

Hanovia Type S 200-w lamp through a Pyrex filter until ultraviolet or vpc analysis of the irradiated solution showed maximum product formation (about 5 hr). The retention time of the photo product on a 10-ft vpc column was 6.3 min and for the dienone, 7.8 min. After solvent removal the crude oil obtained was distilled, bp 60° (0.5 mm), to give 1.5 g (50%) of a crystalline product **18** which on further purification by vpc or sublimation had mp 50–52°; $\lambda_{\text{max}}^{\text{E:OH}}$ 235, 274, and 320 m μ (shoulder) (ϵ 6270, 3240, and 605, respectively); $\nu_{\text{max}}^{\text{C=O}}$ 1690 and 1640 cm⁻¹.

Anal. Calcd for C₁₂H₁₈O: C, 80.86; H, 10.18. Found: C, 81.11; H, 10.15.

The nmr spectrum showed five singlets at τ 8.12, 8.45, 8.78, 8.90, and 9.08, with relative areas 1:1:1:2:1. Measurement of the spectrum at a sweep width of 100 cycles showed the two signals at low field to be quartets with peak separation equal to 1 cps.

(b) Hexaethyldienone **2**. The photolysis procedure was similar to that reported above. The reaction was monitored only by ultraviolet analysis, since the product was shown to be reconverted to starting material by repeated passages through the vpc column or by prolonged heating. Purification of the crude material was best achieved by vpc, since decomposition occurring after the detector stage of the instrument would be small. This yielded material **22** with $\lambda_{\text{max}}^{\text{E:OH}}$ 239, 270, and 332 m μ (ϵ 5300, 2660, and 850); ν_{max} 1638 and 1680 cm⁻¹ liquid film. The nmr spectrum consisted of two complex multiplets running approximately from τ 7.4 to 8.0 (four allylic methylenes) and τ 8.67 to 9.35 (remaining 24 protons).

Degradation of Hexamethylbicyclo[3.1.0]hex-3-en-2-one. The bicyclo derivative **18** (1.2 g) in 170 ml of methylene chloride was treated at -20° with ozone gas for 1 hr. The blue solution was evaporated to an oil, which was then refluxed for 2 hr with 150 ml of

water, 1.5 ml of 30% hydrogen peroxide, and 3 ml of 1 M sodium hydroxide. The aqueous solution was then filtered from any residual gum (<50 mg), and 1 N sulfuric acid was added to adjust the pH to 4.0. The product was extracted into ether, which upon evaporation afforded a crystalline keto acid **19** (0.85 g, 82%) showing $\nu_{\text{max}}^{\text{KBr}}$ 3400 (broad, OH), 1855, 1810, and 1760 cm⁻¹. Esterification of this acid was accomplished with diazomethane. Vpc analysis of the crude ester showed it to be at least 80% one compound. A sample, which was purified by vpc, had $\nu_{\text{max}}^{\text{C=O}}$ at 1720 and 1705 cm⁻¹ and bands in the nmr spectrum at τ 6.34 (ester methyl), 7.90 (ketone methyl), 8.73, 8.80, and 8.90 with relative areas 1:1:2:1:1.

The methyl keto ester **20** was dissolved in 12 ml of dioxane and added dropwise during 30 min to an aqueous solution of sodium hypobromite at 0°. This was prepared from 3.0 g of sodium hydroxide in 4 ml of water and 1.2 ml of bromine. The aqueous dioxane solution was then heated at 35° for 15 min, and after cooling the excess hypobromite was removed with sodium bisulfite. The solution was extracted with ether which removed material (80 mg) that was shown to contain only 10% of the required product. This was discarded. The acidified aqueous solution was then extracted with ether and this afforded crude crystalline anhydride **21** (0.45 g, 65%). After recrystallization from ether the crystals had mp 144–145°; $\nu_{\text{max}}^{\text{C=O}}$ 1875, 1825, and 1775 cm⁻¹.

Anal. Calcd for C₉H₁₂O₃: C, 64.3; H, 7.20. Found: C, 64.87; H, 7.51.

The nmr spectrum in acetone-*d*₆ had singlets at τ 8.63, 8.70, and 8.77 with relative areas 2:1:1. These can be assigned to the equivalent methyls at the ring junctions, the *cis* and then the *trans gem*-methyls. The spectrum in carbon tetrachloride, however, showed only two peaks at τ 8.65 and 8.83 with relative areas 3:1.

Reactions of Carbodiimides. I. The Mechanisms of the Reactions of Acetic Acid with Dicyclohexylcarbodiimide^{1,2}

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Abstract: The mechanisms of the reactions of dicyclohexylcarbodiimide (DCC) and of diisopropylcarbodiimide with acetic acid in acetonitrile and in carbon tetrachloride have been studied. Previously reported products for the reaction of acetic acid with DCC are acetic anhydride, dicyclohexylurea, and acetyldicyclohexylurea, and these have now been shown to account quantitatively for reactants. Furthermore, it has been found that the relationship between product yields and initial concentrations of acetic acid and of DCC can be predicted accurately from eq 1–3 with a k_2/k_3 ratio of about 60 mole⁻¹ l. in acetonitrile and about 400 in carbon tetrachloride. The ratios may be regarded as empirical parameters. The possibility has been investigated that the acylurea might arise in part from reaction of acetic anhydride with carbodiimide or from acylation of urea, but both of these have been excluded. In acetonitrile the reaction is first order in carbodiimide and somewhat higher than first order in acetic acid. The reaction is about 30 times faster in carbon tetrachloride than in acetonitrile. This unusual result, the order with respect to acetic acid, and several trends of product yields can be accounted for on the basis that acetic acid dimer reacts more rapidly with carbodiimide than does the monomer. Predictions based on a mechanism consisting of eq 1–5 are quantitatively in accord with product data in acetonitrile at 30° with $k_1 = 0.013$ mole⁻¹ l. sec⁻¹, $k_2/k_3 = 60$ mole⁻¹ l., $K_4 = 0.5$ mole⁻¹ l., $k_5/k_1 = 10$. The monomer–dimer equilibrium constant for acetic acid in acetonitrile has been found to be 0.5 mole⁻¹ l.

Carbodiimides have a cumulative double-bond system which reacts with many types of functional groups.⁴ They have been particularly valuable in the

synthesis of peptides^{5,6} and of nucleotides⁷ because of their capability of effecting acylations under mild conditions.

(5) J. C. Sheehan and G. P. Hess, *J. Am. Chem. Soc.*, **77**, 1067 (1955).

(6) For reviews see, e.g., (a) J. P. Greenstein and M. Winitz, "Chemistry of the Amino Acids," John Wiley and Sons, Inc., New York, N. Y., 1961, p 1016; (b) N. F. Albertson, *Org. Reactions*, **12**, 157 (1962); (c) M. Goodman and G. W. Kenner, *Advan. Protein Chem.*, **12**, 465 (1957).

(7) (a) M. Smith, J. G. Moffatt, and H. G. Khorana, *J. Am. Chem. Soc.*, **80**, 6204 (1958); (b) H. G. Khorana, "Some Recent Developments in the Chemistry of Phosphate Esters of Biological Interest,"

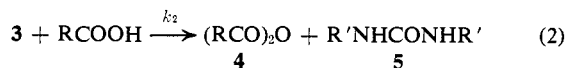
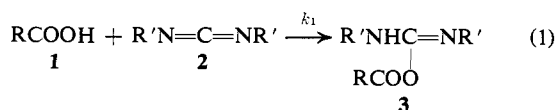
(1) This work received principal support from Research Grant RG 7828 of the Public Health Service.

(2) This work was also supported in part by Contract No. AT-(40-1)-2690 under the Division of Biology and Medicine, U. S. Atomic Energy Commission.

(3) Public Health Fellow 1963–1964.

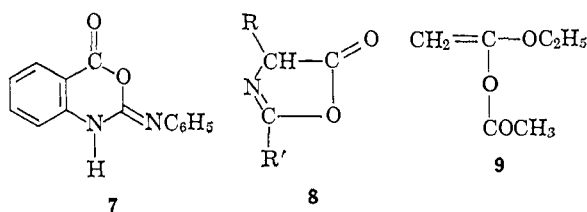
(4) For a review see H. G. Khorana, *Chem. Rev.*, **53**, 145 (1953).

General aspects of these acylations have been studied by several groups⁵⁻¹⁰ and eq 1-3 have been proposed to account for the course of the reaction with carboxylic acids.⁹ Principal products are the anhydride 4, the urea 5, and the acylurea 6.^{7,8}



The purpose of the present investigation has been to study the reaction mechanisms quantitatively. Part I is concerned with the reactions of acetic acid with dicyclohexylcarbodiimide and diisopropylcarbodiimide.¹¹ Part II takes up the influence of bases on the reactions and considers the sequence of steps in the acylation to give *p*-nitrophenyl esters and amides.¹² Part III is devoted to the reactions of peptide acids.¹³

While there is no direct evidence for the acylisourea 3 which has been postulated as a common intermediate, there are many analogies which support this postulate: (1) the addition to the carbodiimide function of related functional groups such as alcohols or phenols,^{14,15} (2) the well-known facile addition of carboxylic acids to vinyl ethers and other close analogs of carbodiimides, and (3) the fact that many structures related to the postulated acylisourea are good acylating agents. Examples are azlactones 8¹⁶ and alkoxyvinyl esters 9.¹⁷ A valuable structural analogy is afforded by 7 which contains the acylisourea moiety.¹⁸



John Wiley and Sons, Inc., New York, N. Y., 1961; (c) H. G. Khorana, and A. R. Todd, *J. Chem. Soc.*, 2257 (1953).

(8) (a) F. Zetsche and A. Friedrich, *Ber.*, 72, 1477 (1939); 73, 1114 (1940); F. Zetsche and G. Röttger, *ibid.*, 73, 465, (1940); (b) G. Schulz and K. Fiedler, *Chem. Ber.*, 89, 2681 (1956); (c) A. Buzas, C. Egnell, and P. Freon, *Compt. rend.*, 252, 896 (1961); 255, 945 (1962); 256, 1804 (1963); (d) H. Zahn and F. Schade, *Chem. Ber.*, 96, 1747 (1963).

(9) (a) Reference 7a; (b) H. G. Khorana, *Chem. Ind. (London)*, 1087 (1955).

(10) H. Schüssler and H. Zahn, *Chem. Ber.*, 95, 1076 (1962).

(11) The following abbreviations are used: DCC, dicyclohexylcarbodiimide; DCU, dicyclohexylurea; DPC, diisopropylcarbodiimide; and DPU, diisopropylurea.

(12) D. F. DeTar and R. Silverstein, *J. Am. Chem. Soc.*, 88, 1020 (1966).

(13) D. F. DeTar, R. Silverstein, and F. F. Rogers, Jr., *ibid.*, 88, 1024 (1966).

(14) E. Schmidt, F. Mousmüller, and R. Schnegg, German Patent 956,499; *Chem. Abstr.*, 54, P5471a (1960).

(15) E. Vowinkel, *Chem. Ber.*, 96, 1702 (1963).

(16) Reference 6a, p 823.

(17) E. G. Tadema, E. Harryvan, H. J. Panneman, and J. F. Arens, *Rec. Trav. Chim.*, 83, 345 (1964).

(18) G. Doleschall and K. Lempert, *Tetrahedron Letters*, 18, 1195 (1963). A further point in favor of the assigned structure is that the isomeric 3-phenyl-2,4-(1H,3H)-tetrahydroquinazolinone is well known and has a melting point of 280° while 7 has a melting point of 193°.

Some suggested reaction mechanisms have included steps other than those shown in eq 1-3. It must be pointed out that equations written with free ions^{6b,9,10} have to be recast into a form involving ion pairs or other ion aggregates since the media used (benzene, carbon tetrachloride, ethyl acetate, etc.) do not support free ions. Such modification is usually more profound than a mere change of terminology and generally results in a quite different concept of the mechanism. This is discussed in part II.¹²

Results

Alternative Routes to Products. Although rearrangement of acylisourea (eq 2) is a plausible route to the acylurea, two other routes must be considered: (1) reaction between anhydride and the carbodiimide to form a diacyl derivative which then acylates acetic acid, a route which assigns a catalytic role to a product, and (2) direct acylation of the dialkylurea.

Carbodiimides have been reported to react with acid chlorides to give the reactive $\text{RN}(\text{COR})\text{CCl}=\text{NR}$.¹⁹ It has also been reported that benzoic anhydride reacts with dicyclohexylcarbodiimide in refluxing dimethylformamide solution to give N-benzoyldicyclohexylurea.^{8b} The analogous $\text{RN}(\text{Bz})-\text{C}(\text{OBz})=\text{NR}$ might be an intermediate. It is presumed that traces of water in the solvent led to the hydrolysis.²⁰

We therefore examined the reactivity of carbodiimides toward anhydrides under typical acylation conditions. A solution of DCC and acetic anhydride in anhydrous acetonitrile (both 0.04 M) showed no diminution of either component after 65 hr at room temperature, and another solution of DCC and benzoic anhydride (both 0.017 M) showed no change after 200 hr. A more rigorous test is afforded by an examination of actual reaction mixtures. Lines 4 and 5 of Table I (see footnotes g and h) show that a large excess of carbodiimide has no effect on product distribution.

Furthermore reaction kinetics (discussed later) show no evidence of acceleration due to anhydride. Hence direct reaction between carbodiimide and anhydride may be ruled out on several counts. This conclusion is of considerable importance in connection with the reactions of benzyloxycarbonyl amino acid anhydrides with DCC, for here the initial products react further with carbodiimides by paths discussed in part III.¹³

The acylation of urea derivatives upon heating with acid chlorides is well known,²¹ and Khorana has reported acylation of di-*t*-butylurea with trifluoroacetic anhydride.⁷ However, we find that the ureas of concern in this work are not acylated by either acetic or benzoic at room temperature. A solution of acetic anhydride (0.04 M) in acetonitrile gave no observable reaction with a saturated solution of DCU (0.001 M) over a period of 19 hr. There was also no reaction with 0.04 M DCU in chloroform. Bases caused no catalysis: in acetonitrile solution over a period of 230 hr no reaction occurred between acetic anhydride (0.04 M), purified triethylamine (0.04 M), and DCU (satu-

(19) H. D. Stachel, *Angew. Chem.*, 71, 246 (1959); 73, 64 (1961); H. Ulrich and A. A. R. Sayigh, *J. Org. Chem.*, 28, 1427 (1963).

(20) Obviously this reaction might also proceed indirectly by hydrolysis of the anhydride to benzoic acid which in turn reacts with DCC to give the urea. The mechanism has not been established.

(21) There are many references in Beilstein, e.g., EI14, 608, for N-ethyl-N'-chloroacetylurea. Examples of acylation of dialkylureas are scarce.

Table I. Products of the Reaction of Acetic Acid with Dicyclohexylcarbodiimide in Acetonitrile^a

Reactants ^b			Time, hr	Products ^c		
AcOH	DCC	Other		DCC	Ac ₂ O	AcDCU
0.02	0.02		17-24	28 ^d	22	48
0.04	0.02		12-52	0	59 ^e	44
0.04	0.04		12-48	32 ^e	31	37
0.04	0.08		12	...	15 ^{f,g}	17 ^g
0.04	0.16		12	...	8 ^{f,h}	9 ^h
0.04	0.04	0.04 Ac ₂ O	42-65	28 ⁱ	24	37
0.04	0.04	0.20 Ac ₂ O	15-43	24 ⁱ	...	41
0.08	0.02		15-24	0	85 ^e	19
0.08	0.04		15-46	0	68 ^e	27
0.08	0.04	0.04 Ac ₂ O	24	0	57 ⁱ	26
0.08	0.04	0.08 Ac ₂ O	24	0	51	30
0.08	0.04	0.20 Ac ₂ O	15-24	0	...	36 ⁱ
0.10	0.04		13-20	0	81 ^d	19
0.08	0.04	0.026 DPU	24	0	69	...
0.04	0.04 ⁱ		185	36	32	...
0.08	0.04 ⁱ		185	0	69	...

^a All reactions were carried out at room temperature, about 25°. ^b Reactant concentrations are moles per liter. ^c Product yields are mole per cent based on DCC taken ((moles of product formed/moles of DCC initial) × 100). All analyses were based on infrared spectra treated by the computer program ANALYZ. In runs in which DCC is a "product," all the acetic acid has disappeared. The accuracy is about 3% relative. Yields are independent of time over the range stated. ^d Average of three runs. ^e Average of four runs. ^f It may be noted that the excess of DCC does not affect the yields of Ac₂O and of AcDCU based on AcOH. These runs are to be compared with the 0.04-0.04 runs immediately above. ^g Stated yield is based on 0.080 M DCC; the respective yields based on 0.04 M are 30 and 34. ^h Based on 0.16 M DCC; the respective yields based on 0.04 M are 32 and 36. ⁱ Average of two runs. ^j DPC.

rated). Acetic anhydride does not acylate diisopropylurea; the concentration of acetic anhydride formed during reaction of acetic acid with DPC remained constant over periods of several days at room temperature. (DPU is completely soluble in such mixtures.)

To exclude the possibility that reaction mixtures might contain a catalyst for direct acylation of the urea, the reaction of acetic acid with DCC in acetonitrile was carried out in the presence of various amounts of initially added acetic anhydride. Yields of acetic anhydride and of DCU were independent of this added anhydride (Table I). The converse experiment was also carried out with a mixture of DCC (0.04 M), acetic acid (0.08 M), and DPU (0.026 M) (DCU is too insoluble), and the yield of acetic anhydride was found to be the same as in the absence of DPU. This excludes the possibility that the urea is acylated by any acylating species present during the course of reaction.

It may be concluded that rearrangement of acylisourea is the only route to acylurea.

Reaction Stoichiometry. The next step was to test the adequacy of eq 1-3 in predicting product yields as a function of reactant concentrations. A quantitative study of the products of the reaction of acetic acid with dicyclohexylcarbodiimide using a variety of initial concentrations is presented in Table I. Acetic anhydride, dicyclohexylurea, and N-acetyldicyclohexylurea were found to account quantitatively for reactants consumed.

The relative amounts of anhydride and acylurea formed at any given instant are given by the differential expression eq 4. This is derived from eq 1-3 by the

$$d[\text{Ac}_2\text{O}]/d[\text{Ac-urea}] = k_2[\text{AcOH}]/k_3 \quad (4)$$

usual steady-state treatment.²² Direct integration does not lead to useful results. We therefore carried out numerical integrations to determine predicted yields of anhydride and acylurea as a function of the k_2/k_3 ratio and the initial concentrations of DCC and of acetic acid. These calculations were facilitated by a special computer program CDIIMD described briefly in the Experimental Section.

Predictions based on eq 1-3 using k_2/k_3 values that gave the best results are summarized in Table II. Comparison with the normalized data from Table I showed that a k_2/k_3 value of 60-65 mole⁻¹l. gives a good correlation of the data. There is, however, a slight trend in that higher values of k_2/k_3 are needed at higher acetic acid concentrations. An explanation for this effect is presented below.

Table II. Determination of Rate Constant Ratio for Partitioning of Acetylisdicyclohexylurea to Acetic Anhydride and Acetyldicyclohexylurea^a

AcOH	DCC	k_2/k_3^b	DCC	Ac ₂ O	AcDCU
0.02	0.02	60	25.4	25.4	49.3
0.04	0.02	60	0	57.6	42.5
0.04	0.04	60	32.7	32.7	34.7
0.08	0.02	60	0	78.7	21.3
0.08	0.04	60	0	70.1	29.9
0.10	0.04	60	0	78.0	22.0
0.02	0.02	70	27.1	27.1	45.9
0.04	0.02	70	0	60.7	39.3
0.04	0.04	70	34.7	31.7	34.7
0.08	0.02	70	0	81.1	18.9
0.08	0.04	70	0	72.7	27.3
0.10	0.04	70	0	80.4	19.6
0.02	0.02		28	23	49
0.04	0.02		0	57	43
0.04	0.04		32	31	37
0.08	0.02		0	81.5	18.5
0.08	0.04		0	71	29
0.10	0.04		0	81	19

^a The first two sets of data give the predicted final yields of DCC, Ac₂O, and AcDCU based on the feed values of AcOH and DCC and upon the given rate constant ratio k_2/k_3 . These were calculated by the computer program CDIIMD which gives integrated values based on eq 4. The final set of data presents the experimentally observed values of the product yields. These are averages derived from Table I and normalized so that the yields total to 100%. ^b The units are mole⁻¹l.²² Assumed mechanism eq 1-3.

Satisfactory analyses for acetic acid and for DCU were also carried out but are not shown in the tables. Those for DCU were based on isolated weights and were a few per cent low due to the small but finite solubility of the DCU. Included in this study are runs with an excess of DCC, runs involving long contacts between products, runs with initially added large excesses of acetic anhydride, and runs with DPC.¹¹ Product yields are insensitive to all of these variations.

In carbon tetrachloride the yields of anhydride are higher than in acetonitrile (Table III). Similar calculations showed correlation between predicted and observed values with a rate constant ratio, k_2/k_3 , of about 300-400.²³

(22) Subscripts on rate and equilibrium constants designate the equation to which the constant applies.

(23) It will be recognized from further discussion that the present approach is oversimplified. The relationship to the more sophisticated treatment is given in eq 9, and it turns out that the simple approach works with acetonitrile because the acetic acid is mostly monomeric and with carbon tetrachloride because it is mostly dimeric. In other solvents the simple approach may not be applicable.

Table III. Products of the Reaction of Acetic Acid with Dicyclohexylcarbodiimide in Carbon Tetrachloride

AcOH	DCC	Time, hr	DCC	Ac ₂ O	AcDCU
0.02	0.02	22	42 ^a	44	18
0.04	0.04	26-70	44 ^b	47	10
0.08	0.04	26-66	0	92 ^b	..

^a See Table I, footnote *i*. ^b See Table I, footnote *d*.

Reaction Kinetics. In an excess of acetic acid the disappearance of diisopropylcarbodiimide is quite accurately first order in carbodiimide within a run and also between runs. This is, of course, in accord with eq 1-3 since eq 1 is rate determining and the acylisourea is a steady-state intermediate. There appears to be a slight increase in the second-order rate constant as the carbodiimide concentration decreases, but present results do not unambiguously establish this.

Table IV. Kinetics of the Reaction of Diisopropylcarbodiimide with Acetic Acid in Acetonitrile

Initial AcOH	Concn, M DPC	$k(\text{app})$ $\times 10^2$ sec^{-1}	$k^{\circ,d}$ \times 10^2	Per cent ^e	Std dev, ^b % <i>T</i>	Calcd DPC ^c
0.197	0.0099	0.352	1.87	11-79	0.6	0.0098
0.391	0.0098	0.930	2.44	17-97	0.7	0.0099
0.390	0.0195	0.815	2.20	25-95	0.8	0.0192
0.389	0.0389	0.848	2.42	15-97	1.1	0.0372

^a Temperature about 30°. The second-order k was derived by dividing $k(\text{app})$ by the average concentration of acetic acid. Units are $\text{mole}^{-1} \text{l. sec}^{-1}$. All values are averages of 2 or 3 runs; standard deviation of average k is about 5%. ^b The data were treated by LST1 which determines the best values of the parameters k , T (zero time per cent transmission), and T (infinity time per cent transmission). The standard deviation of % T represents the closeness of fit. The limit of accuracy in reading the curves is about 0.5%. ^c This is the calculated initial value based on T (zero time) and serves to indicate the reliability of the treatment. Runs for which this value deviated by more than 5% from the true value were disregarded in computing the average value of the rate constant. ^d Second order. ^e Extent of reaction followed.

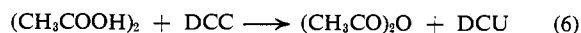
The reaction should also be first order in acetic acid in the presence of excess acid, and it is approximately; however, the rate constants are higher at the higher acetic acid concentrations indicating an order somewhat greater than 1.

Many runs were carried out under conditions less amenable to simple calculation. Most of these used DCC, and the fact that DCU came down as a precipitate throughout the reaction was a minor experimental complication but did not prevent successful analyses for starting materials and for Ac₂O and AcDCU as well. The results are treated below, but it is necessary first to consider the significance of an unusual feature. The reaction of acetic acid with DCC is about 30 times faster in carbon tetrachloride than in acetonitrile. Since acetonitrile should be a much better medium for solvating ionic intermediates, the opposite result might well have been expected.²⁴ We believe that the best

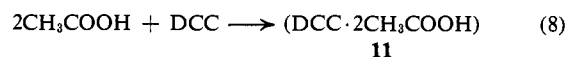
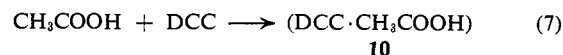
(24) For example, in an elimination reaction (of *p*-toluenesulfonic acid) mediated by various amines the reactions were about nine times faster in acetonitrile than in benzene for triethylamine and 30 times faster for di-*n*-butylamine.²⁵

(25) R. G. Pearson and D. C. Vogelsong, *J. Am. Chem. Soc.*, **80**, 1048 (1958).

explanation is to be found in terms of the relative concentrations of acetic acid monomer and dimer in each of the two solvents. In carbon tetrachloride the dimerization equilibrium constant is about 1500-2500 l. mole⁻¹²⁶ and in acetonitrile we have determined a value of about 0.5. This determination is discussed below. Hence in carbon tetrachloride, acetic acid is present almost entirely as dimer, while in acetonitrile, monomer predominates. The mechanism is therefore expanded to include eq 5 and 6.



The proper description of the reaction should actually be made in somewhat different terms, eq 7 and 8,



which represent formation of an activated complex with the composition one acetic acid and one DCC (10) or with two acetic acid molecules and one DCC (11). Obviously the concentration of complex 11 must be the same whether it is presumed to arise from 10 or from direct reaction of dimer with DCC. It is therefore proper to treat the kinetics in terms of eq 1-6. Because of the high yield of anhydride formed in carbon tetrachloride, it was assumed that dimer gives only anhydride as shown in eq 6; this is adequate as a first approximation.

The hypothesis that dimer reacts considerably faster than monomer is attractive in that it can account not only for the faster rate in carbon tetrachloride but also for several other observations: the tendency for the second-order rate constant in acetonitrile to increase with acid concentration (Table IV), the higher yields of acetic anhydride in carbon tetrachloride, and the tendency for anhydride formation to be favored differentially at higher acetic acid concentrations (Table II). This explains the apparent trend of the k_2/k_3 ratio noted above. It seems reasonable that reaction of acetic acid dimer should give higher yields of anhydride than does monomer, for the required second molecule of acetic acid is already present in the same solvent "cage" as the acylisourea. A theoretical explanation for the faster rate for dimer is presented in part II.¹² It must be noted that the effect of adding eq 5 and 6 is to alter drastically the interpretation of the k_2/k_3 ratio as it applies to carbon tetrachloride, for now most of the anhydride is formed by eq 6.

An interesting parallel is the recent proposal that benzoic acid dimer reacts more rapidly than monomer with diphenyldiazomethane.²⁷

A Quantitative Test of the Mechanism. The postulated five-step mechanism cannot be solved in closed form. Quantitative predictions were therefore obtained numerically by REMECH, a general computer program applicable to a mechanism of almost any complexity.

A large number of comparisons was made and results are illustrated in Figures 1 and 2 which summarize

(26) J. Wenograd and R. A. Spurr, *ibid.*, **79**, 5844 (1957); G. M. Barrow and E. A. Yerger, *ibid.*, **76**, 5248 (1954).

(27) R. A. M. O'Ferrall, W. K. Kwok, and S. I. Miller, *ibid.*, **86**, 5553 (1964).

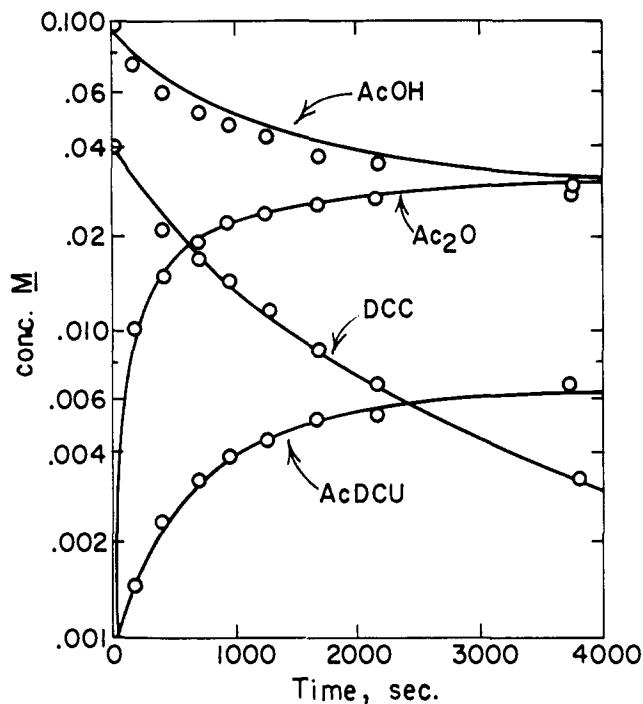


Figure 1. Reaction of DCC with acetic acid in acetonitrile. Solid line predicted by eq 1-5 with $k_1 = 1.25 \times 10^{-2} \text{ sec}^{-1} \text{ mole}^{-1} \text{ l.}$; $k_2/k_3 = 60 \text{ mole}^{-1} \text{ l.}$; $K_4 = 0.5 \text{ mole}^{-1} \text{ l.}$; $k_3/k_1 = 10$. Circles represent observed points. Ordinate scale is logarithmic.

runs at two different reactant concentrations. The agreement between the theoretical curves and the observed points is within experimental error. The simpler mechanism consisting only of eq 1-3 was also tested and was found to give systematic deviations at the concentration extremes. Therefore eq 1-6 represent a minimum satisfactory mechanism.

The question as to the uniqueness of the constants reported in Figure 1 can be answered only in rather general terms. There can be only a few per cent error in k_1 . However, the other constants interact, that is, a decrease in one can be compensated by an increase in another. This interaction is given by eq 9 which can be derived using a mechanism consisting of eq 1, 5, and 6. (Equations 2 and 3 are product determining and affect the rate only indirectly by their effect on total acid concentration.)

$$-d \ln (\text{DCC})/dt = k_1(R/2)a + (-1 + 2/R)(-1 + (1 + 8K_4a)^{1/2})/(4K_4) \quad (9)$$

The parameter k_1 is the rate constant for eq 1, R equals k_3/k_1 , a is total amount of acetic acid present at any time, and K_4 is the dimerization constant. If $R = 2$, then monomer and dimer are equally effective and the right-hand side of eq 9 then becomes k_1a . If K_4 is very large, then the last term on the right becomes $(-1 + 2/R)(a/2K_4)^{1/2}$ and this approaches 0. Therefore the right-hand side becomes $k_1aR/2 = k_3a/2$ and the reaction is first order in either monomer, or in a dimer, $a/2$. For values of R greater than 2 and for intermediate values of K_4 , the apparent reaction order in total acetic acid predicted by eq 9 is greater than 1.²⁸

(28) The reaction of acylisourea with acetic acid monomer and dimer follows an exactly similar expression. If almost all the acid is present as dimer and if dimer reacts, then the order with respect to acetic acid is 1.

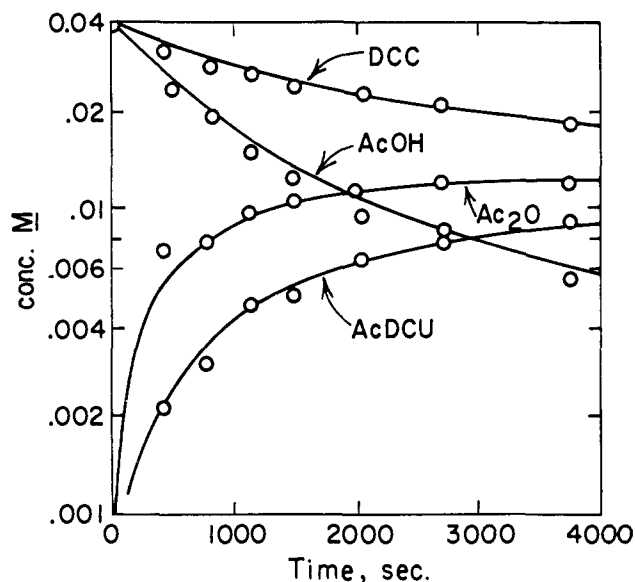


Figure 2. Same as Figure 1 but different reactant ratio.

To illustrate the magnitude of the interaction, if $K_4 = 0.25$, the best $R = 20$, if $K_4 = 0.50$, the best $R = 10$, and if $K_4 = 1.00$, the best $R = 7$.

Application of the rate constants of Figure 1 to the carbon tetrachloride reactions with use of $K_4 = 2500$ for the monomer-dimer equilibrium predicts too slow a reaction. By increasing k_1 to 0.037 sec^{-1} the kinetics of DCC disappearance give an adequate fit, but the predicted yield of AcDCU is about one-fifth as large as it should be. This is due to the assumption in eq 6 that acetic acid dimer gives only anhydride. This could be corrected by adding further equations, but such refinements are beyond the useful scope of the present data. At present, then, the k_2/k_3 ratio is not available for runs in carbon tetrachloride.

Monomer-Dimer Equilibrium Constant. The acetic acid monomer-dimer equilibrium (eq 5) has been studied in several solvents by various techniques.^{26,29} Several investigators have used the infrared spectra, others have measured conductances, and others distribution coefficients.

It seems reasonable to assume that the 1750 band for acetic acid solutions is due primarily to monomer and the 1720 band primarily to dimer, for the 1720 band grows differentially stronger as the acid concentration increases. Similar assignments have been made by others.²⁶

Since the monomer-dimer ratio is much higher in acetonitrile than in carbon tetrachloride, we could not assume that any of the values reported for other solvents were applicable. Our method of measuring the equilibrium constant utilized the usual principle of observing the spectrum as a function of total acetic acid

It is only in intermediate cases that the order is greater than 1. It is apparent from Table II that the data are not particularly sensitive to the k_2/k_3 ratio and by the same token they are not sensitive to small deviations from first order in acetic acid. Provision could readily be made for having both monomer and dimer react with the acylisourea, but the data suggest that monomer and dimer react at roughly the same rate and such calculations would add little at present.

(29) J. T. Harris, Jr., and M. E. Hobbs, *J. Am. Chem. Soc.*, **76**, 1419 (1954); M. M. Davies and G. B. M. Sutherland, *J. Chem. Phys.*, **6**, 755 (1938); Y. Nagai and O. Simamura, *Bull. Chem. Soc. Japan*, **35**, 132 (1962); C. P. Brown and A. R. Mathieson, *J. Phys. Chem.*, **58**, 1057 (1954).

concentration. We assumed various values of K_4 and calculated the corresponding concentrations of monomer and of dimer corresponding to a given total concentration of acetic acid. We then analyzed the resulting spectral data by ANALYZ as a two-component mixture. The criterion of fit was the degree of systematic deviation between concentrations calculated from given values of K_4 and those calculated by the program.

There is considerable interaction among the parameters that describe the spectra, the four extinction coefficients, and the equilibrium constant and the value obtained is therefore uncertain by a large relative factor. The estimate of K_4 rests on estimating a curvature. This begins to show up noticeably for $K_4 = 1$ in Table V. Our measurements indicate a value of $K_4 = 0.5 \pm 100\%$ relative (*i.e.*, 0.25 or 1.0 are also possible values). Typical results are given in Table V. Our evaluation was based on plotting the variances against K_4 to find the minimum.

Table V. Acetic Acid Monomer-Dimer Equilibrium in Acetonitrile^a

Total AcOH	$K = 0.25$		$K = 0.50$	
	Calcd	ANALYZ	Calcd	ANALYZ
0.0106	0.0000	0.0000	0.0001	0.0000
0.0216	0.0001	0.0000	0.0002	0.0001
0.0444	0.0005	0.0010	0.0009	0.0017
0.0774	0.0014	0.0017	0.0026	0.0029
0.307	0.0183	0.0189	0.0303	0.0289
0.481	0.0401	0.0380	0.0630	0.0588
0.729	0.0805	0.0820	0.1200	0.1256

^a Tabulated values are moles per liter of dimer except for column 1.

Discussion

Interpretation of the results requires the consideration of acid-base equilibria, which are taken up in part II.¹² A unified discussion of all the results is presented there.

Experimental Section³⁰

Solvents. Acetonitrile, usually industrial grade, was purified by fractional distillation through a 1.5-m column packed with Cannon packing of stainless steel. When monitored by infrared absorption, impurities which gave bands at 1715 and at 1210 cm^{-1} were removed in the forerun. The center cut then was passed through a column of neutral alumina. There was a single peak with gpc (Aerograph Hy-Fi). Determination of water by the Karl Fischer method using potentiometric detection showed 0.6 mg of water/ml.

Carbon tetrachloride was treated with P_2O_5 and passed through a silica gel column. It showed a single peak with gpc.

Reagents. Dicyclohexylcarbodiimide was commercial material which was distilled at 0.1 mm at a bath temperature of 130–140°. The center cut was used. The purity of the DCC is shown in part by the quantitative values obtained in the stoichiometry studies. The diisopropylcarbodiimide was also commercial material.

Acetyldicyclohexylurea. To a solution of acetic acid (2.85 ml) and of triethylamine (14 ml) in 150 ml of acetonitrile was added 10.3 g of DCC. Filtration (after 18 days at room temperature) gave 1.46 g of DCU. Evaporation gave the AcDCU in 72% yield in two fractions, mp 124.5–125° after recrystallization from acetonitrile (lit.³¹ mp 127–128°); infrared absorption in acetonitrile (PE 221) 1698 and 1657 cm^{-1} . Since the melting points and the spectra did not agree very well, the compound was analyzed.

(30) Nitrogen determinations were made with a semiautomatic apparatus (Coleman nitrogen analyzer) by Mrs. Lillian Ross.

(31) N. A. Smart, G. T. Young, and M. W. Williams, *J. Chem. Soc.*, 3902 (1960).

Anal. Calcd for $\text{C}_{15}\text{H}_{26}\text{N}_2\text{O}_2$: N, 10.52; mol wt, 266. Found: N, 10.64; mol wt, 270 (vapor phase osmometer in acetonitrile).

Analyses. Infrared spectra were measured with an Infracord (Perkin-Elmer Model 137). Most measurements utilized the rugged Perkin-Elmer fixed cells in several thicknesses. Solvent was usually compensated with a variable thickness cell. Cell thickness was determined by the count of interference fringes. Care was taken to avoid leakage, and all runs showing evidence of leakage were discarded.

Comparison of solvent spectra with solution spectra showed that the base line in the 1900 region could serve as an adequate measure of the 100% transmission. Checks were made for the position of the 0% T line.

Some of the data, particularly for DCC, were analyzed by conventional graphing techniques (absorbance *vs.* concentration). However, considerably better results were obtained with ANALYZ. Use of the computer program made it practical to base the extinction coefficients on 40 standard solutions. An illustration of the results is given in Table VI. The largest error in the whole group of 40 curves is that of AcOH in solution 2, Table VI. The absorption peaks used were 2115 (DCC), 1825 (Ac_2O), 1750 (AcOH), and 1700 (AcDCU). The E value at 2115 for DCC was taken to be parabolic, and so was the E value for AcDCU. The former was advisable because of curvature in the plot of absorbance *vs.* concentration, while the latter was actually unnecessary.

Table VI. Analytical Results Obtained with ANALYZ^a

Compd	Obsd concn	Calcd concn
Solution 1		
DCC	0.0135	0.0135
Ac_2O	0.0135	0.0139
AcOH	0	-0.0005
AcDCU	0.0145	0.0146
Solution 2		
DCC	0	0
Ac_2O	0.0280	0.0271
AcOH	0.0110	0.0122
AcDCU	0.0110	0.0105
Solution 3		
DCC	0	0
Ac_2O	0.0175	0.0183
AcOH	0.0400	0.0387
AcDCU	0.0040	0.0036

^a Standard deviations of concentrations: DCC, 2.2×10^{-4} ; Ac_2O , 4.4×10^{-4} ; AcOH, 6.5×10^{-4} ; AcDCU, 3.6×10^{-4} . All with 12 or more degrees of freedom (based on 40 standard solutions).

Rate Studies. Solutions were made up in flasks and transferred to the infrared cells for analysis. Temperatures were not especially controlled in this work but are known to within about 3°. The cells were left in the beam only for the very fast reactions. For the others they were in just long enough for the scan. Room temperature was about 26° and the temperature rise was 2–3°. The present study has been primarily an exploratory one to establish the general features of the carbodiimide reactions.

Computer Programs. Following is a brief discussion of the programs used in the present work.

ANALYZ, written in Fortran II for the 709 IBM series computers by D. F. DeTar, about 4000 source cards total, converts per cent transmission or absorbance data into concentrations *via* a Beer-Lambert calculation. Errors in either per cent transmission or in absorbance may be minimized, and weighting is provided to permit inclusion of data of varying reliability. Furthermore each individual extinction coefficient may be calculated selectively by a quadratic expression so that curvature or nonzero intercept of the absorbance *vs.* concentration relationships may be handled when necessary. Capacity of the program is 8 compounds, 16 wavelengths, and 40 standard spectra upon which extinction coefficients are based. There is essentially no limit to the number of unknowns which may be run. The program has built-in automatic features for checking on most types of errors in data sets to prevent incorrect

calculations. It also makes back calculations on absorbance of per cent transmission data to permit checking of input data. If the number of wavelengths at which data are available is greater than the number of compounds, then the user has the option either of grouping the wavelength data so that program combines data for the peaks pertinent to each compound or else a least-squares calculation can be made for concentrations.

REMECH, written in Fortran II and FAP by C. E. DeTar and D. F. DeTar, about 4000 source cards, accepts a proposed reaction mechanism of relatively unlimited complexity. The mechanism may include acid-base equilibria, equilibria involving ion pairs, etc., steady-state intermediates, and various types of catalysis. A given equation may include from one to several reactants or products as well as a catalyst. It is necessary to present a value for each rate or equilibrium constant, and it is also necessary to specify the time interval (Δt) over which each iteration is to be performed as well as the number of such intervals and the printing frequency. The output of the program consists of tables of concentrations of reactants and products as a function of time. The calculation involves the following steps: on the basis of the concentrations of all relevant reactants and products, the acid-base equilibria are first calculated. This is followed by calculations of other equilibria, then by the calculation of the concentrations of all steady-state intermediates. Finally for each reaction there is calculated a reaction decrement ($\Delta C = k \cdot \Delta t \cdot A \cdot B$, *e.g.*). Concentrations of reactants are decremented and concentrations of products incremented (except for steady-state intermediates). In this calculation the approximation is made that the rate of formation of each product occurs at a characteristic but constant rate over a sufficiently short time interval. The first interval may cover, *e.g.*, the first 5% reaction, the second, the next 4.8% reaction, and so on successively. Useful results may often be obtained by examining yields of products being formed after only 10% reaction, or the process may be continued as far as is desired. In practice a time interval involving less than about 5% reaction at the start gives more than adequate preliminary results. The possibility of error from the choice of too coarse an interval is always checked on final data by making runs with much smaller intervals. Although the program uses iterative procedures for equilibrium and steady-state concentrations which cannot always be expected to converge, any convergence failure results in a print-out of the set of computations which did not converge. It is sometime possible to get around a problem of nonconvergence by better estimates of starting concentrations or by other minor changes. We have tested the program on a mechanism involving almost 200 reaction steps and 10 steady-state intermediates, with results which appear plausible. The program also has been checked on relatively simple mechanisms where the

results can be computed exactly. While this program is a very powerful tool, its use does require careful exercise of judgment.

LSTI, written in Fortran II by D. F. DeTar and C. E. DeTar, is a short program which accepts absorbance or per cent transmission data and computes the parameters for a first-order equation (k_1, A_0, A) by a least-squares method which minimizes the scalar error in per cent transmission. If data are available at three points separated by equal time intervals, the program supplies initial estimates of the parameter.

CDIIMD, written in Fortran II by D. F. DeTar, is a special program which calculates the yields of acetic anhydride and of AcDCU predicted by eq 1, 2, and 3. It also will accept the case where the acetic acid is involved in an acid-base equilibrium. The calculation involves a stepwise numerical integration with increments of the concentration of acetic acid rather than of the time.

Procedure for Adjusting Rate Constants. The observed concentration values in Figures 1 and 2 were obtained from infrared curves of the reaction mixtures taken over the 2100–1650-cm⁻¹ region during the course of the reaction. These curves were analyzed for DCC, AcOH, Ac₂O, and AcDCU *via* ANALYZ as though they represented stable solutions. Actually it took 85 sec to scan from the DCC peak to the last AcDCU peak, and the concentration of the Ac₂O, *e.g.*, is initially changing by about 25% for the first point during the 50 sec required to get to the peak. For later points the change is much less. Since the compounds show relatively minor overlap in their spectra, the above complications do not interfere seriously with the accuracy of the analyses, only with their interpretation.

The values of the rate constants chosen for the comparison were obtained by the following general procedure. Rough preliminary estimates were made of the value of k_1 and calculations were made by REMECH at a variety of k_1 values and at several k_5/k_1 ratios and k_2/k_3 ratios. The best value of k_1 for a given choice of k_5/k_1 and k_2/k_3 ratios was found by an interpolation procedure. The interpolation involved calculation of a ratio $t_{\text{calcd}}/t_{\text{obsd}}$ for each observed concentration value of a "key variable" (DCC). For a given point there is a t_{obsd} and a corresponding value of concentration of DCC. Inspection of the table of calculated values permits calculation of an interpolated t_{calcd} at which the calculated concentration of DCC is equal to the observed value. The corrected k_1 value, $k_{1 \text{ corr}}$, was set equal to $k_1 \cdot (t_{\text{calcd}}/t_{\text{obsd}})$. The values of k_1 then were averaged to obtain a best value for a given run.

To find the best over-all value of the k_5/k_1 ratio, a plot was made of the k_5/k_1 ratio *vs.* k_1 at each of several different initial reactant concentrations; the best estimate of the position of the multiple intersection gave k_5/k_1 . Finally the REMECH calculation was repeated using the best parameters.