at 1661, 820, and 710 cm.$^{-1}$, with no absorption in the 965–990-cm.$^{-1}$ region.

Anal. Calcd. for $C_{17}H_{17}NO$: C, 81.3; H, 6.8; N, 5.6. Found: C, 81.1; H, 7.2; N, 5.5.

The oxime was prepared in the conventional manner and had m.p. 186.5–188°.

Anal. Calcd. for $C_{17}H_{18}N_2O$: C, 76.7; H, 6.8; N, 10.5. Found: C, 77.1; H, 6.7; N, 10.7.

4-Dimethylamino-3-formyl-α-phenylcinnamaldehyde (3).—4-Dimethylaminostilbene (22.3 g., 0.100 mole) was added, with stirring, to the complex prepared from phosphorus oxychloride (61.2 g., 0.400 mole) and 200 ml. of dimethylformamide. A dark, clear solution resulted. The reaction mixture was heated at 70° for 16 hr., then decomposed by the cautious addition of 600 ml. of 10% sodium hydroxide solution. The solid was collected on a funnel, slurried with 200 ml. of water, and air dried to give 16.8 g. (60%) of yellow product, m.p. 103.5–105.5°. Recrystallization from methanol–water gave 12.2 g. of yellow crystals of dialdehyde, m.p. 106.5–108.5°. A second recrystallization from methanol–water raised the melting point to 108–109.5°. Pertinent infrared bands were observed at 1664 (shoulder at 1695), 820 (m), 810 (m), 715, and 700 cm.$^{-1}$ (m). There was no absorption in the region 965–990 cm.$^{-1}$ but there was a medium-weak band at 960 resulting from 1,2,4 aromatic substitution.[9]

Anal. Calcd. for $C_{18}H_{17}NO_2$: C, 77.4; H, 6.1; N, 5.0. Found: C, 77.2; H, 6.0; N, 5.1.

The dioxime was prepared in the conventional manner and had m.p. 191–193°.

Anal. Calcd. for $C_{18}H_{19}N_3O_2$: C, 69.9; H, 6.15; N, 13.6. Found: C, 69.8; H, 5.8; N, 13.5.

Proof of Structure of 4-Dimethylamino-α-phenylcinnamaldehyde (2).—4-Dimethylamino-α-phenylcinnamaldehyde (1) was converted to 4-dimethylamino-α-phenylcinnamonitrile (4) following the procedure of Smith and Walker.[3] The 4-dimethylamino-α-phenylcinnamonitrile consisted of yellow plates having a melting point of 134.5–135.5°. The infrared spectrum of this material and that of the same compound prepared according to Kauffmann[4] by the condensation of phenylacetonitrile with *p*-dimethylaminobenzaldehyde were superimposable. The mixture melting point of the two samples was not depressed on admixture.

4-Dimethylamino-α-(4-nitrophenyl)cinnamaldehyde (5).—4-Dimethylamino-4′-nitrostilbene (5.0 g., 18.7 mmoles) was formylated by essentially the same procedure used to prepare **2**, but with 2 equiv. of the complex prepared from phosphorus oxychloride and dimethylformamide and heating the reaction mixture at 70° for 4.5 hr. Decomposition of the reaction mixture, followed by recrystallization of the crude product from methanol, gave 1.4 g. (25%) of tiny, brick red needles having a melting point of 148–152°. A second recrystallization from methanol raised the melting point to 155–156.5°. Pertinent infrared bands were observed at 1670, 825, and 720 cm.$^{-1}$. There was no absorption in the region 965–990 cm.$^{-1}$.

Anal. Calcd. for $C_{17}H_{16}N_2O_3$: C, 68.9; H, 5.4; N, 9.45. Found: C, 68.7; H, 5.4; N, 9.3.

4,6-Dimethoxy-3-stilbenecarboxaldehyde (8).—2,4-Dimethoxystilbene (12.0 g., 50.0 mmoles) was formylated by essentially the same procedure used to prepare **2**, but with 2 equiv. of the complex prepared from phosphorus oxychloride and dimethylformamide and heating the reaction mixture at 70° for 17.5 hr. Decomposition of the reaction mixture, followed by recrystallization of the crude product from methanol, gave 5.2 g. (39%) of tiny yellow prisms, m.p. 122–124.5°. Recrystallization from ethanol gave tiny, pale yellow needles, having m.p. 123–125°. Pertinent infrared bands were observed at 1680, 966 (m), 815, 755, and 695 cm.$^{-1}$.

Anal. Calcd. for $C_{17}H_{16}O_3$: C, 76.1; H, 6.0. Found: C, 76.2; H, 6.0.

Acknowledgment.—The author wishes to express his gratitude to Dr. T. H. Regan and Mr. D. P. Maier, of the Analytical Chemistry Department, for the n.m.r. and mass spectral work.

(9) See ref. 2, p. 82.

Solvent Significance in the Mechanism of Direct Acylation. Reactions in Cyclic Ethers[1]

EDWARD RONWIN AND DAVID E. HORN[2]

Department of Chemistry, Villanova University, Villanova, Pennsylvania

Received January 23, 1965

The mechanism of direct acylation in anhydrous *p*-dioxane was studied, using L-leucine and dichloroacetyl chloride as the model system, and comparisons are drawn with earlier work in ethyl acetate. Because of its influence on kinetic interpretation, the solubility of L-leucine was investigated in several solvents. The effects of a number of parameters on either the reaction rate or the solubility of the amino acid in the organic solvent were determined. The kinetic data for the reaction in *p*-dioxane fit the same differential equation developed earlier for the ethyl acetate system, which accords with the apparent over-all similarity of the reaction in the two different solvent types. However, the specific reaction intermediates that can be reasonably suggested for both systems are at considerable variance with each other. Several amino acids not previously acylated by this procedure were converted to products and the number of solvents allowing this over-all reaction type has been increased.

In the initial investigation of the mechanism of direct acylation[3] the kinetics in dry ethyl acetate for the reaction between L-leucine and dichloroacetyl chloride were shown to fit closely to a differential equation which was developed from theoretical considerations. Because of its pertinence to the kinetic study, the solubility of L-leucine in the solvent under various conditions was investigated and the reaction was observed to proceed in other ester acetates. This initial study permitted the suggestion of a proposed reaction intermediate, which is essentially an anhydride type formed between the original acyl chloride and the enol form of the acetate ester. The present work was undertaken to investigate other potential solvents, to compare such reactions with the acetate (ethyl) system and to explore further aspects of the mechanism and nature of this heterogeneous reaction in which the rate of dissolution of the suspended, crystalline reactant (the amino acid or related compound) is rate controlling. *p*-Dioxane was one of the several "new" solvents found

(1) Presented in part before the Division of Biological Chemistry at the 148th National Meeting of the American Chemical Society, Chicago, Ill., Sept. 1964.

(2) Excerpted from the thesis submitted by D. E. H. in partial fulfillment of the requirements for the degree of Master of Science.

(3) (a) E. Ronwin and C. B. Warren, *J. Org. Chem.*, **29**, 2276 (1964). (b) In the derivation of this equation, the surface area, S, appears in the intercept because the generally accepted equilibrium situation between a solid dissolving in a liquid and the reverse crystallization process is given by (using the symbols applicable to this case) $k_4S = k_5[L_s]S$ and *not* by $k_4S = k_5[L_s]$. See G. H. Nancollas and N. Purdie, *Quart. Rev.* (London), **18**, No. 1, 13 (1964).

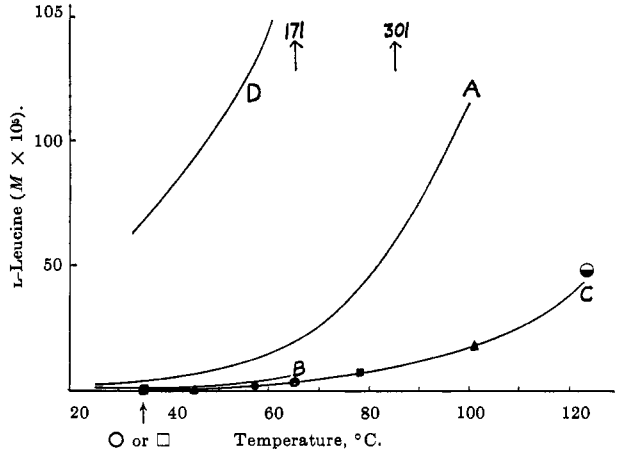


Figure 1.—Comparative solubility of L-leucine in various organic solvents as a function of temperature: A, *p*-dioxane; B, tetrahydrofuran (curves end at boiling points under atmospheric pressure); C, esters; O, starting temperature for solubility determination in methyl acetate; □, in ethyl acetate; △, in *n*-propyl acetate; ◓, in *n*-butyl acetate. Acetate boiling points at atmospheric pressure: ●, methyl; ■, ethyl; ▲, *n*-propyl; ◒, *n*-butyl; D, hydrochloride salt of L-leucine in *p*-dioxane. The number above the arrow point is the value of the solubility of the hydrochloride salt of L-leucine in *p*-dioxane at the temperature to which the shaft of the arrow points.

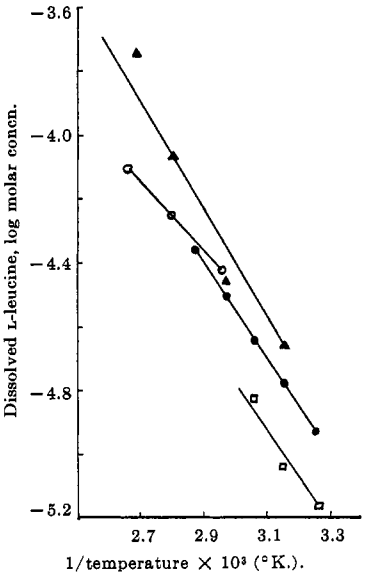


Figure 2.—Determination of the heats of solution of L-leucine in acetate esters: □, methyl acetate; ●, ethyl acetate; ▲, *n*-propyl acetate; O, *n*-butyl acetate.

to allow reaction. This work deals essentially with the results obtained in *p*-dioxane and their comparison to the ethyl acetate system.

Experimental

Materials.—Recrystallized, thoroughly dried, and pulverized (Waring Blendor) L-leucine powder was forced through sieves of proper mesh to yield 250-, 297-, and 500-μ average particle size preparations.

Dichloroacetyl chloride, Eastman reagent grade, was distilled under nitrogen before use, b.p. 40–41° (30 mm.).

Solvents were purchased as anhydrous grades and distilled at atmospheric pressure. They were dried over molecular sieves and the water content was determined by the Karl Fischer method. Water contents were often reduced to lows in the vicinity of 0.005%.

Kinetic Reaction Procedure.—Except that dry *p*-dioxane was employed, the performance of kinetic runs was done using apparatus and procedure identical with those which have been described in detail.[3]

Solubility Determinations.—The solubility of L-leucine in the various acetates and in tetrahydrofuran was performed as previously described.[3] However, as the solubility of L-leucine and its hydrochloride in *p*-dioxane is considerably higher, no prior reduction of the solution volume was required and suitable aliquots were removed from the solution as such for analysis by the ninhydrin method.

Some Standard Conditions.—All kinetic reactions, solubility determinations, and synthetic runs were made using 50 ml. as the initial volume of the anhydrous solvent. *Unless otherwise stated,* the following conditions applied. Solvent water contents were methyl acetate, 0.003%; ethyl acetate, 0.005–0.007%; *n*-propyl acetate, 0.008%; *n*-butyl acetate, 0.007%; *p*-dioxane, 0.004%; and tetrahydrofuran, 0.004%. Amounts of initially suspended L-leucine were 0.656 g. This quantity is equivalent to a concentration of 0.1 *M* in the 50 ml. of solvent were it the case that all the amino acid could dissolve. In all other cases, the amount of initially suspended L-leucine was 0.164 g., which, as above, is equivalent to a concentration of 0.025 *M* and will be noted in parentheses following the statement of the gram weight. Average particle size of suspended amino acid was 250 μ.

Results and Discussion

Comparison of L-Leucine Solubility in Acetate Esters, *p*-Dioxane, and Tetrahydrofuran.—The solubility of L-leucine was determined in the acetates of methanol, ethanol, 1-propanol, and 1-butanol, as well as in *p*-dioxane and tetrahydrofuran, both for comparative purposes and as a result of the influence of solubility on the kinetic interpretation. The data are presented in Figure 1. At the lower temperatures (35–55°), the solubility of the amino acid appears to be essentially identical in all four acetates and a smooth curve can be drawn for the entire temperature range covering the acetates. It appears as if the solubility of the amino acid is indifferent to the exact identity of the acetate so that were the boiling point of ethyl acetate at atmospheric pressure above 77° then the solubility of the L-leucine in it would be expected to reach a higher maximum along the curve. We may infer from this result that the solubility of the amino acid is a function of a common property of grouping, which points to at least the ester group or possibly to the entire acetate function as responsible for inducing the amino acid solubility.

By comparison the solubility of L-leucine is much greater in *p*-dioxane than in any of the acetates. On the other hand, the amino acid is only slightly more soluble in tetrahydrofuran than in the acetates.

In the form of the hydrochloride salt, L-leucine is extremely soluble in *p*-dioxane compared with the free base form.

An Arrhenius plot of the data for variation in solubility of L-leucine with temperature in the various acetates (Figure 2) heightens the suspicion of a common influence in the process. Thus, the slopes of the methyl, ethyl, and *n*-propyl acetates are virtually identical and that for *n*-butyl acetate varies slightly. The average value for the heats of solution is 6.3 kcal./mole.

Analogous plots for the cases of *p*-dioxane and tetrahydrofuran yield values of 11.5 and 9.8 kcal./mole, respectively. These results also point to a similar group influence in the amino acid solubilizing process with these solvents and to one which is different

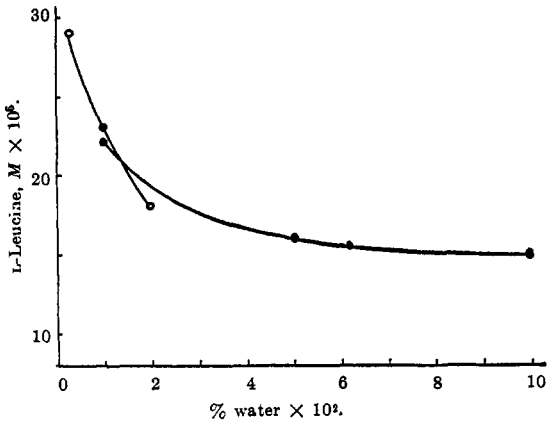


Figure 3.—Effect of water content on L-leucine solubility in ethyl acetate at 65°. Data are for two separate runs.

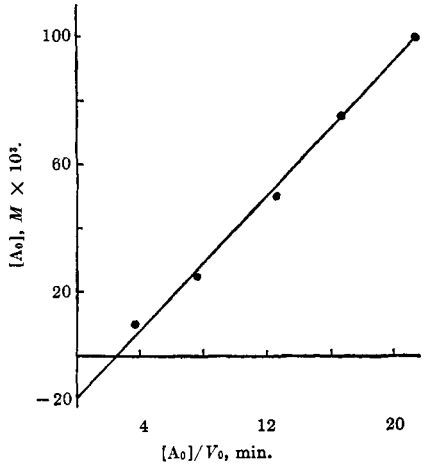


Figure 4.—Plot of the initial concentration of dichloroacetyl chloride *vs.* the initial concentration of dichloroacetyl chloride/initial rate of reaction run at 25° in *p*-dioxane saturated with L-leucine; amount of L-leucine initially suspended was 0.164 g. (0.025 *M*).

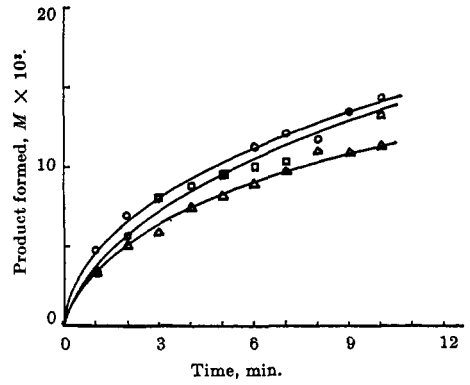


Figure 5.—Influence of particle size of the suspended L-leucine on reaction rate in *p*-dioxane at 25°: amount of L-leucine initially suspended, 0.164 g. (0.025 *M*); concentration of initial dichloroacetyl chloride, 0.050 *M*. Average particle size of L-leucine: O, 250 μ; □, 297 μ; and △, 590 μ.

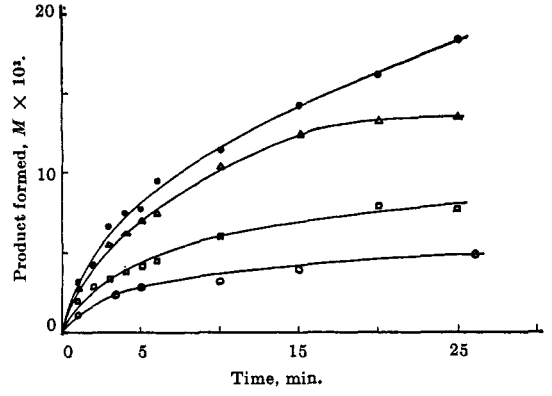


Figure 6.—Effect of variation in water content of *p*-dioxane on reaction rate at 25°: per cent water content: ●, 0.0013; △, 0.038; □, 0.075; O, 0.176. Amount of L-leucine initially suspended, 0.164 g. (0.025 *M*); initial concentration of dichloroacetyl chloride, 0.050 *M*.

from the influence operating in the acetates. It is likely that the common influence is the cyclic ether structure.

The effect of the water content of ethyl acetate on L-leucine solubility was investigated. The results of two separate runs are given in Figure 3. It is obvious that the solubility of the amino acid *decreases* as the water content of the solvent increases. This seemingly unusual result is in agreement with earlier work.[3] No immediate explanation is apparent. However, the effect is certainly real as the magnitude of the decreases observed is well above the error of measurement. Increasing the water content some tenfold decreases the solubility by approximately one-half.

Kinetic Studies.—Analysis of the ethyl acetate system led to the expression[3]

$$S \underset{k_5}{\overset{k_4}{\rightleftharpoons}} [L_s] + [A] \xrightarrow{k_1} [p]$$

where S = suspended L-leucine (a surface area); $[L_s]$ = dissolved L-leucine; [A] = acid chloride; $[p]$ = products, from which, assuming that the rate of reaction is controlled by the rate of solution of the amino acid, eq. 1 is derived.[3a] Plots of the initial acid chloride concentration, [A], *vs.* the initial acid chloride concentration divided by the initial rate of reaction, [A]/v, in ethyl acetate yielded straight lines[3] in agreement with eq. 1.

$$[A] = k_4 S[A]/v - k_5 S/k_1 \quad (1)$$

In this study, the same analysis was applied to the reaction in *p*-dioxane (between dichloroacetyl chloride and L-leucine) and the data was plotted according to eq. 1. A representative, least-squares curve is presented in Figure 4. Obviously, eq. 1 is also obeyed in the *p*-dioxane system which permits the tentative inference that the basic mechanisms of the reaction in the acetate system and in the cyclic ethers are quite similar.

Effect of Various Parameters on the Reaction Rate.—From the results given in Figure 5, it is apparent that a variation in particle size of the suspended L-leucine over the range 250–590 μ has little influence on the reaction rate. This observation supports the notion that such reaction as occurs does so essentially between truly dissolved components only.

On the other hand a variation in the water content of the solvent over a roughly 100-fold range is seen to have a marked effect on reaction rate (Figure 6). At the higher water content, the rate is initially about one-fourth that at the lower water content. This result probably reflects a competition between amino acid and water molecules for the acid chloride or the acid chloride–solvent reaction intermediate.

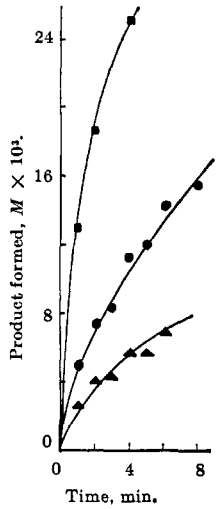


Figure 7.—Effect of solvent on the reaction rate at 45°: ■, *p*-dioxane; ▲, ethyl acetate; ●, ethyl acetate–*p*-dioxane (1:1). Amount of L-leucine initially suspended, 0.164 g. (0.025 *M*); initial concentration of dichloroacetyl chloride, 0.050 *M*.

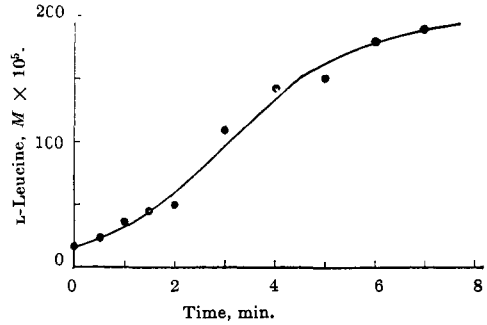
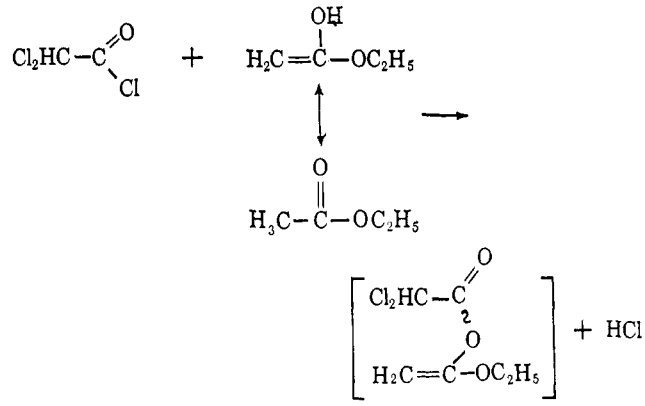


Figure 8.—Solubility of L-leucne during the course of a reaction at 65° in *p*-dioxane. Initial concentration of dichloroacetyl chloride, 0.100 *M*.

A graphic display of the effect of solvent variation on the reaction rate is presented in Figure 7. Most striking is the roughly tenfold greater initial reaction rate in *p*-dioxane compared to that in ethyl acetate. Interesting, too, is the moderating effect observed when *p*-dioxane is diluted with ethyl acetate. The greater rate for the reaction in *p*-dioxane may be due to the significantly higher saturation solubility of the amino acid in *p*-dioxane (Figure 1), which, however, is only a factor of 3, or to the nature of the solvent–acid chloride intermediate formed as discussed in the next section.

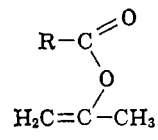
The amount of L-leucine in solution during a reaction in *p*-dioxane (as determined by ninhydrin on unhydrolyzed samples of reaction media) is graphed in Figure 8. The amount of amino acid starts at its normal solubility at 65° but soon follows an upward curve which rapidly approaches a maximum that is well above its saturation solubility within 7 to 8 min. of reaction. The amount present at the 8-min. point is equivalent to roughly 2% of the initial total suspended L-leucine (approximately 18 × 10^{-4} mole dissolved) and is approximately ten times greater than the normal solubility of the amino acid at this temperature (Figure 1). Earlier work demonstrated that, during the reaction, HCl gas is released which converts part or all of the remaining suspended amino acid to its hydrochloride salt.[3] Since the solubility of the hydrochloride salt in *p*-dioxane at 65° is 17.1 × 10^{-4} moles/l. (Figure 1), an explanation for the curve resides in the notion that, as reaction proceeds, the newly formed hydrochloride salt pulls more L-leucine into solution. However, the ninhydrin reaction will not distinguish between the free amino acid and its hydrochloride; thus, it appears at first sight that an increased L-leucine solubility above its normal maximum in the solvent is being observed.

Suggested Reaction Intermediate in *p*-Dioxane. Comparison with the Acetates.—In the previous paper[3] (and reproduced here for comparison) a reactive acid–anhydride-type intermediate, formed between the acid chloride and the solvent, was suggested as the actual acylating agent in ethyl acetate (and, presumably, too, in the other acetate esters in which the reaction proceeds).



This suggestion was invoked to account for the immediate conversion of the suspended amino acid to its hydrochloride salt and therefore for the rapid formation of HCl under conditions wherein insufficient water was present to bring about any significant formation of HCl through hydrolysis of the acid chloride. It also explained the observation that free acid corresponding to the acid chloride did not react in the solvent with the amino acid hydrochloride salt, but hydrochloride salt of the amino acid and acid chloride did permit reaction. In further support, analogy between the intermediate, in brackets above, and the structure of phospho enol pyruvate was drawn.[3]

Additional evidence in support of the above suggested intermediate for acetate ester solvents comes from the work of Rothman *et al.*,[4,5] who synthesized various isopropenyl esters of fatty acids and demonstrated their utility as acylating agents. These compounds have the general structure



which is obviously analogous to the above-suggested intermediate.

Further, if the suggested intermediate is correct, then any liquid capable of yielding a reactive hydrogen atom, such as an enolate hydrogen, and also capable of reacting through the reactive hydrogen to give rise

(4) E. S. Rothman, S. Serota, T. Perlstein, and D. Swern, *J. Org. Chem.*, **27**, 3123 (1962).
(5) E. S. Rothman, S. Serota, and D. Swern, *ibid.*, **29**, 646 (1964).

TABLE I

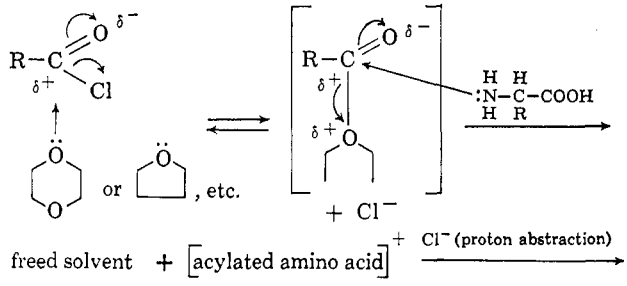
SUCCESSFUL DIRECT ACYLATIONS IN *p*-DIOXANE OF PREVIOUSLY RESISTANT OR UNTRIED AMINO ACIDS

Compound	M.p., °C. Obsd.	M.p., °C. Lit.	Nitrogen, % Found	Nitrogen, % Calcd.	Reaction temp., °C.	Reaction time, hr.	Yield, %	Recrystn. solvent
N-Benzoyl-DL-serine	165	159, 171[a]	6.5	6.7	101	1	12	Acetone–CCl_4
N-Chloroacetyl-β-alanine	95	95[b]	8.6	8.5	35	3	27	Acetone–hexane
N-Chloroacety-*p*-aminobenzoic acid	259	250–252[c]	6.3	6.5	50	0.25	59	Dil. NaOH and HCl

[a] Sorensen and Andersen, *Z. physiol. Chem.*, **56**, II, 297 (1908). [b] H. T. Hanson and E. L. Smith, *J. Biol. Chem.*, **175**, 833 (1948). [c] T. Ueda and S. Kato, Japanese Patent 10,972 (1961); *Chem. Abstr.*, **56**, 4683*b* (1962).

to an anhydride type, should likely prove to be a solvent for the reaction. Since ethyl acetoacetate exists approximately 8% in the enol form at room temperature, it was tried as a solvent medium and found to permit reaction. As it might be argued that the ester function in this compound, as well as in the acetate esters, is the responsible element fostering reaction, 2,4-pentanedione, which lacks an ester function but exists approximately 80% in the enol form at room temperature, was also employed as a solvent. The reaction proceeds smoothly in 2,4-pentanedione which could permit the formation of an analogous anhydride intermediate type.

An identical reaction intermediate in the cyclic ethers is difficult to imagine; however, a reasonable suggestion for a reactive intermediate and for subsequent reaction to products and freed solvent is the following. This



intermediate would be quite analogous to a pyridinium-type salt and would be expected to be an effective acylating agent for two reasons: (1) the somewhat positive nature of both the ether oxygen atom and the carbonyl carbon yields a dipositive-bond situation[6] and makes for a weakened bond; and (2) the intermediate carries an over-all positive charge which would attract nucleophilic agents such as the amino nitrogen shown in the above diagram. This probably accounts for the considerably higher initial rate in *p*-dioxane as compared to that in ethyl acetate, Figure 7 (the reaction rate is ten times greater in dioxane while the leucine solubility is only three times greater), since the intermediate proposed for the enolate solvents is uncharged. Also, the number of particles formed at each proposed step in the reaction for both solvent types is identical and accounts in part for the observed identical kinetic behavior, albeit with specific rate differences.

It is likely that other cyclic ethers than the two tried here will permit reaction as possibly cyclic thioethers and analogous compounds.

Molecular Weight Studies.—Ronwin and Warren[3] reported that the apparent molecular weights of dichloroacetyl chloride and benzoyl chloride in ethyl acetate, determined by the boiling point elevation, were approximately one-half the actual molecular weights of these compounds. Therefore, molecular weight determinations on these compounds, as well as on the corresponding free acids, were done in *p*-dioxane. The molecular weights observed in *p*-dioxane agreed with the actual values in each case. Since this result was at variance with the above-mentioned report on the acid chlorides in ethyl acetate, a recheck of the molecular weights of the acid chlorides in ethyl acetate was performed. Contrary to the earlier report, the acid chlorides yield observed values in ethyl acetate in agreement with actual values. As the primary data for the studies in ethyl acetate in this and in the earlier work corresponded, a check of the computations in both studies was made which revealed a simple, arithmetical error in the calculation of the molal boiling point constant in the earlier work. Therefore, the earlier, unfortunately erroneous, report is hereby withdrawn.

Since the above-proposed mechanisms both require reaction between acid chloride and solvent in such manner as to lead to two particles as product (the intermediate and either Cl^- or HCl), the over-all change in particles in the solution is zero. Hence, the molecular weights of the acid chlorides in the solvent which should be observed are the actual molecular weights. As this is the case for both *p*-dioxane and ethyl acetate, the results are in agreement with the proposed mechanisms in each solvent type.

Synthetic Efforts.—In the original work on direct acylation[7,8] several amino acids were found resistant to acylation by the direct method using ethyl acetate as the solvent. These amino acids, along with some others not previously tested, were subjected to direct acylation using *p*-dioxane as solvent. The following common amino acids could still not be acylated: L-arginine, L-asparagine, L-cysteine (free base and as hydrochloride salt), L-cystine, L-threonine, L-lysine, sarcosine, L-histidine, and DL-tryptophan. However, β-alanine, *p*-aminobenzoic acid, and DL-serine were successfully acylated in *p*-dioxane. Table I contains the results. Contrary to the usual situation, the N-chloroacetyl-*p*-aminobenzoic acid was insoluble in the medium, whereas both reactants were quite soluble.

L-Glutamic acid, which did not yield a satisfactory product in monochloroacetylation attempts, was easily *p*-toluenesulfonylated in *p*-dioxane at room temperature. The reaction medium was magnetically stirred for 1 hr. A 29% yield of the product, m.p. 158–161° (lit.[9] m.p. 131°), was obtained. Washing with acetone then with water, followed by drying at 120°

(6) E. Ronwin, *Enzymologia*, **16**, 81, 179 (1953).

(7) E. Ronwin, *J. Org. Chem.*, **18**, 127 (1953).

(8) E. Ronwin, *ibid.*, **18**, 1546 (1953).

(9) C. R. Harington and R. C. G. Moggridge, *J. Chem. Soc.*, 706 (1940).

in an oven, was sufficient to produce a pure product.

Anal. Calcd.: N, 4.6; neut. equiv., 151. Found: N, 4.4; neut. equiv., 151.

As check on the synthetic utility of the various "new" solvents mentioned above, a preparation of dichloroacetyl-L-leucine was made in each. The yield in *p*-dioxane was 73%, 56% in anhydrous tetrahydrofuran, 40% in acetoacetic ester, and 33% in 2,4-pentandione. In each case the product was identified by its melting point, 120–122°,[8] and reactions were conducted at room temperature. As judged by the complete solution of the amino acid, reaction in tetrahydrofuran was over in just 10 min. and within 0.5 hr. in the other solvents. Removal of the solvent left a yellow oil which was induced to crystallize by the addition of benzene aided by deep-freeze temperatures. Pure product was then obtained merely by washing the crystals with benzene. However, removal of tetrahydrofuran yielded crystals immediately; these were recrystallized from acetone–heptane.

Notes

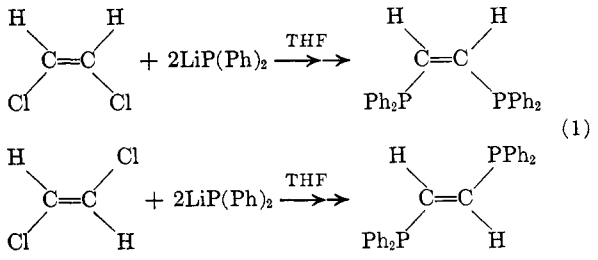
Vinylic Halide Displacement by Metallo Organophosphides. Preparation of *trans*-β-Styryldiphenylphosphine Oxide and Sulfide

ADAM M. AGUIAR AND DONALD DAIGLE

Newcomb College, Department of Chemistry, Tulane University, New Orleans, Louisiana 70118

Received November 23, 1964

The stereospecific substitution of the vinyl halides in *cis*- and *trans*-1,2-dichloroethenes by diphenylphosphorus employing lithium diphenylphosphide was reported recently (eq. 1).[1] Although these results remove an elimination–addition sequence from consideration as a mechanistic explanation, little else can be concluded about the path of reaction.



(1)

In order to obtain more information on the stereospecific replacement of vinylic halogen by diphenylphosphorus we have examined the reaction of β-bromostyrene with lithium diphenylphosphide in tetrahydrofuran (THF).

Commercially obtained (Eastman) β-bromostyrene has been shown to consist of at least 90% *trans* isomer.[2] Using gas chromatography, infrared, and n.m.r. spectroscopy we have obtained similar results with the Eastman sample of β-bromostyrene used in this work.[2-4] Seyferth has shown that isomerization of either isomer does not occur to any appreciable extent at 140–160° on a cyanoethylsilicone column.[2] Grovenstein has demonstrated that the *trans* isomer is not changed after 4 hr. at 115° nor upon moderate exposure to diffuse daylight or artificial illumination.[3] Cristol has shown that *cis*-β-bromostyrene can be prepared in refluxing acetone containing sodium bicarbonate.[5] The equilibrium ratio is known to be *ca.* 90% *trans* and 10% *cis*.[6]

No noticeable change of isomer ratio occurred after refluxing in tetrahydrofuran containing lithium halide salts. It can reasonably be assumed that the β-bromostyrene used in this work consisted of at least 90% *trans* isomer and that little or no isomerization occurred prior to reaction with lithium diphenylphosphide in tetrahydrofuran. Following rapid exothermic reaction of these reagents and oxidation using 1% hydrogen peroxide, *trans*-β-styryldiphenylphosphine oxide (I) was isolated as the major component. The structure of I was established by chemical analysis, infrared and p.m.r. spectra, hydrogenation to β-phenylethyldiphenylphosphine oxide (II, prepared unequivocally from β-chloroethylbenzene and lithium diphenylphosphide), and synthesis from 2-bromo-2-phenylethyldiphenylphosphine oxide (III, prepared from II and N-bromosuccinimide, eq. 2). Aside from the expected bands for a vinylphenylphosphine oxide, the infrared spectrum of a potassium bromide pellet of I also exhibited bands at 10.0 (m) and 10.1 (m) μ which are indicative of a *trans* structure. Bromination of II to III rather than to 1-bromo-β-phenylethyldiphenylphosphine oxide is expected by the general theory of allylic halogenation[7] and supported by the fact that identical conditions failed to brominate ethylenebis(diphenyl-

(1) A. M. Aguiar and D. Daigle, *J. Am. Chem. Soc.*, **86**, 2299 (1964).

(2) D. Seyferth, L. G. Vaughan, and R. Suzuki, *J. Organometal. Chem.*, **1**, 437 (1964).

(3) E. Grovenstein, Jr., and D. E. Lee, *J. Am. Chem. Soc.*, **75**, 2645 (1953).

(4) A private communication from the manufacturers, Synfleur Scientific Laboratories, Inc., of Monticello, N. Y., stated that the sample (P283) was made "in the usual manner by the decarboxylation of bromocinnamic acid and it contains approximately 5 to 10% of the *cis* isomer with the balance being the *trans* isomer."

(5) S. J. Cristol and W. P. Norris, *J. Am. Chem. Soc.*, **75**, 2645 (1953).

(6) C. Dufraisse, *Compt. rend.*, **172**, 67 (1921).

(7) C. Walling, "Free Radicals in Solution," John Wiley and Sons, Inc., New York, N. Y., 1957, pp. 381.