

ORGANIC AND BIOLOGICAL CHEMISTRY

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY, RUTGERS, THE STATE UNIVERSITY AND THE STERLING CHEMISTRY LABORATORY, YALE UNIVERSITY]

Some Mechanistic Aspects of the Reaction of Anhydrides with Nucleophiles¹BY DONALD B. DENNEY AND MICHAEL A. GREENBAUM²

RECEIVED JANUARY 19, 1957

Anhydrides, which were specifically labeled with oxygen-18, have been treated with various nucleophiles under several conditions. The oxygen-18 content of the products of these reactions coupled with data from the literature can be utilized to define a multi-step process for the course of these reactions. Several reactions have been devised to test this mechanism and have been shown to be in agreement with the postulate.

Introduction

Evidence from several sources can be used to construct a tentative mechanism for the reaction of anhydrides with nucleophiles. Berliner and Altschul³ have made a study of the kinetics of hydrolysis of several aroyl anhydrides. Their data indicate that the rate-determining step in the hydrolysis involves attack by the nucleophile on the carbonyl carbon. The observed effect of ring substituents is in accord with this view. Bunton, Lewis and Llewellyn⁴ have shown by using an oxygen-18 tracer that

an intermediate $\text{C}_6\text{H}_5-\text{C}(\text{OH})_2-\overset{\text{O}}{\parallel}{\text{C}}-\text{C}_6\text{H}_5$ must be in equilibrium with the starting materials in the aqueous hydrolysis of benzoic anhydride. Gold and Jefferson⁵ have studied the tertiary amine catalyzed hydrolysis of acetic anhydride and have concluded

that the reactive species is $[\text{CH}_3-\overset{\text{O}}{\parallel}{\text{C}}-\overset{+}{\text{N}}(\text{R})_3]$ although rigorous evidence for its formation was not obtained. Emery and Gold⁶ have studied the product ratios obtained from the reaction of anilines with mixed aliphatic anhydrides. They have found a marked effect of solvent on these ratios as well as an apparent steric factor which alters the ratio of the products.⁷ These observations indicate strongly that the attack by the nucleophile, $:\text{NH}$, on an anhydride proceeds by a slow rate-determining step to give I which is in equilibrium with starting materials. Conversion of I to products will depend to some degree on the nature of the nucleophile. If, for example, it is an anion then proton transfer will not be required; on the other hand, amines, alcohols, etc., will require

that a proton be transferred before the products are formed. It is the latter situation which is of concern here. There are two attractive paths for the formation of products from I. Path A involves an ionization of I to give the fragments of II. Reaction of some base, $:\text{B}$, *i.e.*, solvent, nucleophile or $\text{R}-\text{COO}^-$ completes the process and one obtains the observed products. If Path A is followed and one uses an anhydride which has been labeled as indicated, then the distribution of oxygen-18 in the products will depend on the rate of return from II to starting materials as compared to the rate of collapse of II to products.⁸ If return to starting materials is much faster than product formation, then the oxygen-18 in the anhydride will become equilibrated, since in II $\text{R}-\text{COO}^-$ allows equilibration of the label. If k_4 is much larger than k_{-1} and k_{-2} , then there will be no equilibration, as II will never return to starting materials. It can be readily seen that product formation by Path B will not lead to equilibrated products. If one uses a labeled anhydride and if these two paths are the ones being followed, it is possible to get some measure of the relative importance of return from II as compared to the non-equilibrating routes by measuring the oxygen-18 distribution in the products. Unfortunately, a further complication arises since benzoic acid, a product of the reaction, can react with the anhydride to give equilibrated material. It has been possible to show that this reaction contributes very little to the oxygen-18 equilibration.

Results and Discussion

Synthesis.—The preferred method of preparing the monocarbonyl labeled benzoic anhydride is to allow silver benzoate to react with labeled benzoyl chloride. This reaction affords good yields of specifically labeled anhydride. It was by this procedure that IV was converted *via* the acid chloride to VII (see Table I). Another method used for preparing the monolabeled anhydride was to allow sodium benzoate in water to react with labeled benzoyl chloride (from III) in chloroform. Using this procedure VI was prepared; however, because of the unpredictableness of the method, it cannot be recommended. When labeled benzoic acid, V, was allowed to react with benzoyl chloride and pyridine in ether, an excellent yield of VIII was obtained.

(8) The reasoning which is being applied here depends upon the fact that the products are not in equilibrium with the starting materials; that this is the case is abundantly demonstrated by qualitative organic chemical data.

(1) A portion of this work has been reported as a Communication. D. B. Denney and M. A. Greenbaum, *THIS JOURNAL*, **78**, 877 (1956).

(2) Alfred P. Sloan Postdoctoral Fellow at Rutgers, The State University.

(3) E. Berliner and L. H. Altschul, *THIS JOURNAL*, **74**, 4110 (1952).

(4) C. Bunton, T. Lewis and D. Llewellyn, *Chem. and Ind.*, 1154 (1954).

(5) V. Gold and E. Jefferson, *J. Chem. Soc.*, 1409 (1953).

(6) A. Emery and V. Gold, *ibid.*, 1443 (1950).

(7) A study in this Laboratory of the ratio of products obtained from mixed aroyl anhydrides as yet has not led to the large solvent effects found by Emery and Gold. Further discussion of the points raised by these experiments will be deferred until a later paper as they do not affect the arguments advanced in this paper.

TABLE II^a

Reactants and conditions	Amide or ester-O ¹⁸	Benzoic acid-O ¹⁸	% Equilibration	Dev. from total O ¹⁸
VI + NH ₃ at -33°	0.86, 0.85	0.66, 0.65	0	0.00
VII + NH ₃ at -33°	.57, .57	0.40	0	-0.02
VIII + NH ₃ at -33°	0.85	1.03	35	-0.06
VII + NH ₃ at -78°	0.46, 0.46	0.46	100	-0.01
VI + C ₆ H ₅ -NH ₂ in ether	.64, .64	0.64, 0.64	100	0.00
VII (after C ₆ H ₅ NH ₂ in ether) + NH ₃	0.50	0.43	69	-0.03
VI + C ₆ H ₅ -NH ₂ acetone/H ₂ O(1:2)	0.81, 0.80	0.55, 0.56	23	0.00
VII + cyclo-C ₆ H ₁₁ NH ₂ in C ₆ H ₅ -N(CH ₃) ₂	0.51	0.44	62	0.00
VII + cyclo-C ₆ H ₁₁ ND ₂ in C ₆ H ₅ -N(CH ₃) ₂	.46	.47	100	+0.01
VII + CH ₃ OH	.46	.47	100	+0.01
IX + C ₆ H ₅ -NH ₂ in ether	.67		74	
VII + cyclo-C ₆ H ₁₁ -NH ₂ in acetonitrile	.47	.46	100	+0.01
VII + CH ₃ OH in acetonitrile	.46	.45	100	-0.03
VII + C ₆ H ₅ -NH ₂ in acetonitrile	.47	.47	100	+0.02
VII + C ₆ H ₅ -NH ₂ in DMF	.46	.45	100	-0.03

^a Analyzed by the method of W. E. Doering and E. Dorfman, *THIS JOURNAL*, **75**, 5595 (1953), as slightly modified by D. B. Denney and M. A. Greenbaum, *ibid.*, **78**, 979 (1957). In the case of the anhydrides and products the observed oxygen-18 values appear to be good to ± 0.01 atom % oxygen-18. In general, in work of this sort the tendency is to obtain low values for the oxygen-18 content since any dilution or exchange causes a decrease in oxygen-18 content. The deviation from the expected total oxygen-18 content of the products has been listed in the table, and in all cases but one it is equal to or less than ± 0.03 . These values represent the sum of the errors over three positions. The calculated per cent. equilibration is accurate to about $\pm 8\%$, in the case of products from VII. In the case of products from VI it is about $\pm 5\%$. The reason for the difference between VII and VI is because of the greater oxygen-18 content of VI.

The presence of added base in the reaction mixture should lead to a net decrease in equilibration, all other things being equal. This will arise since the rate of conversion of II to products will be increased as will the rate of formation of III. The reaction in ammonia demonstrates the importance of base concentration in controlling the amount of equilibration. In order to find other examples of this behavior, the labeled benzoic anhydride was allowed to react with aniline in acetone-water (1:2). Analysis of the products showed that 23% equilibration had occurred. Under these conditions the water is functioning as a base and therefore decreases the rate of return from II. II is also probably much more stable in this solvent mixture than in solvents of lower dielectric constant, and the ions should therefore be much more loosely bound. Any diffusion away from the cation by benzoate ion will lead to a lowering in the rate of return from II to I.

Prof. Philip A. Vaughan (Rutgers) has derived an equation which relates the ratio of the rate of return from II to the rate of those processes which lead to products, *i.e.*, k_4 and Path B. This equation only applies to those situations in which an effective base is present in excess throughout the course of the reaction. The equation is

$$V = 0.333 + \frac{0.166}{0.75r + 1}$$

where V = the observed excess oxygen-18 content in the product benzoyl species normalized to a starting value of 1.00.

r = the ratio of the rate of return from II to product formation by all paths, and r is also equal to the average number of returns from II.

Using this equation r can be calculated for the reaction in acetone/water and it is 0.22. This result is indicative of the delicate balance of rates between return and product formation.

It was deemed desirable to have an example of the reaction in a basic organic solvent. The choice

of such a solvent is rather difficult since they can in general react with the anhydride to cause equilibration. It was found that the reaction of cyclohexylamine with labeled anhydride in dimethylaniline afforded products which were 62% equilibrated. In this example at least some of the equilibration may have been caused by the dimethylaniline. A calculation of r for the above reaction shows it to be 1.4. In this case it is interesting to note that although dimethylaniline is a stronger base than water, more equilibration takes place than occurred in the aqueous solution. At least a part of this effect is due to the lower dielectric constant of dimethylaniline which will cause II to be "tighter" and will facilitate return. When methanol was used as the solvent as well as the nucleophile, the products contained completely equilibrated oxygen-18. Since methanol is a weaker base than either water or dimethylaniline and since its dielectric constant is rather low as compared to water, it is not surprising that one finds complete equilibration in the reaction.

Effect of Deuterium Substitution.—Inspection of the proposed reaction scheme indicates that any diminution in the rate of conversion of II to products or in the rate of Path B should lead to increased oxygen-18 equilibration. Deuterium substitution for hydrogen to give :N-D will lead to intermediates containing deuterium and presumably to a diminution in rate of hydrogen transfer since the energy required to transfer the deuterium will be larger than that required for the proton. When cyclohexylamine-ND₂ was allowed to react with labeled anhydride in dimethylaniline, the products showed complete equilibration of the label. These results are to be compared with the undeuterated material in which the amount of equilibration was 62%. Clearly there is an isotope effect which leads to the predicted behavior.

Effect of Substituent.—When *p*-nitrobenzoic benzoic anhydride-*p*-nitrobenzoyl-carbonyl-O¹⁸ (IX)

was allowed to react with aniline in ether, the *p*-nitrobenzanilide contained 52% of the excess oxygen-18. Several factors can contribute to the difference found between the amount of oxygen-18 equilibration in the substituted and unsubstituted cases. One difference is that in the substituted case one can isolate product containing only the original labeled position, *i.e.*, *p*-nitrobenzanilide. In this manner the dilution factor which was present in the symmetrical case is removed. The presence of the *p*-nitro group will enhance the rate of attack at the carbonyl adjacent to the ring bearing the *p*-nitro group. Increased attack at this position causes a slower equilibration than an equal number of statistical attacks. There are considerable complications attendant with any attempt to calculate the number of returns from II in this case, since II now consists of two different ion pairs which are formed at different rates and which have different k_{-1} 's, etc. It is possible to make a very naive calculation if several assumptions are made. It has been assumed that the ratio of the rate of attacks at the substituted benzoyl moiety as compared to the benzoyl is 3:1. This assumption is based on the product ratio, there being 75% *p*-nitrobenzanilide to 25% benzanilide. It is also necessary to assume that k_4 and k_3 are zero until the proper degree of equilibration is reached and then become infinite. Such an assumption leads to a value for the number of returns (the ratio of the rates is not being calculated here) that is smaller than the actual value. The equation used in this calculation is one that arose during the derivation of the equation reported above. It is

$$P_N = \frac{1}{3} + \frac{2/3g_2 - 1/6 - 1/3x}{g_2 - g_1} g_1 N + \frac{1/6 + 1/3x - 2/3g_1}{g_2 - g_1} g_2 N$$

where P_N = observed excess oxygen-18 in the benzoyl product normalized to a starting value of 1.0.

x = probability of attack at the labeled position here $3/4$.

$$g_1 = \frac{1 + \sqrt{1 - 3x + 3x^2}}{2} \quad g_2 = \frac{1 - \sqrt{1 - 3x + 3x^2}}{2}$$

N = number of returns, with the limitations discussed above

Calculation of N for the reaction of the *p*-nitrobenzoic benzoic anhydride gives a value between four and five. This average value is low since the rate of formation of product has been ignored.

Effect of Solvent.—The reaction of the labeled anhydride with aniline in dimethylformamide, acetonitrile and ether have been investigated. In all of these cases the products were completely equilibrated. In going from ether to dimethylformamide and acetonitrile, the dielectric constant of the solvent has changed from 4.34 to 37.5. An increase in dielectric constant of the solvent should markedly increase k_1 and decrease k_{-1} . An increase in k_2 should also be observed if, as seems likely, the charges in II are separated farther apart than in I. If such is the case, one would expect k_2 to decrease. The effect of increased dielectric on k_4 should be a slight decrease since in the transition state leading from II to products, *i.e.*, the proton transfer, there will be a dispersal of positive charge.

In Path B k_3 should increase and k_{-3} decrease if the charge separation in III is greater than in II. The effect on k_3 should be relatively slight. The predicted over-all effect of increased dielectric constant is less equilibration of the oxygen-18, since the large decrease in k_{-1} relative to the changes of the other constants should make return a slower process. Since in all of the non-basic solvents studied to date the products have been equilibrated, it is impossible to test this prediction. Future experiments using monolabeled *p*-nitrobenzoic benzoic anhydride should give a quantitative measure of the solvent effect in this reaction.

Effect of Nucleophile.—Cyclohexylamine in ether and methanol in acetonitrile were allowed to react with the labeled anhydride. In both of these cases the products contained completely equilibrated oxygen-18. These findings are not unexpected since the controlling factors for these reactions do not appear to involve the rate of formation of I which will be affected markedly by a change in the power of the nucleophile.

Acknowledgment.—We wish to thank the Esso Research Corporation for making available the mass spectrometer used in this work.

Experimental

Benzoic Anhydride (V).—A solution of 6.70 g. (0.048 mole) of benzoyl chloride- O^{18} (from III) in 30 ml. of chloroform was shaken intermittently over a 48-hr. period with a solution of 6.00 g. (0.050 mole) of benzoic acid and 2.00 g. (0.050 mole) of sodium hydroxide in 50 ml. of water. The chloroform solution was dried and concentrated *in vacuo* to afford material which after two crystallizations from petroleum ether had m.p. 41.5–42°; yield 5.80 g. (55%).

Benzoic Anhydride (VII).—To an ice-cold stirred suspension of 40.0 g. (0.175 mole) of silver benzoate and 25 g. of glass beads in 250 ml. of dry ether was added 24.0 g. (0.171 mole) of benzoyl chloride- O^{18} (from IV) in 25 ml. of ether. The mixture was stirred at 0° for 12 hr. The ether solution was evaporated to give 31.5 g. of crude anhydride which after crystallization from hexane afforded 26.4 g. (68%) of VII, m.p. 43–43.5°.

Benzoic Anhydride (VIII).—To a stirred solution of 43.8 g. (0.312 mole) of benzoyl chloride in 60 ml. of ether was added over 15 minutes a solution of 38.0 g. (0.312 mole) of benzoic acid- O^{18} (V) and 24.7 g. (0.312 mole) of pyridine in 100 ml. of ether. The solution was washed with water, 10% hydrochloric acid and 10% sodium bicarbonate solution. After drying the ether, it was evaporated to afford 67.0 g. of crude VIII. The crude material was crystallized from hexane–benzene to afford 61.0 g. (86%) of VIII, m.p. 41–42°.

Reactions and Reagents.—In general the solvents and reagents were purified by standard methods. The products in all cases were isolated easily in high yield with a minimum amount of effort. All of the products were purified before analysis. Table III contains the experimental data.

Cyclohexylamine- ND_2 .—A solution of 5.0 g. of cyclohexylamine in 25 ml. of ether was shaken with 3 ml. of deuterium oxide followed by four 1-ml. washes. The ether layer was dried over magnesium sulfate and evaporated to yield the deuterated amine. The infrared spectrum of this material indicated the presence of deuterium in the molecule. The amine was used as such in the reaction with the anhydride.

***p*-Nitrobenzoic Benzoic Anhydride-*p*-nitrobenzoyl Carbonyl- O^{18} (IX).**—The labeled anhydride was prepared as described by Denney and Greenbaum.⁹

Reaction of VI in the Presence of Benzoic Acid- C^{14} .¹⁰—To a solution of 0.465 g. (0.005 mole) of aniline, 0.61 g. (0.005 mole) of benzoic acid- C^{14} , activity 4.07 $\mu\text{mc./mg. C}$ and

(9) D. B. Denney and M. A. Greenbaum, *THIS JOURNAL*, **79**, 979 (1957).

(10) The authors wish to thank Dr. A. P. Wolf of the Brookhaven National Laboratory for his kind assistance in carrying out these experiments.

TABLE III

Reactants ^a	Temp., °C.	Solvent	% Yield C ₆ H ₅ -CO-	% Yield C ₆ H ₅ -COOH
VI ^b + NH ₃	-33	Ammonia, 25 ml.	70	65
VII + NH ₃	-33	Ammonia, 25 ml.	93	86
VII + NH ₃	-78	Ammonia, 25 ml.	91	85
VI + C ₆ H ₅ -NH ₂	25	Ether, 30 ml.	80	70
VI + C ₆ H ₅ -NH ₂	25	Acetone/H ₂ O, 20 ml.	81	75
VII + cyclo-C ₆ H ₁₁ -NH ₂	25	Dimethylaniline, 25 ml.	85	80
VII + CH ₃ OH	25	Methanol, 25 ml.	92	80
VII + CH ₃ OH	25	Acetonitrile, 30 ml.	25 ^c	21
VII + cyclo-C ₆ H ₁₁ -NH ₂	25	Acetonitrile, 35 ml.	89	92
VII + C ₆ H ₅ -NH ₂	25	Acetonitrile, 40 ml.	86	82
VII + C ₆ H ₅ -NH ₂	25	Dimethylformamide, 40 ml.	86	90

^a Unless otherwise specified the quantities of reactants used were 0.01 mole. ^b 0.0018 mole of VI used. ^c A large recovery of starting material indicated that this reaction was not completed.

0.61 g. (0.005 mole) of dimethylaniline in 50 ml. of anhydrous ether was added 1.13 g. (0.005 mole) of benzoic anhydride. After standing 1 hr., 10 ml. of 10% hydrochloric acid was added and the ether was evaporated. The heterogeneous mixture was treated with chloroform to dissolve the solid. The chloroform was washed with 10% sodium carbonate solution and water. The dried chloroform was evaporated to afford 1.01 g. of benzanilide which was recrystallized from methanol-water to afford 0.70 g. (71%) of material, m.p. 162.2–163.4°. The basic extracts were acidified to yield crude benzoic acid which was recrystal-

lized from hexane to afford 0.90 g. (74%) of benzoic acid, m.p. 121–122°.

The recovered benzoic acid had an activity of 2.02 mμc./mg. C and the benzanilide showed 0.093 mμc./mg. C. These data indicate that 15% of the theoretical amount of C¹⁴ has been incorporated into the benzanilide.

When benzoic anhydride was allowed to stand under the same conditions but in the absence of aniline, the recovered benzoic anhydride had 0.63 mμc./mg. C which corresponds to 46% equilibration of the C¹⁴.

NEW BRUNSWICK, N. J.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, IOWA STATE COLLEGE]

Electronic Effects in Elimination Reactions. I. Pyrolysis of Acetates¹

BY C. H. DEPUY AND R. E. LEARY

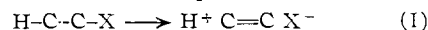
RECEIVED FEBRUARY 8, 1957

Pyrolytic eliminations of some acetates of substituted 1,3-diphenyl-2-propanols lead to the formation of that olefin which also predominates when the possible olefins are equilibrated and not to the olefin which would be formed by loss of the most acidic hydrogen. It is suggested that in the transition state for acetate pyrolysis reactions, a large amount of double bond character has been developed.

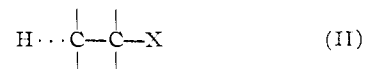
Although the Saytzeff and Hofmann rules—which allow the position of the double bond in unsymmetrical elimination reactions to be predicted—have been formulated for nearly a century, the underlying steric and electronic effects which determine this position still are not fully understood. The most generally accepted interpretation of the rules is that of Hughes and Ingold.² According to their view, in the Hofmann elimination (elimination from trialkylammonium or dialkylsulfonium salts with base) the most acidic hydrogen is removed and the direction of elimination is determined by this factor. In the Saytzeff elimination (elimination of halogen or other neutral anions), the stability of the resulting olefinic product is the more important factor and controls the direction of elimination. Hyperconjugative factors were postulated to be of primary importance. Recently Brown and co-workers³ have demonstrated the

importance of steric effects in directing eliminations.

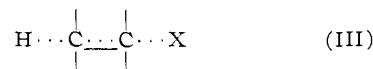
A priori, an elimination of the type I might be imagined to have a whole spectrum of transition



states available to it, depending upon the nature of the group X, the particular mechanism of the elimination, the type of solvent and a host of other factors. As one extreme, a case might be imagined in which the carbon-hydrogen bond is completely broken before the C-X bond has even started to rupture, II. At the other extreme, both the C-H



and C-X bonds might be very much broken in the transition state, III. Other situations may be imagined. An understanding of the structural



factors that affect the transition state configuration could allow more control over the nature of the product to be expected in eliminations and the amount of olefin being formed in competing reac-

(1) This work was supported by a grant from the Research Corporation.

(2) For a general discussion of elimination reactions and for the conclusions of Ingold and co-workers about the Hofmann and Saytzeff rules, see C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, pp. 420–472.

(3) H. C. Brown and I. Moritani, THIS JOURNAL, **78**, 2203 (1956), and preceding papers.