General Acid–Specific Base Catalyzed Isomerization of *tert*-Butyl Thiolbut-3-enoate to *tert*-Butyl Thiolcrotonate[1,2]

Leo Fedor* and Patrick H. Gray

Contribution from the Department of Medicinal Chemistry, School of Pharmacy,
State University of New York at Buffalo, Buffalo, New York 14214.
Received July 22, 1975

Abstract: Isomerization of *tert*-butyl thiolbut-3-enoate (**1**) to *tert*-butyl thiolcrotonate (**2**) is catalyzed by tertiary amines and hydroxide ion in water solution and by tertiary amines in anhydrous acetonitrile. The reaction is distinguished by an experimental deuterium solvent kinetic isotope effect, $k_2(H_2O)/k_2(D_2O)$, greater than six for reactions catalyzed by *N,N*-dimethylaminoethanol, *N,N*-dimethylisopropylamine, and triethylamine. In CD_3OD the rate of methylene proton exchange (NMR) in **1** exceeds the rate of isomerization. General base catalyzed formation of **1** carbanion followed by rate-determining general acid catalyzed formation of **2** is proposed. *Calculated* rate constants for formation of **1** carbanion and its partitioning to **1** and **2** have values expected for these proton transfers. Isomerization in acetonitrile is subject to a deuterium isotope effect, $k_2(R_3NH^+)/k_2(R_3ND^+)$, greater than 1, and the isotope effect increases with increasing concentration of R_3ND^+. Intramolecular proton transfer via an ion pair intermediate which exchanges H of $R_3NH^+\text{-}\mathbf{1}^-$ with R_3ND^+ in a concentration-dependent way is proposed for isomerization in acetonitrile.

Introduction

α-Methylene proton transfer from thiol esters to acceptor bases initiates a number of reactions of biochemical importance.[3] One of these involves dehydration of β-hydroxy thiol esters catalyzed by such enzymes as β-hydroxydecanoyl thioester dehydrase[4] and enoyl coenzyme A hydratase (crotonase),[5] enzymes which also possess isomerase activity (eq 1).

$$RCH{=}CHCH_2COSR' \rightleftarrows RCH_2CH{=}CHCOSR' \quad (1)$$

Vinylacetyl isomerase from *C. kluyveri* possesses isomerase activity only, catalyzing a nearly quantitative conversion of *N*-acetylcysteaminyl vinylacetate to the crotonyl derivative (eq 1).[6] Vinyl acetyl isomerase from ox liver catalyzes conversion of β-methylvinylacetyl coenzyme A to β-methylcrotonyl coenzyme A.[7] Despite the importance of such enzyme catalyzed reactions in fatty acid biosynthesis and degradation, little is known of the details of these reactions, although in the case of β-hydroxydecanoyl thioester dehydratase, experimental evidence suggests an E1cB or a concerted mechanism may operate.[4,8,9] It is noteworthy that no kinetics studies have been done on nonenzyme-mediated isomerization reactions of thiol esters, one of the simplest models for proton transfer from such carbon acids to acceptor bases which initiates a chemical change. Here we report the results of a kinetic study of the base catalyzed isomerization of *tert*-butyl thiolbut-3-enoate (**1**) to *tert*-butyl thiolcrotonate (**2**).

$$\underset{\mathbf{1}}{CH_2{=}CHCH_2COSC(CH_3)_3} \rightarrow \underset{\mathbf{2}}{CH_3CH{=}CHCOSC(CH_3)_3} \quad (2)$$

Experimental Section

Apparatus. Gilford Model 2400 spectrophotometers and a Beckman Model DBG spectrophotometer were used. Temperature was maintained with Tamson T9 circulating water baths connected to thermospacers in the spectrophotometers. pH measurements were made with a Radiometer PHM 26 meter. A Varian A-60 NMR spectrometer was used.

Reagents. All reagents were Fisher Certified ACS grade, except vinylacetic acid, *N,N*-dimethylaminoethanol, *N*-ethylmorpholine, and *N*-methylmorpholine (Aldrich), *N,N*-dimethyl-*tert*-butylamine, triethylamine, *N,N*-dimethylisopropylamine, and *tert*-butylmercaptan (Eastman), and D_2O and DCl (99.8% D) (Stohler Isotope Chemicals). Triethylammonium-*1-d* chloride was prepared from triethylammonium chloride by dissolving it in D_2O and removing solvent. The process was repeated three times, and the denatured salt was crystalized from anhydrous acetonitrile. Line distilled water was redistilled through a Corning AGla still before use. Acetonitrile was refluxed with P_2O_5 and distilled. It was then refluxed with CaH_2, distilled, and stored under nitrogen.[10] *tert*-Butyl thiolbut-3-enoate was synthesized from vinylacetyl chloride[11] and *tert*-butylmercaptan: a solution of *tert*-butylmercaptan, 23.4 g (0.26 mol), in 25 ml benzene was added dropwise to a solution of 27.5 g (0.26 mol) of vinylacetyl chloride in 100 ml of benzene at room temperature during 0.5 hr. The solution was stirred for 24 hr, following which the benzene was removed in vacuo with gentle heating. The residue was clarified to a colorless liquid by distillation at 5 mm, and the distillate was redistilled to give four fractions. The second fraction, bp 60° (8 mm) (14.6 g, 35%), was used for kinetics and submitted for analysis (Galbraith Laboratories, Inc.).

Anal. Calcd for $C_8H_{14}OS$: C, 60.70; H, 8.91; S, 20.06. Found: C, 60.52; H, 8.86; S, 20.06.

Kinetics. All solutions were maintained at an ionic strength of 0.1 *M* by addition of KCl to water solutions and tetraethylammonium bromide to acetonitrile solutions unless otherwise stated. The reaction temperature was 30 ± 0.1°, and pH's of water solutions were measured and found to be constant to ±0.03 pH unit for virtually all serial dilutions of constant buffer ratio. Amine hydrochloride salts were generated in water by addition of known amounts of 1 *N* HCl to the amines and in acetonitrile solutions by addition of weighed amounts of dry amine hydrochloride or amine deuteriochloride. Reactions were run under pseudo-first-order conditions ([**1**] ca. 3×10^{-5} *M*) and were initiated by addition of **1** in acetonitrile or methanol to amine solutions. The optical density (OD) increase at 265 nm due to generation of the conjugated olefin was monitored as a measure of the reaction progress. Michael addition to **2** was monitored as the loss of OD with time and was found to be sufficiently slow for amine-catalyzed reactions (nonexistent for reactions run in acetonitrile) to be ignored. Accordingly, pseudo-first-order rate constants were obtained by plotting log $(OD_\infty - OD_0)/OD_\infty - OD_t)$ vs. time and multiplying the least-squares slope of the line by 2.303. Plots were linear to 75% reaction or beyond. For reactions run in dilute potassium hydroxide solutions, pseudo-first-order rate constants were calculated for A → B → C reactions[12] because Michael reaction of hydroxide ion with **2** destroyed the 265 chromophore too rapidly to permit assumption of A → B reactions. The rate of loss of methylene protons of **1** in CD_3OD was measured using NMR spectrometry. Typically, into an NMR tube were placed 0.4 ml of 0.2 *M* triethylamine in

Table I. Rate Data for Isomerization (1 → 2) in Aqueous Solution[a]

Base	Fraction of base	k_2, M^{-1} min^{-1}	No. of k_{obsd}	Concn range of base, M
EM	0.8	0.058 ± 0.001	11	0.02–0.2
MM	0.8	0.062 ± 0.002	11	0.01–0.5
DMAE	0.167	0.63 ± 0.01	6	0.002–0.02
	0.5	0.56 ± 0.01	5	0.02–0.10
	0.8	0.70 ± 0.02	6	0.05–0.5
	0.83	0.59 ± 0.03	6	0.05–0.5
	0.8	0.094 ± 0.001[b]	6	0.05–0.5
DMIA	0.5	3.18 ± 0.2	8	0.02–0.2
	0.5	2.9 ± 0.08[c]	5	0.08–0.4
	0.8	3.0 ± 0.07	6	0.02–0.2
	0.5	0.45 ± 0.025[b]	6	0.02–0.2
TEA	0.5	2.06 ± 0.05	6	0.02–0.2
	0.5	0.22 ± 0.01[b]	6	0.02–0.2
OH		12.2 ± 1.8	19	0.01–0.1

[a] $t = 30 \pm 0.1°$; $\mu = 0.1\ M$ unless otherwise stated; reported errors are standard deviations; bases used are *N,N*-dimethylaminoethanol (DMAE), *N,N*-dimethylisopropylamine (DMIA), hydroxide ion (OH), *N*-methylmorpholine (MM), *N*-ethylmorpholine (EM), triethylamine (TEA). [b] Solvent = D_2O. [c] $\mu = 0.2$.

Table II. Rate Data for Isomerization (1 → 2) in Acetonitrile[a]

Base	Fraction of base	k_2, M^{-1} min^{-1}	No. of k_{obsd}	Concn range of base, M
DMIA	1.0	0.38 ± 0.01[b]	6	0.1–1.0
DMTA	0.167	0.71 ± 0.002	6	0.002–0.02
	0.5	0.80 ± 0.017	6	0.01–0.10
	0.5	0.84 ± 0.016	6	0.01–0.10
	0.833	0.90 ± 0.029	6	0.05–0.20
	1.0	0.68 ± 0.025[b]	6	0.05–0.50
TEA	0.67	0.35 ± 0.007[c]	6	0.03–0.3
	0.9	0.37 ± 0.03	6	0.05–0.3
	1.0	0.33 ± 0.004[b]	6	0.02–0.2

[a] $t = 30 \pm 0.1°$; $\mu = 0.1\ M$ (($(C_2H_5)_4NBr$ unless otherwise stated; reported errors are standard deviations; bases used are *N,N*-dimethyl-*tert*-butylamine (DMTA), *N,N*-dimethylisopropylamine (DMIA), triethylamine (TEA). [b] $\mu = 0$. [c] Variable μ (constant buffer ratio but no added $(C_2H_5)_4NBr$).

CD_3OD, 0.01 ml of CH_3CN for reference standard, and 0.1 ml of **1**. The signals from the methylene protons were integrated at timed intervals, and the agnitudes of the signals were determined relative to those for CH_3CN. First-order rate constants for exchange-isomerization were obtained by multiplying slopes of plots of log $(P_i - P_\infty)/(P_t - P_\infty)$ vs. time by 2.303, where P_i is the corrected peak height at arbitrary time zero, P_t is the corrected peak height at any time, and P_∞ is the corrected peak height at time infinity. A small residual signal remained after runs, which was due to CH in CD_3OD which absorbed at the analytical δ. Each rate constant so obtained was divided by $[(C_2H_5)_3N]$ to give, after correction for the isomerization rate (vide infra), k_2 (exchange) = 1.2 ± 0.2 M^{-1} min^{-1} (six values) at ca. 25°. Isomerization of **1** in 0.2 M triethylamine in CD_3OD as determined spectrophotometrically gave $k_2 = 0.034 \pm 0.001\ M^{-1}$ min^{-1} (three values) at 25°; under identical conditions, $k_2 = 0.15 \pm 0.006\ M^{-1}$ min^{-1} (three values) in CH_3OH.

Product Analysis. For reactions of **1** in 0.6 M *N,N*-dimethylaminoethanol, fraction of base = 0.83, the uv spectrum is identical with that of *tert*-butyl thiolcrotonate[12] in the same buffer solution. Isomerization of **1** in this buffer solution gave a molar absorption coefficient ϵ of 6605 ± 107; for **2**, ϵ is 6460 ± 76 so that the yield in this reaction is 102 ± 2%. From this and other similar experiments we conclude that the equilibrium $\mathbf{1} \rightleftarrows \mathbf{2}$ lies virtually completely on the side of **2**. For reactions run in dilute potassium hydroxide solutions, the absorbance vs. time curves pass through a maximum, and absorbance (265 nm) gradually decreases. This indicates that **2** is formed as initial product, and that it is unstable and is converted to a nonolefinic thiol ester, presumably by Michael addition (hydration) of hydroxide ion to the β carbon of **2**. The rate of loss of absorbance is characterized by $k_{OH} = 1.11$ (±0.07) M^{-1} min^{-1}; for **2**, similar absorbance loss is characterized by $k_{OH} = 1.17$ (±0.02) M^{-1} min^{-1}.

Results

In water solution at constant pH, isomerization of **1** to **2** catalyzed by tertiary amines follows the rate law of eq 3.

$$d[\mathbf{2}]/(dt)[\mathbf{1}] = k_{obsd} = k_2 f[\text{amine}]_{total} + bK_w/a_H + c \tag{3}$$

The second-order rate constant for amine catalysis, k_2, was obtained by dividing the slopes of linear plots of k_{obsd} vs. concentration of total amine by f, the fraction of free amine present in the catalytic buffer at a constant pH (Table I). Evaluation of the intercept terms for these plots will be discussed below. In dilute potassium hydroxide solution, isomerization of **1** to **2** obeys the rate law of the equation

$$d[\mathbf{2}]/(dt)[\mathbf{1}] = k_{obsd} = k_{OH}K_w/a_H \tag{4}$$

The constant k_{OH} was obtained as the slope of a plot of k_{obsd} vs. K_w/a_H for reactions run in dilute potassium hydroxide solution (Table I). Equation 3 and the proposed mechanism require a small intercept (ca. 10^{-3} min^{-1}) at $K_w/a_H \rightarrow 0$; however, its value constitutes ca. 0.3-3.5% of k_{obsd} values determined for reactions run in dilute hydroxide solutions, and we could not distinguish the intercept value from zero. For isomerization of **1** to **2** catalyzed by *N,N*-dimethylaminoethanol, *N,N*-dimethylisopropylamine, and triethylamine, $k_2(H_2O)/k_2(D_2O)$ = 6.6, 6.7, and 9.4, respectively. In CD_3OD solution, k_2(exchange)/k_2(isomerization) = 35 for isomerization catalyzed by triethylamine (Experimental Section). Isomerization in anhydrous acetonitrile follows the rate law of eq 5. The second-order rate constants for amine catalysis

$$d[\mathbf{2}]/(dt)[\mathbf{1}] = k_{obsd} = k_2 f[\text{amine}]_{total} \tag{5}$$

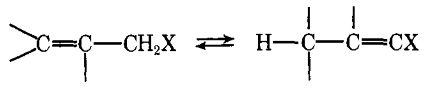
were obtained by dividing the slopes of linear plots of k_{obsd} vs. total amine concentration by f, the fraction of free amine present in amine-amine hydrochloride (deuteriochloride) solution (Table II). The value of k_2 is independent of the concentration of ammonium ion present in solutions with amine, not only in the kinetic sense, but also in the absolute sense: a proton source exclusive of **1** is not required for reaction. For isomerization of **1** catalyzed by triethylamine in acetonitrile solution containing triethylamine deuteriochloride, a deuterium isotope effect is obtained, which is dependent on the concentration of added triethylamine deuteriochloride (Tables III and IV). From the data of Table III, eq 6 may be obtained. From similar data (Table IV) obtained for constant, instead of varied, buffer ratio, eq 7 may be obtained.

$$k_{obsd}((C_2H_5)_3N)/k_{obsd}((C_2H_5)_3N/(C_2H_5)_3NDCl) = 9.7\ (\pm 0.62)[(C_2H_5)_3NDCl] + 0.96 \tag{6}$$

$$k_{obsd}((C_2H_5)_3N/(C_2H_5)_3NHCl)/k_{obsd} \times ((C_2H_5)_3N/(C_2H_5)_3NDCl) = 8.7\ (\pm 0.56)[(C_2H_5)_3NDCl] + 1.01 \tag{7}$$

Discussion

Base catalyzed allyl-propenyl isomerizations of the type



$$>C{=}\underset{|}{C}{-}CH_2X \rightleftarrows H{-}\overset{|}{\underset{|}{C}}{-}\overset{|}{C}{=}CX$$

3 4

(X = CN, CO_2R, CO_2^-, COR)

have been extensively studied, primarily from the viewpoint of the influence of various groups on the position of equilibrium.[13-17] Two mechanisms evolved from these investigations, the stepwise carbanion mechanism of Ingold et al.[18]

Table III. Rate Data for Isomerization (1 → 2) in 0.2 *M* Triethylamine with Variable Triethylamine Deuteriochloride in Acetonitrile[a]

$(C_2H_5)_3NDCl$	k_{obsd}, min^{-1}	$(C_2H_5)_3NDCl$	k_{obsd}, min^{-1}
0	0.0675	0.06	0.044
0.01	0.064	0.08	0.037
0.02	0.059	0.10	0.0355
0.04	0.053		

[a] $t = 30 \pm 0.1°$.

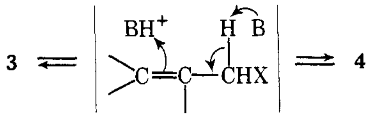
Table IV. Rate Data for Isomerization (1 → 2) in Triethylamine–Triethylamine Deuteriochloride at Constant Buffer Ratio in Acetonitrile[a]

Et_3N/Et_3NDCl	$k_{obsd}(Et_3N/Et_3NHCl)/k_{obsd}(Et_3N/Et_3NDCl)$
0.02/0.01	0.00708/0.00648
0.04/0.02	0.0133/0.0108
0.08/0.04	0.0254/0.019
0.12/0.06	0.0415/0.028
0.16/0.08	0.0557/0.0336
0.2/0.1	0.069/0.0355

[a] $t = 30°$, rate constants have units of min^{-1}.

$$\mathbf{3} \underset{k_{ii}BH^+}{\overset{k_i(B)}{\rightleftarrows}} \mathbf{3}^- \underset{k_{iv}(B)}{\overset{k_{iii}(BH^+)}{\rightleftarrows}} \mathbf{4} \tag{8}$$

and the concerted mechanism of Lowry[19]



Following the demonstration by Ingold et al.[20] that the rate of deuterium for hydrogen exchange in cyclohexenylacetonitrile (0.1 *M* $C_2H_5O^-/C_2H_5OD$) greatly exceeds the rate of isomerization of that compound to cyclohexylidinylacetonitrile, the mechanism of Ingold has been "generalement admis".[21,22] To our knowledge there has been no unequivocal kinetics demonstration of the concerted mechanism. Ingold et al.,[16] developing the carbanion mechanism, summarized experiences with tautomeric equilibria with the general rule that protonation of the carbanion formed from weak acid tautomers of unequal stability results in quicker formation of the thermodynamically less stable tautomer, which tautomer is most quickly ionized by base. In the case of isomerization of **1** to **2**, this rule predicts that $\mathbf{1}^-$ will be more quickly formed from **1** than **2** and that partitioning of $\mathbf{1}^-$ will favor formation of **1**: in terms of eq 8, $k_{ii} > k_{iii}$.

Apparent general base catalyzed isomerization of **1** to **2** (eq 3) requires that the critical transition state contain **1** and base or their kinetic equivalent such as $\mathbf{1}^-$ and BH^+. For this reaction we shall attempt to show that the carbanion mechanism of Scheme I is the simplest mechanism accordant with our results.

Scheme I

$$\mathbf{1} \underset{k_b(BH^+),\,k_e(H_2O),\,k_h(H^+)}{\overset{k_a(B),\,k_d(OH^-),\,k_g(H_2O)}{\rightleftarrows}} \mathbf{1}^- \xrightarrow{k_c(BH^+),\,k_f(H_2O),\,k_i(H^+)} \mathbf{2}$$

This mechanism leads to the steady state rate law of eq 9.

$$d[\mathbf{2}]/(dt)[\mathbf{1}] = k_{obsd} = \frac{(k_a[B] + k_d[OH^-] + k_g[H_2O])(k_c[BH^+] + k_f[H_2O] + k_i[H^+])}{(k_b + k_c)[BH^+] + (k_e + k_f)]H_2O] + (k_h + k_i)[H^+]} \tag{9}$$

Two assumptions, based on *estimates* of the various rate constants of eq 9 discussed below (Table V), will be made: (1) $(k_b + k_c)[BH^+] > (k_e + k_f)[H_2O] + (k_h + k_i)[H^+]$ under our reaction conditions; (2) $(k_dk_f[OH^-][H_2O] + k_fk_g[H_2O]^2 + k_dk_iK_w + k_gk_i[H^+][H_2O]/(k_b + k_c)[BH^+])$ is significantly small to be negligible. If for the moment these assumptions are accepted, then eq 9 reduces to the equation

Table V. Calculated Rate Constants for Tertiary Amine and Hydroxide Ion Catalyzed Isomerization of 1 → 2[a]

Base	pK_a	k_a (k_d)	k_b (k_e)	k_c (k_f)
MM	7.41	4.4	6.8×10^{11}	9.8×10^9
EM	7.70	4.1	3.3×10^{11}	4.7×10^9
DMEA	9.13	44	1.3×10^{11}	1.9×10^9
DMIA	10.30	213	4.3×10^{10}	6.1×10^8
TEA	10.87	146	7.9×10^9	1.1×10^8
OH	15.57	(866)	(9.3×10^5)	(1.3×10^4)

[a] The method of calculation of constants is described in the Discussion section; bases are those described in Table I; pK_a determined by the method of fractional neutralization except $pK_a(OH) = -\log(K_w/55.5)$; constants have units of M^{-1} min^{-1}.

$$d[\mathbf{2}]/(dt)[\mathbf{1}] = k_{obsd} = \frac{(k_ak_c)[B]}{(k_b + k_c)} + \frac{(k_ck_dK_w + k_ak_fK_a[H_2O][OH^-]}{(k_b + k_c)K_w} + \frac{(k_ck_g[H_2O] + k_ak_iK_a)}{(k_b + k_c)} \tag{10}$$

which has the form of eq 3. For reactions run in dilute potassium hydroxide solutions, B and BH^+ terms of eq 9 are zero, and H^+ terms are negligible so that for these reactions the equation

$$d[\mathbf{2}]/(dt)[\mathbf{1}] = k_{obsd} = k_dk_f[OH^-]/(k_e + k_f) + (k_fk_g[H_2O]^2 + k_dk_iK_w)/(k_e + k_f)[H_2O] \tag{11}$$

obtains. The second term is not detectable at high pH; however, evidence for its existence was obtained from results of isomerization of **1** to **2** in *N*-methylmorpholine and *N*-ethylmorpholine solutions at pH 8.0 and 8.3, respectively, where hydroxide ion catalysis is negligible. For these reactions, the intercept rate constants represent 10-50% of the k_{obsd} values through the serial dilutions of buffer, and we believe that, in catalytic amine buffers, these intercept rate constants largely represent the third term of eq 10, that water is therefore a catalyst for isomerization, and that the second term of eq 11 likely exists. If k_i is assumed to have a value as great as one associated with a diffusion-controlled proton transfer process, or any lesser value, it can be shown from estimates of the rate constants of Scheme I (vide infra, Table V) that the third term of eq 10 reduces to $k_ck_g[H_2O]/(k_b + k_c)$. The value of $k_g = 3.6 \times 10^{-3}$ M^{-1} min^{-1} was obtained by equating intercepts from plots of k_{obsd} vs. concentration of *N*-methylmorpholine and *N*-ethylmorpholine to this latter term, substituting values for k_c and k_b from Table V and dividing the result by 55.5 *M*. All of the intercept values of this study were accountable on the basis of the last two terms of eq 10 and values for the calculated constants of Table V. However, by and large, the fraction of isomerization catalyzed by water and hydroxide ion in catalytic amine buffers is very small. Given that the spontaneous rate contributes negligibly to isomerization in dilute potassium hydroxide solutions, it may be seen that k_{OH} of eq 4 is equal to $k_dk_f/(k_e + k_f)$ of eq 11.

Following predictions of the Ingold generalization, we sought evidence for the rapid formation of $\mathbf{1}^-$ from **1** and, indeed, found that the rate of hydrogen for deuterium exchange of methylene hydrogens in CD_3OD catalyzed by triethylamine exceeds the rate of isomerization. Accepting that exchange and isomerization reactions share a common pathway, we conclude that k_a is not rate determining in the direction **1** → **2**. From the relationship k_2(exchange)/k_2(isomerization) = k_b/k_c (Scheme I, eq 10) for the triethylamine-catalyzed reactions in CD_3OD, assuming CD_3O^- contributions to rate are quite small, a maximum value for the partitioning ratio of $\mathbf{1}^-$ to **1** and **2** can be calculated. If k_2(exchange) is statistically corrected,[23,24] k_b/k_c 70; i.e., protonation at the α carbon atom to give **1** is favored over protonation at the γ carbon atom to give **2** by ca. 2.5 kcal mol^{-1}.

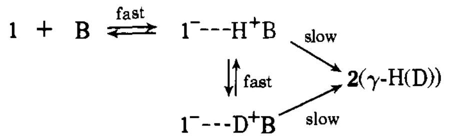
In order to check the reasonableness of Scheme I and to justify our assumptions regarding the limiting form of eq 9, we estimated values for k_a, k_b, k_c, k_d, k_e, and k_f using the relationships k_2 (Table I) = $k_ak_c/(k_b + k_c)$, k_{OH} (Table I) = $k_dk_f/(k_e + k_f)$, and $k_a/k_b = k_d/k_e = K_{SH}/K_a$, where K_{SH} is the ionization constant of **1**, and K_a is the dissociation constant for tertiary ammonium ions of this study (or $K_w/55.5$ in the case of hydroxide ion) and the assumption that k_b/k_c (=k_e/k_f) = 70 throughout. To estimate k_a/k_b we required an estimate of K_{SH} which we based on an estimate of K_{SH} for vinylacetone and the similar acidities of ketones (acetylacetone) and thiol esters (*N*-acetylcysteaminyl acetoacetate).[28] Using $\sigma^*(H) = 0.49$, $\sigma^*(Cl) = 0.89$, and $\sigma^*(CH_2{=}CH) = 0.65$,[26] and using pK_{SH}(acetone) = 20 and pK_{SH}(chloroacetone) = 16.5,[27] we estimate pK_{SH}(vinylacetone) = 18.6 by interpolation and assigned this estimated value of pK_{SH} to **1**. From these relationships and assumptions, $k_a = 71k_2$, $k_b = k_aK_a/K_{SH}$, $k_c = k_b/70$, $k_d = 71k_{OH}$, $k_e = k_dK_w/55.5K_{SH}$, and $k_f = k_e/70$ (Table V). Examination of the *calculated* constants of Table V reveals the following. (1) Values of k_a increase with increasing basicity of the general base catalyst, $\beta = 0.52$, and are of the same order of magnitude as those constants reported for elimination reactions of β-acetoxythiol esters[12,29] and β-oxy ketones,[25] reactions postulated to occur via ElcB mechanisms where kinetics evidence for carbanion formation was obtained. The value for k_a for isomerization catalyzed by triethylamine is low, compared with k_a values for other amines; omission of that data point from the Bronsted plot gives $\beta = 0.62$ with a higher correlation coefficient (0.994 vs. 0.972). Diminished relative reactivity of triethylamine as a catalyst may reflect steric hindrance to proton transfer.[30] (2) Values of k_b and k_c appear to approach the diffusion-controlled limit[31] as acidity of ammonium ions increases and rate constants of these magnitudes are expected for proton transfer to a highly basic carbanion.[27] The Bronsted α values for k_b (=k_c) are 0.48 (0.38 without triethylamine constants), which could be interpreted to mean that proton transfer occurs about midway along the reaction coordinate.[32] This interpretation finds support in the result that experimental deuterium solvent kinetic isotope effects are greater than six, a result we shall address below. Although the "data" of Table V are fictitious, they are useful reminders that, for isomerization of **1** to **2**, a slow proton transfer (k_a) coupled by an equilibrium with a quick proton transfer (k_c) gives rise to a situation wherein the rate-determining step is the quick proton transfer. As well, the Bronsted coefficients are likely correct indicators of the sensitivity of the reactions in qestion to catalyst basicity (acidity) since their values are dependent on relative rate constants which were derived from those of Table I. Constants (Table V) for hydroxide ion catalysis follow trends set for amine catalysis, but they were not included with amine constants for purposes of determining Bronsted coefficients because of the different charge type, solvation characteristics, etc.

From the foregoing discussion, the rate-determining step in the isomerization of **1** to **2** is general acid catalyzed conversion of $\mathbf{1}^-$ to **2**, a process which should be subject to an isotope effect. In fact, large deuterium solvent kinetic isotope effects (>6) were experimentally obtained. The isotope effect for k_c was estimated from assumed values for $K_{SH}{}^H/K_{SH}{}^D$ and $K_a{}^D/K_a{}^H$ and the relationship $k_2(H_2O)/k_2(D_2O) \simeq (k_c{}^H/k_c{}^D)(K_{SH}{}^H/K_{SH}{}^D)(K_a{}^D/K_a{}^H)$. This approximate relationship rests on the assumption that 1 is sufficiently large compared to k_c/k_b (Table V) (=0.014) so that $k_ak_c/k_b + k_c) \simeq k_ak_c/k_b$. Inexact as it may be for $K_{SH}{}^H/K_{SH}{}^D$ for carbon acids, the Rule-La Mer[33] plot gave 6.3 for this ratio; we know of no literature values for carbon acids. Values for $K_a{}^D/K_a{}^H$ were similarly estimated to be 0.2, which may be compared with the experimental value 0.22 for *N,N*-dimethylethylamine.[12] From these estimates and the experimentally determined deuterium solvent kinetic isotope effects (Table I), $k_c{}^H/k_c{}^D = 4.3$ (*N,N*-dimethylaminoethanol), 5.3 (*N,N*-dimethylisopropylamine), and 7.5 (triethylamine). The trend in isotope effects suggests a progression of proton transfer from BH^+ to $\mathbf{1}^-$ in the critical transition states for the three reactions; proton transfer tends toward half-completion as the acidity of BH^+ decreases, i.e., the isotope effect tends toward a maximum.[34]

At this point in the discussion we wish to direct attention to the isomerization of **1** to **2** in acetonitrile. We studied this reaction to see if evidence could be found for a mechanism change along the lines of the concerted mechanism. As well, the possibility of intramolecular proton transfer from β to γ carbon through the agency of an ion pair, as described by Cram et al.,[35,36] in this solvent of lower dielectric was considered. Evidence for intramolecular proton transfer could be pertinent to considerations of isomerase catalyzed isomerization in unsaturated thiol esters[4,7] and Δ^5-3-ketosteroids.[37] Isomerization of **1** in acetonitrile solution is apparently general base catalyzed (eq 5) by *N,N*-dimethylisopropylamine, *N,N*-dimethyl-*tert*-butylamine, and triethylamine (Table II). Isomerization occurs equally well in the presence or absence of added proton sources (BH^+), and the reaction is subject to a deuterium isotope effect which is dependent on the concentration of BD^+ present in the reaction. The result that a proton source other than **1** is unnecessary for isomerization, coupled with the result that a concentration-dependent isotope effect operates under conditions of relatively high $BD^+/\mathbf{1}$, suggests to us that in acetonitrile an intramolecular proton transfer from β to γ carbon atom occurs through the agency of an ion pair consisting of carbanion and BH^+; in the presence of added BD^+, the ion pair experiences a rapid partial concentration-dependent hydrogen for deuterium exchange followed by rate-determining proton transfer to give **2** (Scheme II). This mechanism remains a variant of the Ingold mechanism and as for isomerization of **1** to **2** in water solution features general acid catalysis as the rate-determining step in the direction **1** → **2**. Here we note that the results and predictions of Ingold on the mechanisms of allyl-propenyl isomerizations are sometimes overlooked by the finding experimentally of general base catalysis of isomerization in certain of these systems.[21] Certainly, observed general base catalysis in isomerization of **2** to **1** would indeed reflect critical transition state events, but they surely do not for isomerization of **1** to **2** and care should be exercised in assuming that proton transfer from carbon to general bases, demonstrably slow reactions, in chemical transformations of carbon acids will always be rate determining.

Finally we consider some enzyme-catalyzed isomeriza-

Scheme II



tions of olefinic thiol esters similar to **1**. pH-rate profiles for thioester isomerases implicate general catalysis in isomerization of *N*-acetylcysteaminyl but-3-enoate to *N*-acetylcysteaminyl crotonate[6] and β-methylbut-3-enoyl coenzyme A to β-methylcrotonyl coenzyme A.[7] For the latter isomerization in tritium oxide, no incorporation of tritium into product was detected, suggesting βH is transferred to γ carbon without exchanging with solvent; the active site by its nature may exclude solvent water, or it may mediate an efficient intramolecular proton transfer.[35] Results of the isomerization of **1** to **2** suggest general acid catalyzed proton transfer to the γ carbon of either an ion pair, or a carbanion may be rate determining for the enzyme catalyzed reactions; apparent general base catalysis may in fact be general acid-specific base catalysis. It has been shown for the enzyme catalyzed isomerization of Δ^5-3-ketosteroids that a large isotope effect in $\nu_{\max}$ results when 4-deuterio substrate is isomerized and that the proton at C-4 is transferred to the C-6 position. The favored mechanism was rate-determining enolization although proton transfer to γ carbon was not excluded.[37] Similarities of chemistry of ketones and thiol esters as carbon acids and the results of this study suggest rate-determining intramolecular proton transfer from β to γ carbon be more seriously considered in enzyme catalyzed isomerizations.

References and Notes

(1) This work was supported in part by grants from the U.S. Public Health Service.

(2) Taken in part from the M.S. thesis of P.H.G.

(3) T. C. Bruice and S. J. Benkovic, "Bioorganic Mechanisms", Vol. 1, W. A. Benjamin, New York, N.Y., 1966, Chapter 3.
(4) K. Bloch, "The Enzymes", Vol. 5, P. D. Boyer, Ed., Academic Press, New York, N.Y., 1971, p 441.
(5) J. R. Stern and D. Campillo, *J. Biol. Chem.*, **218**, 985 (1956).
(6) R. G. Bartsch and H. A. Barker, *Arch. Biochem. Biophys.*, **92**, 122 (1961).
(7) H. C. Rilling and M. J. Coon, *J. Biol. Chem.*, **235**, 3087 (1960).
(8) C. H. Birge and P. R. Vagelos, *J. Biol. Chem.*, **247**, 4921 (1972).
(9) F. E. Hull, R. A. Waugh, and M. Malone, *Arch. Biochem. Biophys.*, **149**, 69 (1972).
(10) J. F. Coetzee, *Prog. Phys. Org. Chem.*, **4**, 45 (1967).
(11) G. H. Jeffery and A. I. Vogel, *J. Chem. Soc.*, 661 (1948).
(12) L. R. Fedor, *J. Am. Chem. Soc.*, **91**, 913 (1969).
(13) C. K. Ingold, "Structure and Mechanism in Organic Chemistry", Cornell University Press, Ithaca, N.Y., 1953, Chapter 10.
(14) R. P. Linstead and E. G. Noble, *J. Chem. Soc.*, 610 (1934).
(15) C. K. Ingold, *Annu. Rep. Prog. Chem.*, **24**, 106 (1927); **25**, 111 (1928).
(16) A. G. Catchpole, E. D. Hughes, and C. K. Ingold, *J. Chem. Soc.*, 8 (1948); A. G. Catchpole, E. D. Hughes, and C. K. Ingold, *ibid.*, 17 (1948).
(17) D. J. Cram, "Fundamentals of Carbanion Chemistry", Academic Press, New York, N.Y., 1965.
(18) C. K. Ingold, C. W. Shoppee, and J. F. Thorpe, *J. Chem. Soc.*, 1477 (1926).
(19) T. M. Lowry, *J. Chem. Soc.*, 2554 (1927).
(20) C. K. Ingold, E. DeSalas, and C. L. Wilson, *J. Chem. Soc.*, 1328 (1936).
(21) Y. Mialhe and R. Vessière, *Bull. Soc. Chim. Fr.*, 4181 (1968).
(22) H. C. Volger and W. Brackman, *Rec. Trav. Chim. Pays-Bas*, **84**, 1017 (1965).
(23) A. A. Bothner-By and C. Sun, *J. Org. Chem.*, **32**, 492 (1967).
(24) C. Rappe, *Acta Chem. Scand.*, **20**, 2236 (1966).
(25) L. R. Fedor and W. R. Glave, *J. Am. Chem. Soc.*, **93**, 985 (1971).
(26) J. E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions", Wiley, New York, N.Y., 1963, Chapter 7.
(27) R. G. Pearson and R. L. Dillon, *J. Am. Chem. Soc.*, **75**, 2439 (1953).
(28) L. Wessely and F. Lynen, *Fed. Proc., Fed. Am. Soc. Exp. Biol.*, **12**, 685 (1953).
(29) ρ for β-elimination reactions of *tert*-butyl 3-(para-substituted phenoxy)thiolpropionates and *tert*-butyl 3-(para-substituted benzoyloxy)thiolpropionates catalyzed by triethylamine in aqueous dioxane is essentially zero, a result which could be interpreted in terms of the E1cB mechanism with carbanion formation rate determining: L. R. Fedor and R. C. Cavestri, unpublished results.
(30) J. Hine, B. C. Menon, J. Mulders, and J. P. Idoux, *J. Org. Chem.*, **32**, 3850 (1967).
(31) M. Eigen, *Angew. Chem., Int. Ed. Engl.*, **3**, 1 (1964).
(32) R. P. Bell, "The Proton in Chemistry", Cornell University Press, Ithaca, N.Y., 1959, Chapter 10.
(33) Reference 32, p 189.
(34) Reference 32, Chapter 11.
(35) Reference 17, Chapter 5.
(36) D. J. Cram and R. T. Uyeda, *J. Am. Chem. Soc.*, **84**, 4358 (1962).
(37) S. K. Malhotra and H. J. Ringold, *J. Am. Chem. Soc.*, **87**, 3228 (1965).

Dehydration of a Carbinolhydrazine in the Solid State. Correlation with Crystal Structure of the Dehydration of 2-Hydroxy-2-(β-benzoyl-β-phenylhydrazyl)indan-1,3-dione[1,2]

Sherrill A. Puckett, Iain C. Paul,* and David Y. Curtin*

Contribution from the Department of Chemistry, University of Illinois, Urbana, Illinois 61801.

Received June 14, 1975

Abstract: 2-Hydroxy-2-(β-benzoyl-β-phenylhydrazyl)indan-1,3-dione (**1**) has been found to undergo thermal dehydration in the solid state to indantrione 2-(*N*-benzoyl-*N*-phenylhydrazone) (**2**). The white crystals of **1** are monoclinic, a = 10.069 (5), b = 9.205 (5), c = 24.913 (16) Å, and β = 124.2 (1)°; the space group is $P2_1/c$, and the structure has been refined to an R factor of 0.058 on 2589 nonzero reflections. The relationship of the crystal structure to the mechanism of dehydration in the solid state is discussed. The structure of **1** appears to be the first example of a structure of the type of intermediate that is formed in the reactions of carbonyl compounds with arylhydrazines and related compounds.

A recent upsurge of interest in organic reactions in the solid state[3,4] and in reactions between organic crystals and gases[4,5] has resulted in studies which have included thermal and photochemical intramolecular transformations and photochemical dimerizations of unsaturated compounds.

A particularly interesting type of thermal reaction is that in which reactants crystallize together as a complex which can then be caused to undergo reaction in the solid state. (Such reactions would be somewhat analogous to the well-known photochemical dimerizations that occur in the crys-