

Enolization of Ketones

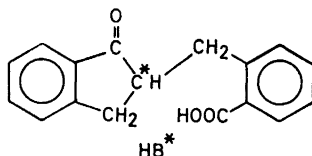
V.¹ The Racemization of *d*-2-*o*-Carboxybenzyl-1-indanone

CHRISTOFFER RAPPE and HÅKAN BERGANDER

Institute of Chemistry, University of Uppsala, Box 531, S-751 21 Uppsala 1, Sweden

The base-catalyzed racemization of *d*-2-*o*-carboxybenzyl-1-indanone has been studied. Experiments were performed with deficiencies, equivalent amounts, and excesses of various oxygen and nitrogen bases. The enolization was found to be intramolecularly catalyzed.

In 1936 Hsü and Wilson found that the rate of acetate-catalyzed halogenation and racemization of *d*-2-*o*-carboxybenzyl-1-indanone (HB*) was equal.² This paper has often been cited as evidence that enolization is the rate deter-



mining step in the base-catalyzed halogenation of ketones.³⁻⁵ In fact it seems to be the only example where such an identity is reported.

In a series of papers one of us has studied the orientation of base-catalyzed halogenation and deuteration of 2-butanone.⁶⁻¹⁰ Evidence was found that for this ketone two different base-catalyzed halogenations exist, and unexpectedly in neither of these is the orientation of halogenation the same as the orientation of deuteration. This leads to the hypothesis that different mechanisms operate for halogenation and deuteration of 2-butanone.⁸ Halogenations performed in D₂O and experiments where hypobromous acid was used as the halogenating agent gave indication that base-catalyzed halogenation and deuteration of this ketone are not competitive reactions. It was suggested that non-enolic mechanisms operate in the halogenations.^{9,10}

Recently Bell and Fluendy¹¹ and Harper and Bender¹² studied the base-catalyzed halogenation of a number of aliphatic and aromatic keto-acids.

The kinetics of the reaction were measured in aqueous solutions from pH 0 to 11 and the rates were calculated from spectroscopically determined rates of halogenation.^{11,12} Catalysis by the carboxylate anion was found to be very important which is interpreted in terms of intramolecular catalysis in the enolization. This is in harmony with the traditional enolate mechanism, and not with the mechanisms proposed for the halogenations of 2-butanone.⁶⁻¹⁰ The intramolecular catalysis was very strong for the acids where the enolizable carbon-atom is γ or δ to the carboxylate group.

It is of importance to establish if 2-*o*-carboxybenzyl-1-indanone like other keto-acids with the enolizable carbon-atom in the position γ or δ to the carboxylate group, represents a class of ketones, where intramolecular catalysis by the carboxylate anion is of major importance in the enolization and the halogenation of the ketone. Thus the kinetic data obtained from these ketones might be without importance in the discussion of the mechanisms of base-catalyzed halogenations of 2-butanone and other structurally similar mono-ketones, where the possibility of intramolecular catalysis does not exist.

In the present investigation we have studied the kinetics of the racemization of *d*-2-*o*-carboxybenzyl-1-indanone. In our opinion this kinetic method is more reliable than halogenation kinetics, the amount of possible side reactions being minimized. The results are given in Tables 1-7.

We chose first to study the racemization without any added base (expts. 1 and 2, Table 1). The rate constants were low, indicating that the intra- and intermolecular catalysis by the acid HB can be neglected when discussing the rates of base-catalyzed racemization. The addition of acetic acid decreased the rate: thus the main contribution to the observed rates in expts. 1 and 2 comes from the base-catalyzed reaction (intra- or intermolecular) using the carboxylate anion as base. In the discussion below it is assumed that the prototropic equilibrium between the acid and the carboxylate anion is very fast compared with the racemization.

A careful examination of the situation reveals that the kinetic expression is different for intramolecular and intermolecular base-catalyzed racemization, thus affording a method for the mathematical separation of the two types of catalysis.

Table 1. Racemization experiments with less than or one equivalent of sodium hydroxide.

Expt. No.	[HB] $\times 10^3$ mole l ⁻¹	[B ⁻] $\times 10^3$ mole l ⁻¹	$k^{obs} \times 10^3$ sec ⁻¹	$k^{intra} \times 10^3$ sec ⁻¹
1	1.36	—	0.019	—
2	0.77	—	0.022	—
3	1.30	0.99	0.57	0.75
4	1.28	0.90	0.55	0.78
5	1.28	0.60	0.34	0.72
6	0.91	0.91	0.72	0.72
7	1.17	1.17	0.79	0.79
8	1.26	1.26	0.75	0.75

The intramolecular reaction is of first-order and the rate expression contains only the concentration of optically active carboxylate anion, $[B^{*-}]$.

$$\text{rate} = k^{\text{intra}} \times [B^{*-}] \quad (1)$$

The term $[B^{*-}]$ is a function of the degree of dissociation, D , and the total amount of optically active acid, or the amount of rotation, α .

$$\text{rate} = k^{\text{intra}} \times D \alpha \quad (2)$$

The intermolecular racemization is a pseudo-first-order reaction, and the rate expression is a function of the total amount of carboxylate anion, $[B^-]$, which is constant during the experiment, and the total amount of optically active acid or carboxylate anion, which is given by the amount of rotation, α .

$$\text{rate} = k^{\text{inter}} \times [B^-] \times \alpha \quad (3)$$

Examining the rate constants of expts. 1 and 2, Table 1, it is evident that increasing the concentration did not increase the rate of racemization and in fact the rate was somewhat decreased. This is in conflict with an intermolecular reaction but in perfect harmony with an intramolecularly catalyzed reaction. The degree of dissociation, D , increases at lower concentrations.

Another set of experiments were run with less than one equivalent of sodium hydroxide (expts. 3, 4, and 5). The rate constants could be calculated if it is assumed that either the intra- or the intermolecular reaction predominates. Under this assumption we found the mean value for $k^{\text{intra}} = 0.75 \times 10^{-3} \text{ sec}^{-1}$ and $k^{\text{inter}} = 6.0 \times 10^{-2} \text{ l mole}^{-1} \text{ sec}^{-1}$. These values also seem to favour an intramolecular attack, in other case the carboxylate ion, which is a weak base, would be about 15 % as efficient as the strong base hydroxylic ions (expts. 9 and 10). Moreover, it is difficult to understand the efficiency of the carboxylate ion if it is an intermolecular attack since sodium acetate, which is a stronger base than B^- was found to give no contribution to the observed rates (expts. 11–13).

In expts. 6–8 we attempted to investigate the rate of racemization at the equivalence point, where the degree of dissociation is =1 (the amount of base was determined by titration and the pH was checked after the experi-

Table 2. Racemization experiments with more than one equivalent of base.

Expt. No.	$[HB] \times 10^2$ mole l ⁻¹	$[B^-] \times 10^2$ mole l ⁻¹	Base, A	$[A] \times 10^2$ mole l ⁻¹	$k^{\text{obs}} \times 10^3$ sec ⁻¹	k_A l mole ⁻¹ sec ⁻¹
9	1.16	1.16	NaOH	0.096	1.11	3.8×10^{-1}
10	1.11	1.11	»	0.190	1.54	4.2×10^{-1}
11	1.23	—	NaOAc	9.9	0.61	—
12	0.88	—	»	10.6	0.62	—
13	0.87	—	»	7.9	0.62	—
14	1.19	—	NaHCO ₃	0.86	0.64	—
15	0.91	—	»	2.57	0.66	—

ments). It can be noted that expts. 6, 7, and 8 all gave the same rate constants, in spite of the fact that $[B^-]$ varied with a factor of 1.4. This must be taken as a strong indication for an intramolecularly catalyzed reaction. The mean value for the rate constant was $0.75 \times 10^{-3} \text{ sec}^{-1}$, in good agreement with the mean values determined in expts. 3–5 ($0.75 \times 10^{-3} \text{ sec}^{-1}$).

The experiments in Table 2 are performed with an excess of base A (sodium hydroxide, sodium bicarbonate, and sodium acetate). Rate constants in experiments with an excess of base can be calculated from the general eqns. (4) and (5).

$$\text{rate}^{\text{obs}} = \text{rate}^{\text{intra}} + k_A[A] \alpha \quad (4)$$

$$k_{\text{tot}}^{\text{obs}} = 0.75 \times 10^{-3} + k_A[A] \quad (5)$$

In experiments with an excess of the strong base sodium hydroxide $D=1$ (expts. 9 and 10) k_{OH^-} is calculated to be $4.0 \times 10^{-1} \text{ l mole}^{-1} \text{ sec}^{-1}$. In experiments with an excess of sodium acetate (expts. 11–13), a large excess of acetate must be used to achieve complete dissociation, because the keto-acid was found to be about 0.5 power of ten stronger than acetic acid.¹³ In spite of a more than tenfold excess of acetate, the observed rate constants were lower than $0.75 \times 10^{-3} \text{ sec}^{-1}$ giving $D=0.8$. Moreover, the catalytic power of sodium acetate is too small to give a contribution to the total rate. The same is the situation in expts. 14 and 15, where an excess of the stronger base sodium bicarbonate was used. In these experiments the degree of dissociation was found to be 0.9.

In expts. 16 and 17, Table 3, the keto-acid was neutralized with less than one equivalent of diazabicyclo[2,2,0]octane (DABCO). In spite of a twofold variation in $[B^-]$ the same value was found for the quotient k^{obs} and the degree of dissociation. This is an additional support for the intramolecular mechanism. This value ($0.72 \times 10^{-3} \text{ sec}^{-1}$) is nearly the same as the value reported above using sodium hydroxide. Moreover, the results in Table 3 also indicate that the catalytic power of HDABCO⁺ can be neglected.

In expts. 18–34 Tables 4–7 an excess of DABCO, triethylamine (TEA), trimethylamine (TMA), and 2,4,6-collidine (2,4,6) was used. The observed rate constants are expected to follow eqn. (4). A plot of $k_{\text{tot}}^{\text{obs}}$ vs. the excess of base gave one straight line for each base, and from this plot k^{intra} and k_A (the catalytic rate constant for the base) could be obtained, cf. Ref. 13. Using a linear least-squares program, eqns. (6), (7), (8), and (9) were obtained.

$$k_{\text{DABCO}}^{\text{obs}} = 0.64 \pm 0.01 \times 10^{-3} + 3.07 \pm 0.12 \times 10^{-2} [A] \quad (6)$$

$$k_{\text{TEA}}^{\text{obs}} = 0.74 \pm 0.05 \times 10^{-3} + 3.73 \pm 1.00 \times 10^{-3} [A] \quad (7)$$

$$k_{\text{TMA}}^{\text{obs}} = 0.76 \pm 0.08 \times 10^{-3} + 2.37 \pm 0.23 \times 10^{-2} [A] \quad (8)$$

$$k_{2,4,6}^{\text{obs}} = 0.65 \pm 0.01 \times 10^{-3} + 3.28 \pm 0.19 \times 10^{-4} [A] \quad (9)$$

Table 3. Racemization experiments with less than one equivalent of DABCO.

Expt. No.	[HB] $\times 10^2$ mole l ⁻¹	[B ⁻] $\times 10^2$ mole l ⁻¹	[DABCO] _{tot} $\times 10^2$ mole l ⁻¹	D	k ^{obs} $\times 10^3$ sec ⁻¹	k ^{intra} $\times 10^3$ sec ⁻¹
16	0.876	0.525	0.525	0.600	0.44	0.73
17	0.868	0.263	0.263	0.303	0.22	0.72

Table 4. Racemization experiments with excess of DABCO.

Expt. No.	[HB] $\times 10^2$ mole l ⁻¹	[DABCO] _{tot} $\times 10^2$ mole l ⁻¹	k _{tot} ^{obs} sec ⁻¹
18	1.875	2.626	0.86
19	0.909	1.398	0.80
20	0.789	1.855	0.96
21	0.887	2.698	1.20

Table 5. Racemization experiments with excess TEA.

Expt. No.	[HB] $\times 10^2$ mole l ⁻¹	[TEA] _{tot} $\times 10^2$ mole l ⁻¹	k _{tot} ^{obs} sec ⁻¹
22	1.29	5.90	0.93
23	0.53	3.84	0.89
24	1.33	7.30	0.96
25	1.12	4.79	0.84
26	1.04	7.69	0.99

Table 6. Racemization experiments with excess TMA.

Expt. No.	[HB] $\times 10^2$ mole l ⁻¹	[TMA] _{tot} $\times 10^2$ mole l ⁻¹	k _{tot} ^{obs} sec ⁻¹
27	1.42	7.46	2.17
28	1.37	3.47	1.19
29	1.23	4.36	1.58
30	1.08	3.09	1.24

Table 7. Racemization experiments with excess 2,4,6-collidine.

Expt. No.	[HB] $\times 10^2$ mole l ⁻¹	[2,4,6] _{tot} $\times 10$ mole l ⁻¹	k _{tot} ^{obs} sec ⁻¹
31	0.504	1.244	0.694
32	0.567	2.489	0.717
33	0.567	5.208	0.821
34	0.560	7.768	0.901

The lower value for the intramolecular rate constants using DABCO and 2,4,6 indicates that the weaker bases (DABCO, 2,4,6) did not neutralize the acid completely ($D < 1$).

The results discussed above establish that the enolization and racemization of *d*-2-*o*-carboxybenzyl-1-indanone is an intramolecularly catalyzed reaction. This seems to be a general feature for keto-acids with the enolizable carbon-atom in the position γ or δ to the carboxylate group. The kinetic data and other conclusions from investigations of this group of ketones²⁻⁵ is therefore of minor importance in the discussion of the mechanisms of the base-catalyzed halogenations of ordinary monoketones, where the possibility of intramolecular catalysis does not exist.

A comparison between the three nitrogen bases DABCO, TEA, and 2,4,6 revealed that the weaker base DABCO ($pK_b = 5.70$)¹⁴ was about ten times more efficient than the more than two powers of ten stronger, but sterically hindered base TEA ($pK_b = 3.25$) and about one hundred times more efficient than the somewhat weaker but also sterically hindered base 2,4,6 ($pK_b = 6.55$). This is in harmony with the results from the enolization of isobutyraldehyde studied by Hine *et al.*¹⁴ They found that steric factors were of major importance for the catalytic power of nitrogen bases. Since the DABCO molecule contains two nitrogen atoms the rate constant for DABCO should be multiplied with 1/2 giving the rate ratios 5 and 50.¹⁵

EXPERIMENTAL

The racemization experiments were followed with a Perkin Elmer model 141 polarimeter. Measurements were made every minute (except for 2,4,6). The bases were dissolved in a water-ethanol solution (3:7 by volume) and the strength determined by titration. *d*-2-*o*-Carboxybenzyl-1-indanone was prepared according to Leuchs *et al.*¹⁶ and Ingold.¹⁷ The amount of active keto-acid was determined by weighing.

The acidity constant for the keto-acid was determined by potentiometric titration in a water-ethanol solution (3:7 by volume). A 4.1×10^{-2} M solution of the acid was prepared and the curve was compared with that one determined for a 4.5×10^{-2} M solution of acetic acid in the same solvent. The keto-acid was found to be 0.4–0.5 powers of ten stronger than acetic acid.

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