carbomethoxyl group.

(22) Although the extent of isomerization was studied only for the less stable α-phenyl-*cis*-cinnamic acid, it is a thermodynamic consequence that the rate of equilibration of the more stable isomer must be slower.

(23) A stereoselective reaction has been defined (ref. 1) as one in which there is no relation of the product configuration to that of the reactant (as is true for a stereospecific reaction) but in which there is preferential formation of one of the possible stereoisomeric products due to some driving force.

(24) L. Fieser, "Experiments in Organic Chemistry," 3rd. ed., D. C. Heath and Co., Boston, Mass., p. 182.

propionic acid (Ia), the isomer which could not lead directly to product by *trans* elimination, was carried out in the presence of radioactive phenylacetic acid. In agreement with the results of the *m*-nitrobenzaldehyde experiments it was found that the α-phenyl-*trans*-cinnamic acid product was devoid of activity and that the recovered phenylacetic acid was essentially unchanged (note Table II). Incorporation of radioactive phenylacetic

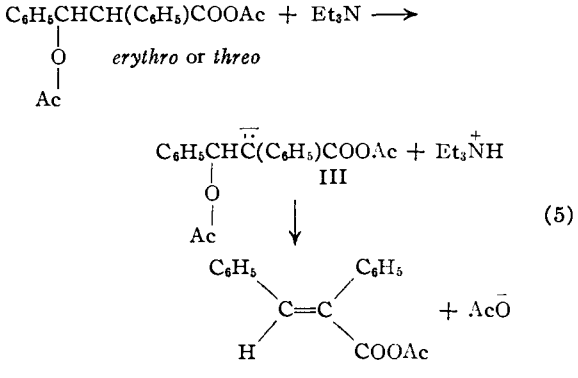
TABLE II

RESULTS OF TRACER EXPERIMENT

Substance	Activity, counts/min./millimole[a]
Phenylacetic acid-carboxyl-C^{14} reactant	1.51×10^6
α-Phenyl-*trans*-cinnamic acid product	0
Recovered phenylacetic acid	1.43×10^6

[a] Corrected for background count.

acid would have been certain[25] had Ia reverted to benzaldehyde and phenylacetic acid. Thus the condensation step of the Perkin reaction is not reversible[26] and the mechanism indicated by equation 4 may be excluded. Instead, the reaction course may be depicted as being eliminatively controlled as in equation 5.[27] The elimination of the *erythro* isomer is *trans* while that of the *threo* isomer is *cis*. That a *cis* elimination is



involved in the case of the *threo* intermediate is unexceptional; reactions initiated by abstraction of a relatively acidic hydrogen atom have been shown by Bordwell[28] to proceed in cases by a net *cis* elimination. Exceptional, however, is the highly stereoselective formation of α-phenyl-*trans*-cinnamic acid from both stereoisomers, a result which now requires discussion.

For this purpose there must be considered the two elimination transition states available to a reacting molecule, IVa leading to α-phenyl-*cis*-cinnamic acid (IIa) and IVb leading to α-phenyl-*trans*-cinnamic acid (IIb) (note Fig. 1); these

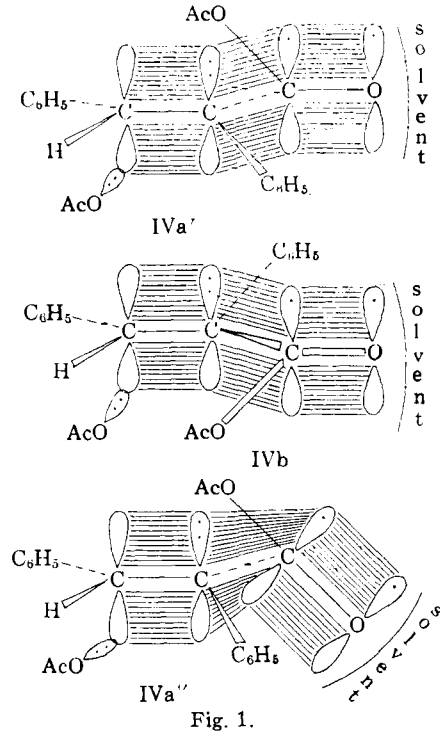


Fig. 1.

differ by a 180° rotation about the central carbon-to-carbon bond. With the literature of elimination reactions in mind, one would be inclined to select IVa as the lower energy transition state, this having the *S-trans* conformation of phenyl groups; van der Waals repulsions of the *cis* oriented phenyl groups of IVb would be expected to raise the energy by up to 5 kcal./mole. However, since the product actually obtained is derived from transition state IVb, this argument must not be complete and a driving force not previously encountered in elimination reactions must be operative.

It is suggested that the energies of both intermediate III and transition state IV are highly sensitive to steric interactions involving the anhydride carbonyl group stabilizing the electron pair and accompanying negative charge. The effect of steric interaction of a *cis* group with the anhydride function is to tend to force the carbonyl group involved in delocalization out of the plane of the incipient double bond with consequent poor orbital overlap (transition state IVa'', Fig. 1) and decreased electron delocalization (steric inhibition of resonance). Thus overlap control favors the transition state IVb having an unhindered electron delocalizing group. Since complete localization of the electron pair on carbon would raise the transition state energy by *ca.* 28 kcal./mole,[29] the driving force available to overlap control is large. As a consequence transition state IVb is preferred despite the unfavorable, but energetically less important, phenyl-phenyl interaction.

Further support for the concept of overlap control is available from the literature. For

(25) In proceeding from ground to transition state the total order of bonding to C^{14} very likely increases; this would suggest enhanced reactivity of the labeled phenylacetic acid compared to the unlabeled substance.

(26) The failure of the intermediate to revert to benzaldehyde and phenylacetic acid at a competitive rate is probably due to rapid acetylation of the β-hydroxyl group preventing ready reversal of the condensation step.

(27) It is possible that the reaction does not proceed through a discrete carbanion intermediate as III and that instead, loss of acetate anion is partially concerted with proton removal. In any event it is certain that the α-carbon atom is electron rich in the transition state IV, and the reaction may be termed carbanionoid.

(28) F. G. Bordwell and R. J. Kern, THIS JOURNAL, **77**, 1141 (1955).

(29) *Cf.* the *ca.* 28 kcal./mole decrease in free energy of ionization of acetone compared to methane.

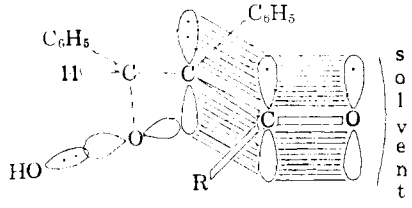
example, it is known that the base-catalyzed condensation reactions of benzaldehyde with phenylacetone,[1] with phenylacetaldehyde[1] and with desoxybenzoin[30] afford α-phenyl-*trans*-benzalacetone, α-phenyl-*trans*-cinnamaldehyde and α-phenyl-*trans*-benzalacetophenone, respectively, these being the products with the unhindered electron delocalizing groups.

A critical case is the condensation of benzaldehyde with phenylacetonitrile. Here the electron delocalizing group is the axially symmetric nitrile function which has no conformational requirement for overlap, and delocalization should not be diminished by proximity to a large group. Consequently, it would be predicted that overlap control would not be operative and that avoidance of phenyl–phenyl interaction would dominate. In agreement with these considerations it is known[31] that the product of this base-catalyzed condensation reaction is α-phenyl-*cis*-cinnamonitrile, the isomer having *trans*-phenyl groups.

A number of elimination reactions reported in the literature appear to be overlap controlled. For example, it has been reported by Stevens and Emmons[32] that base-catalyzed elimination of each of the diastereomeric 1,2-dinitro-1,2-diphenylethanes affords α-nitro-*cis*-stilbene as the major product.

Similarly, the potassium acetate-catalyzed elimination of the diastereomeric benzalacetophenone dibromides leads[33] preferentially to α-bromo-*trans*-benzalacetophenone; the reaction of the *threo*-dibromide was reported to lead exclusively to the *trans* product while from the *erythro*-dibromide the *trans* product, formed by a *cis*-elimination, predominated (2:1 ratio).[34]

In conclusion, it is of interest to contrast the present results with those observed in the alkaline hydrogen peroxide epoxidation reaction of ketones where overlap control has also been shown to be operative.[1] In the following series of delocalizing



V, preferred alkaline epoxidation transition state.

groups of decreasing size and decreasing susceptibility to inhibition of delocalization by steric interaction it is clear that at some given point for each reaction overlap control must cease to operate: $-COC_6H_5$, $-COCH_3$, -COOAc, $-NO_2$, -CHO, -CN. Interestingly, the point of discontinuity occurs between $-COCH_3$ and -CHO for the alkaline epoxidation reaction[1] while for β-elimination it has been seen to lie between -CHO and -CN. That overlap control extends to smaller delocalizing groups for β-elimination than for alkaline epoxidation is reasonable in view of the expected greater interaction of the delocalizing function with a large *cis* group in the planar elimination transition state as contrasted with the non-planar epoxidation transition state (V).

Experimental[35]

α-Phenyl-*cis*-cinnamic and α-phenyl-*trans*-cinnamic acids were prepared, following the procedure of Fieser,[34] from 25.0 g. of phenylacetic acid, 30.0 ml. of benzaldehyde, 20.0 ml. of triethylamine and 20.0 ml. of acetic anhydride. Using the method described by Fieser for separation of the isomers by acidification first with acetic acid and then with hydrochloric acid, there were obtained 31.1 g. of crude α-phenyl-*trans*-cinnamic acid and 4.55 g. of pure α-phenyl-*cis*-cinnamic acid, m.p. 138–139°. Recrystallization of the *trans*-acid brought the m.p. to 174°.

Thirty-five Minute Isomerization of α-Phenyl-*cis*-cinnamic Acid.—A solution of 250 mg. of α-phenyl-*cis*-cinnamic acid, in 2.0 ml. of acetic anhydride and 2.0 ml. of triethylamine was refluxed for 35 minutes, cooled and 3.0 ml. of concd. hydrochloric acid was added slowly with cooling and the solution was diluted with water. The ether extracts of this solution were extracted with 5% sodium carbonate. Acidification of the alkaline extract with hydrochloric acid to a congo red end-point followed by ether extraction, drying of the extracts over calcium chloride and concentration *in vacuo* afforded 233 mg. (90%) of crystalline material which was subjected to infrared analysis. This showed it to be 21% isomerized to a α-phenyl-*trans*-cinnamic acid.

Five and One-half Hour Isomerization of the α-Phenyl-*cis*-cinnamic Acid.—A solution of 481 mg. of α-phenyl-*cis*-cinnamic acid in 10.0 ml. of acetic anhydride and 5.0 ml. of triethylamine was refluxed for 5.5 hr. The mixture was then cooled in an ice-bath and 5.0 ml. of concentrated hydrochloric acid was added slowly with cooling, and the solution was diluted with water. The same isolation procedure described above for the 35-min. run was utilized, giving 459 mg. (96%) of solid which on infrared analysis was found to contain 77% α-phenyl-*trans*-cinnamic acid.

A second experiment run under exactly the same conditions gave material analyzing for 74% *trans* isomer.

Twenty-two Hour Isomerization of α-Phenyl-*cis*-cinnamic Acid.—A solution of 500 mg. of α-phenyl-*cis*-cinnamic acid in 5.0 ml. of acetic anhydride and 5.0 ml. of triethylamine was refluxed for 22 hr. The procedure described above for isolation of product from the shorter isomerizations was employed to yield 479 mg. (96%) of solid analyzing for 81% α-phenyl-*trans*-cinnamic acid.

Reaction of *threo*-3-Hydroxy-2,3-diphenylpropionic Acid Under Perkin Conditions.—A solution of 256 mg. of *threo*-3-hydroxy-2,3-diphenylpropionic acid, m.p. 176–177°,[14] in 2.0 ml. of acetic anhydride and 2.0 ml. of triethylamine was refluxed for 35 minutes. The product was isolated as described in the isomerization experiments above to afford 225 mg. (95%) of solid, m.p. 172–173°. Infrared analysis showed this to contain 99% α-phenyl-*trans*-cinnamic acid.

Reaction of *erythro*-3-Hydroxy-2,3-diphenylpropionic Acid under Perkin Conditions.—A solution of 253 mg. of *erythro*-3-hydroxy-2,3-diphenylpropionic acid in 2.0 ml. of acetic anhydride and 2.0 ml. of triethylamine was refluxed for 35 min. and the product was isolated in exactly the same way as in the case of *threo*-acid reaction. There was obtained 215 mg. (92%) of solid, m.p. 171–173°, which analyzed for 100% α-phenyl-*trans*-cinnamic acid.

Perkin Condensation of Benzaldehyde with Phenylacetic Acid under the Short and Mild Conditions Employed for Reaction of the β-Hydroxy acids.—A solution of 150 mg. of phenylacetic acid, 0.18 ml. of benzaldehyde, 2.0 ml. of acetic anhydride and 2.0 ml. of triethylamine was refluxed

(30) The base-catalyzed condensation of benzaldehyde with desoxybenzoin has been shown by E. Knoevenagel and R. Weissgerber, *Ber.*, **26**, 442 (1893), to give the 102° isomer of α-phenylchalcone. This is known from the work of W. B. Black and R. E. Lutz, THIS JOURNAL, **75**, 5990 (1953), to have *cis*-phenyl groups.

(31) P. Pfeiffer, I. Engelhardt and W. Alfuss, *Ann.*, **467**, 181 (1928).

(32) T. E. Stevens and W. D. Emmons, THIS JOURNAL, **80**, 338 (1958).

(33) R. E. Lutz, D. F. Hinkley and R. H. Jordan, *ibid.*, **73**, 4647 (1951).

(34) It seems likely that where the department group is the conjugate base of a strong acid, added driving force results from synchronization of the anion loss with proton removal. In the case considered here this tendency manifests itself in partial stereospecificity.

(35) All melting points were taken using a Hershberg apparatus whose thermometer had been checked with compounds of known melting point.

for 35 min. The reaction mixture was worked up in the manner used for the β-hydroxy acid reactions, yielding 115 mg. (83%) of solid analyzing for 96% α-phenyl-*trans*-cinnamic acid.

Reaction of *threo*-3-Hydroxy-2,3-diphenylpropionic Acid under Perkin Conditions in the Presence of *m*-Nitrobenzaldehyde.—A solution of 1.00 g. (4.15 mmoles) of *threo*-3-hydroxy-2,3-diphenylpropionic acid, 1.60 g. (10.6 mmoles) of *m*-nitrobenzaldehyde, 8.0 ml. of acetic anhydride and 8.0 ml. of triethylamine was refluxed for 35 min., cooled, acidified with 10.0 ml. of concd. hydrochloric acid and diluted with water. The mixture was then ether extracted. These extracts were themselves extracted with sodium carbonate solution and the resulting basic solution was acidified with concd. hydrochloric acid to a congo red end-point affording 1.3 g. of crystalline material, m.p. *ca.* 130°. This material was dissolved in chloroform and hexane was added slightly past the initial point of turbidity, causing 370 mg. of pale yellow *m*-nitrocinnamic acid to crystallize, m.p. 199–200°, neutralization equiv. 200 (reported[36] m.p. 199–200°, theoretical neut. equiv. 193).

Anal. Calcd. for C_9H_7N: C, 55.96; H, 3.65. Found: C, 56.98; H, 3.72.

The filtrate when concentrated yielded 893 mg. of crystalline material. This was dissolved in chloroform and an aliquot containing 180 mg. of this material was chromatographed on a silica gel column (18 × 500 mm., Davidson 60–200 mesh, slurry packed with 20% ether in hexane). Eleven fractions of 25 ml. each were obtained by elution with pure ether. The first nine fractions contained a total of 167 mg. of pure α-phenyl-*trans*-cinnamic acid, identified by its infrared spectrum and its 174–176° melting point. Then followed two fractions containing 10 mg. of crystals, m.p. 180–187°, whose infrared spectrum indicated it to be *m*-nitrocinnamic acid.

The original ether extract was concentrated *in vacuo* to yield 1.2 g. of *m*-nitrobenzaldehyde.

Isolation of α-phenyl *trans*-cinnamic acid was 89% of theoretical; recovery of *m*-nitrobenzaldehyde, 75%; *m*-nitrobenzaldehyde incorporated in isolated *m*-nitrocinnamic acid, 23%.

Reaction of *erythro*-3-Hydroxy-2,3-diphenylpropionic Acid under Perkin Conditions in the Presence of *m*-Nitrobenzaldehyde.—A solution of 250 mg. (1.04 mmoles) of *erythro*-3-hydroxy-2,3-diphenylpropionic acid, 400 mg. (2.65 mmoles) of *m*-nitrobenzaldehyde, 2.0 ml. of triethylamine and 2.0 ml. of acetic anhydride was refluxed for 35 minutes and treated with 3.0 ml. of concd. hydrochloric acid and diluted with water. The mixture was then worked up as in the reaction of the *threo*-acid. The yield of crude acidic material was 231 mg. One crystallization from chloroform containing a small amount of hexane afforded 110 mg. of *m*-nitrocinnamic acid, m.p. 198–200°.

The filtrate was chromatographed on a silica gel column (18 × 500 mm. slurry packed with 20% ether in hexane); 25-ml. fractions were obtained by elution with 20% ether in hexane. The first eight fractions were void. The next eleven fractions contained a total of 174 mg. of pure α-phenyl-*trans*-cinnamic acid, m.p. 173–175°. Then followed ten fractions containing 40 mg. of material, m.p. 165–175°, whose infrared spectrum was that of α-phenyl-*trans*-cinnamic acid. After one empty fraction there followed two fractions containing 17 mg. of material, m.p. 155–165°, apparently impure *m*-nitrocinnamic acid. Finally seven fractions were collected containing 67 mg. of *m*-nitrocinnamic acid, m.p. 196–200°.

The neutral fraction afforded 266 mg. of *m*-nitrobenzaldehyde.

Isolation of α-phenyl-*trans*-cinnamic acid was 96% of theoretical; recovery of *m*-nitrobenzaldehyde, 66.5%; *m*-nitrobenzaldehyde incorporated in isolated *m*-nitrocinnamic acid, 28.5%.

Phenylacetic acid-carboxyl-C^{14} was prepared according to the procedure of Dauben, *et al.*,[37] using 2.60 g. (0.11 mole) of magnesium and 12.7 g. (0.10 mole) of benzyl chloride in 100 ml. of dry ether, 3.6 mg. (0.13 millicurie) of radioactive barium carbonate together with 3.00 g. (28.2 mmoles) of sodium carbonate. The carbon dioxide was generated by treatment of the mixed carbonate with 30 ml. of concd. sulfuric acid using the apparatus and procedure of Shaw,[38] There was obtained 2.31 g. (61%) of phenylacetic acid, m.p. 73–74°. This showed an activity of 1.51 × 10^6 counts/min.-millimole.

(36) "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., p. 390.

(37) W. G. Dauben, J. C. Reid, P. E. Yankwich and M. Calvin, THIS JOURNAL, 72, 121 (1950).

TABLE III

KNOWN MIXTURES OF THE α-PHENYLCINNAMIC ACIDS

Actual % *trans*-isomer	*D'*	*D''*	*Q*	Actual R	Calcd. F	Calcd. R	Calcd. % *trans*-isomer
100.0	0.347	0.143	...	...	...	...	..
70.2	.342	.252	2.60	2.35	0.970	2.48	71.2
49.2	.305	.301	0.970	0.967	.993	0.926	48.0
27.2	.174	.301	0.433	0.374	.900	0.413	29.2
0.0	.080	.337	...	...	...	...	..

TABLE IV

UNKNOWN MIXTURES

Mixtures analyzed	*D'*	*D''*	*Q*	*R*	% *trans*
35 min. isomerization	0.120	0.252	0.289	0.275	21
5.5 hr. isomerization I	.432	.288	3.54	3.38	77
5.5 hr. isomerization II	.328	.221	3.02	2.28	74
22 hr. isomerization	.328	.197	4.45	4.25	81
35 min. Perkin reaction	.415	.187	22.3	21.3	96
threo-elimination	.256	.108	70.5	67.2	99
erythro-elimination	.319	.131	infin.	infin.	100

Reaction of *threo*-3-Hydroxy-2,3-diphenylpropionic Acid under Perkin Conditions in the Presence of Phenylacetic Acid-carboxyl-C^{14}.—A solution of 250 mg. (1.03 mmoles) of *threo*-3-hydroxy-2,3-diphenylpropionic acid, 170 mg. (1.16 mmoles) of phenylacetic acid-carboxyl-C^{14}, 2.0 ml. of acetic anhydride and 2.0 ml. of triethylamine was refluxed for 35 minutes. The cooled reaction mixture was treated with 3.0 ml. of concd. hydrochloric acid and then diluted with water and ether extracted. The ether extracts were themselves extracted with 5% aqueous sodium carbonate; the alkaline extracts were then acidified with acetic acid affording by filtration 215 mg. of α-phenyl-*trans*-cinnamic acid, m.p. 172–173°. An activity of only 45 counts/min. was obtained using 20.0 ml. of scintillation solution and 2.00 ml. of a solution prepared by dissolving 33.4 mg. of the acid in 50.0 ml. of toluene. The background count was also 45 counts/min.

The aqueous filtrate was acidified with hydrochloric acid to a congo red end-point. The solution was then ether extracted, the extracts dried over sodium sulfate and concentrated *in vacuo* to yield 100 mg. of a low melting solid which was crystallized from hexane to give 45 mg. of phenylacetic acid crystals, m.p. 70–72°. An activity of 1.43 counts/min.-millimole was observed. This was obtained by mixing 20.0 ml. of scintillation solution with 2.00 ml. of solution prepared by dissolving 10.1 mg. of the acid in 25.0 ml. of toluene.

Measurement of Activity.—A Packard Tricarb Liquid Scintillation Spectrometer model 314 was utilized using the extra digit scale. The samples were kept in 22-ml. vials and stored in the freezer for 30 min. before counting. All counts are averages of three runs and were taken on the same day. The scintillation solution was prepared by dissolving 3.0 g. of 2,5-diphenyloxazole and 100 mg. of 1,4-di-2-(5'-phenyloxazolyl)-benzene in 1000 ml. of toluene.

Infrared Analyses.—The method used was that described earlier.[17] All samples were prepared by dissolving 13.0–14.0 mg. of sample in 0.45 ml. of CS_2; 0.10-mm. sodium chloride cells were used. Calibration data are recorded in Table II. The optical density of all mixtures was taken as zero at 2.0 μ.

Here *D'* and *D''* are the optical densities at 14.21 and 14.42 microns, respectively; *F* is defined by $R = Q \cdot F$ where $Q = (D''_m D'_c - D'_m D''_c)/(D'_m D''_t - D''_m D'_t)$. Here the subscripts c, t and m refer to pure *cis*-isomer and a given mixture, respectively; *R* is the ratio of *trans* to *cis* isomer in a mixture. The average value of $F = 0.954$ was used in calculating the results in the last two column of Table III and the composition of unknown mixtures.

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EVANSTON, ILL.

(38) A. W. Shaw, Ph.D. Thesis, Northwestern University, 1956, pp. 74–77.