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On the Possible Correlation between the Configuration of Optically Active Bases and the Velocity of Decarboxylation of Dextro- and Levo-Camphocarboxylic Acids in their Presence[1]

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A parallelism between the configuration of some optically active organic bases possessing a center of asymmetry and the catalytic effect on the decarboxylation of camphocarboxylic acid in their presence has been demonstrated. Using bases with the same configuration one antipode of the acid always undergoes decarboxylation faster than the other. The investigation of the relationship between the optical configuration and the catalytic effect should allow the configuration of bases with one center of optical asymmetry to be determined.

Many years ago Bredig and Balcom,[2] Bredig and Fajans,[3] and Fajans[4] demonstrated that in several non-ionizing solvents camphocarboxylic acid undergoes a kinetically first-order decomposition to camphor and carbon dioxide.

In basic solvents or in neutral solvents with added organic bases, the velocity of decarboxylation is remarkably enhanced and, within wide limits of concentration of the base, it still obeys first-order kinetics.

According to Fajans,[4] salt formation of the ketonic form of camphocarboxylic acid is responsible for the higher rate of decarboxylation in the presence of organic bases. The bases would increase the velocity of decarboxylation of camphocarboxylic acid only in those solvents where the possibility of the formation of complex acid salts between base and camphocarboxylic acid exists.[5]

With symmetrical bases in inactive solvents, the velocity constants for decarboxylation of the two antipodes of camphocarboxylic acid are the same within the limit of experimental error.[2-4] However in the presence of optically active bases, such as nicotine, quinine and quinidine, the velocities of decarboxylation of dextro and levo acid are different, ranging in the experiments of the above-mentioned authors[3,4] from a minimum of 8% in the case of nicotine in nitrobenzene (for the dextro acid) to a maximum of 46% in the cases of quinine and quinidine (respectively, for *levo* and *dextro* acid) in acetophenone.

In optically active but "indifferent" solvents, such as dextro- and levo-limonene, the kinetics of the decarboxylation of the two antipodes do not show an appreciable difference.[2]

Although it is difficult to elucidate the nature of the accelerating effect shown by the bases (among the various hypotheses that of the activated complex between acid and base may be suggested), the question of the role played by the configuration of the base on the reaction velocity arises.

It seems logical to inquire whether bases of the same configuration may influence the decarboxylation of one or the other antipode of camphocarboxylic acid in the same direction.

Substances with identical configuration have not previously been examined with the exception of the pairs quinine–cinchonidine and quinidine–cinchonine for which no clear results have been obtained.[4] These bases contain four centers of asymmetry and have two basic groups; they therefore represent very complicated cases with which to study these relations.

We have examined, under similar conditions, a series of basic substances possessing a single center of optical asymmetry to which the basic group is directly bound and having comparable constitution and chemical character, namely, the ethyl esters of L-alanine, L-leucine, L-phenylalanine, L-tyrosine, L-aspartic acid, L-glutamic acid and L-proline. The velocities of decarboxylation of the optical antipodes of camphocarboxylic acid and of racemic camphocarboxylic acid in nitrobenzene in the presence of equivalent amount of the above-mentioned substances have been determined.

In the presence of these esters, camphocarboxylic acid in nitrobenzene solution undergoes decarboxylation much more rapidly than in pure nitrobenzene (see Table I). After preliminary researches, a temperature of 60° was chosen; at this temperature even glycine ethyl ester, which condenses readily to diketopiperazines, gives constant values for k until decarboxylation has become extensive. The other esters, except that of glutamic acid,[6] are much more stable.[7] In every case the reaction follows first-order kinetics to at least 70% completion.[8]

In the presence of the ethyl esters of L-alanine, L-leucine, L-phenylalanine, L-tyrosine, L-aspartic acid and L-proline, dextro-camphocarboxylic acid always undergoes decarboxylation faster than the levo-acid, with differences, measured from the value of the reaction constant, from 6% in the case of proline to 44% in the case of tyrosine. The average deviation in our experiments was not greater than 2%.

With the racemic acid values intermediate between those with the dextro- and levo-acid are obtained.

(1) Presented before Section 12 of the XIIth International Congress of Pure and Applied Chemistry, New York, N. Y., September, 1951. Abstracts of papers, p. 439.

(2) G. Bredig and R. W. Balcom, *Ber.*, **41**, 740 (1908).

(3) G. Bredig and K. Fajans, *ibid.*, **41**, 752 (1908).

(4) K. Fajans, *Z. physik. Chem.*, **73**, 25 (1910).

(5) G. Bredig and R. A. Joyner, *Z. Elektrochem.*, **24**, 285 (1918). See also H. J. Creighton, *Z. physik. Chem.*, **81**, 543 (1913); W. Pastanogoff, *ibid.*, **112**, 448 (1924).

(6) In this case, in consequence of cyclization to carbethoxypyrrolidone (ethanol was found in the refrigerated coil-condenser), the value of k rapidly decreases to that found for the camphocarboxylic acid alone. This demonstrates the ineffectiveness of the carbethoxypyrrolidone (amide N) as catalyst.

(7) Only in the case of L-phenylalanine ethyl ester (*ca.* 0.8 g. acid and 0.8 g. base) a small amount of 3,6-dioxo-2,5-dibenzylpiperazine (30–40 mg.) was obtained at the end of the experiments).

(8) The formation of amides, which could happen at different rates employing dextro or levo acid and the esterification of the two carboxylic acids by means of aminoesters, is therefore very slight.

Results are given in the following Table I.

TABLE I

Dextro-camphocarboxylic acid in nitrobenzene at 60 ± 0.1°, $k \times 10^5 = 8.5$.

Ethyl ester of	$k \times 10^5$ in nitrobenzene at 60 ± 0.1° Dextro-acid	Levo-acid	Diff., %	*rac*-Acid
L-Alanine	92.4	77.8	18.8	85.6
L-Leucine	94.6	85.7	10.4	...
	93.4	85.7	9.0	...
L-Phenylalanine	101.0	84.3	19.8	93.3
L-Tyrosine	106.3	73.7	44.2	81.8
L-Aspartic acid	110.8	82.1	34.9	...
L-Proline	149.0	143.2	4.0	...
(at 55°)	80.0	75.2	6.4	...

With (−)nicotine, for which a configurative relationship with the amino acids of the L-series has been definitely established, dextro-camphocarboxylic acid undergoes decarboxylation more rapidly than the levo-isomer[3,4] as with the aminoesters of the L-series.

There is thus a parallelism between the configuration of these bases and the direction of the catalytic effect shown by them. These experiments are being extended in order to ascertain whether it is possible to generalize the regularity we have found and to ascertain the effect of the constitution of the bases and other factors.

The results have been confirmed by examining the behavior of the two stereoisomeric camphocarboxylic acids toward the optical antipodes of the same base. Decarboxylations were carried out in the presence of equivalent amounts of the two antipodes of *threo*-1-*p*-nitrophenyl-2-amino-1,3-propanediol in nitrobenzene. The results were as follows.

TABLE II

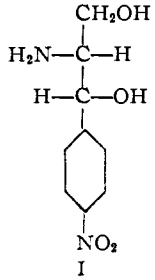
Dextro-camphocarboxylic acid in nitrobenzene at 90 ± 0.1°, $k \times 10^5 = 347$.

	$k \times 10^5$ in nitrobenzene at 90 ± 0.1° Dextro-acid	Levo-acid
(−)*threo*-base	712	645
	713	643
(+)*threo*-base	655	717

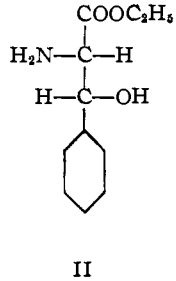
The effect of the (−)base is the same as that of the (+)base but in the opposite direction to it.

The levo-isomer (I) of *threo*-1-*p*-nitrophenyl-2-amino-1,3-propanediol, corresponding to the natural chloroamphenicol, shows the same behavior as the L-amino esters. It is possible that this analogy may have biochemical significance.

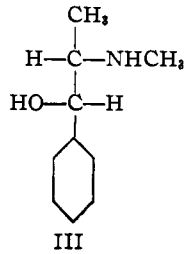
The results with these *threo*-bases induced us to examine other substances with two asymmetric carbon atoms to see in what way the optical con-



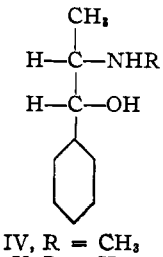
I



II



III



IV, R = CH_3
V, R = H

figuration may influence the direction of the catalytic effect. We have examined (+)*threo*-β-phenylserine ethyl ester (II), (+)ψ-ephedrine (III), (−)ephedrine (IV) and (−)nor-ephedrine (V).

The results are given in Table III.

TABLE III

	$k \times 10^5$ in nitrobenzene Dextro-acid	Levo-acid	Diff., %
(+)*threo*-β-Phenylserine ethyl ester at 60°	71.5	92.1	28.8
(+)ψ-Ephedrine at 80°	511.2	476.5	7.3
(−)Ephedrine at 80°	228.3	228.1	0
(−)Nor-ephedrine at 80°	277.0	223.4	24.0

(+)*threo*-β-Phenylserine ethyl ester, although it has the same configuration as (−)Chloroamphenicol base, acts in the opposite way.

(+)ψ-Ephedrine, which possesses the same configuration as (−)*threo*-β-phenylserine ethyl ester, can be classed with this substance.

The two camphocarboxylic acids do not show any difference in their velocities of decarboxylation in the presence of (−)-ephedrine. (−)Nor-ephedrine, however, which differs from (−)-ephedrine by a methyl on the amino group, produces a considerable effect.

With these bases possessing two asymmetric carbon atoms, a parallelism between configuration and the catalytic effect is not evident; here structural factors probably exert a prevailing influence on the course of the reaction. Conditions under which the correlation between optical configuration and direction of catalytic effect permit the kinetic determination of configuration of bases with one center of optical asymmetry can thus be outlined.

Experimental

The apparatus used was essentially that described by Bredig, Fajans and Creighton (*l.c.*).

A 30-cc. capacity long-necked flask, closed by a ground glass joint, provided with a mercury seal and containing the solutions of the acids and bases, measured by weighing or pipetting, was supported in a thermostated bath ($t \pm 0.1°$). The glass stopper holds two tubes, one for the entrance and one for the escape of gas; the latter is sealed to a condenser (freezing mixture) followed by a coil-condenser cooled with Dry Ice. The uncondensed gas passes through a sulfuric acid bubble-counter and a calcium chloride U-tube, and then through a three-way stopcock into two pairs of absorption tubes. Each pair consists of an ascarite U-tube and a soda-lime U-tube and is protected by a calcium chloride U-tube. The carbon dioxide produced is swept through the apparatus by a stream of pure dry nitrogen.

The velocity of the nitrogen stream was chosen in such a way that the measured reaction constant is independent of it. We observed that from velocities above 350 cc. an hour to 1000 cc. an hour, the highest tried, all carbon dioxide was fixed in the absorption apparatus. The same velocity for both optical antipodes of camphocarboxylic acid (500 or

750 cc. an hour) was used; with these velocities the results are independent of the velocity.

The value of the velocity constant k was obtained from the equation for a first-order reaction

$$k = \frac{1}{0.4343t} \log_{10} \frac{A}{A - x}$$

where $A - x$ is the quantity of the acid still present at the time t, calculated in milligrams from the carbon dioxide obtained and A is the initial quantity of the acid.

Taking zero time as the moment at which the homogeneous system reaches the temperature of the thermostated bath, A is determined by subtracting from the total quantity of carbon dioxide corresponding to the weighed acid, the carbon dioxide evolved during this short equilibration interval (15–30 minutes). As the velocity of reaction at the beginning is not regular, we have tried to make the values of A correspond as closely as possible. The error from this source was always within the limit of the experimental error.

In some cases the reaction ceased to be first order, but this by using nitrobenzene as solvent did not occur in any case before at least 70% of the acid underwent decarboxylation.

The apparatus was calibrated by decomposing weighed quantities of pure sodium carbonate with dilute sulfuric acid.

Weighed 0.5984 g. Na_2CO_3. Calcd. CO_2, 248.4 mg. Found, CO_2, 248.2 mg. Weighed 0.6442 g. Na_2CO_3. Calcd. CO_2, 267.4 mg. Found, CO_2 267.0 mg.

At the temperature used carbon dioxide was not retained either by the bases or by the solvent as was shown by passing a known quantity of carbon dioxide into the flask containing the base and the solvent. No loss of carbon dioxide was occasioned by the change of direction of the gas stream by means of the three-way stopcock.

The camphocarboxylic acids were prepared by Brühl's method[9]; improved by Pitré and Luchetti.[10]

The dextro acid was obtained from optically pure dextro-camphor and showed $[\alpha]^{20}D$ +61.1° (*c* 15, abs. ethanol).

We had a small sample of optically pure levo-camphor, which had been given to one of us by Prof. C. Sannié, Paris. Another sample of levo-camphor, not optically pure, had also been given to one of us by Prof. J. Read, St. Andrews (Scotland). We wish to thank them most sincerely. With the optically pure sample of levo-camphor we prepared levo-acid, which was mostly mixed with that less pure optically, giving an acid $[\alpha]^{20}D$ −56.4° (*c* 4.4, alcohol), which corresponds to a content of 96% of the levo-isomer.

The determination of the reaction constant in nitrobenzene at 90° in the presence of *threo*(−)1-*p*-nitrophenyl-2-amino-1,3-propanediol gave $k \times 10^5 = 643$ with optically pure levo-acid and 645 with 96% levo-acid. We did not observe any substantial difference due to the slight amount of optical antipode. All the measurements were therefore carried out with 96% levo-acid.

The control of purity of the acids was as follows.

Acids	M.p., °C.	$[\alpha]^{20}D$	Analysis Calcd. C, 67.32 H, 8.22	Decarboxyl. by melting (CO_2, %)	$k \times 10^5$ at 90° in nitrobenzene
Dextro	127–128	61.1°	C, 67.37; H, 8.31	99.9	347
Levo	126–127	56.4°	C, 67.29; H, 8.33	99.1	350
Racemic	136–137	0.0°	C, 67.24; H, 8.26	99.5	...

The ethyl esters of the amino acids were prepared according to Fischer[11]: ethyl ester of L-alanine b.p. (30 mm.) = 56°; of L-leucine b.p. (17 mm.) = 85–86°; of L-phenylalanine b.p. (18 mm.) = 150.5–152.5°; of L-aspartic acid b.p. (2 mm.) = 91–92°; of L-proline b.p. (17 mm.) = 82–83°; of L-tyrosine, m.p. 107°. The aminoacids and the corresponding esters were controlled as far as their optical purity was concerned. The same is true for the optical antipodes of *threo*-1-*p*-nitrophenyl-2-amino-1,3-propanediol (m.p. 163°), for (+)*threo*-β-phenylserine ethyl ester (m.p. 64–65°),[12] (+)ψ-ephedrine (m.p. 118–119°), (−)ephedrine (b.p. 2.5 mm.) = 105−107°) and for (−)nor-ephedrine (m.p. 49–50°).[13]

The solvent (nitrobenzene) was thoroughly dried and repeatedly rectified. The action of glycine ethyl ester was also measured in acetophenone.

The average error and the fluctuations of the average value in our experiments were not above 2%.

The determination of the rate constant of the two isomer camphocarboxylic acids at 90° (0.8 g. acid in 16 cc. of nitrobenzene) gave $k_d \times 10^5 = 347.0$ and $k_l \times 10^5 = 350.0$.

The action of glycine ester was measured at 60° in nitrobenzene (0.9 g. *rac.* acid and 0.47 cc. of glycine ester in 18 cc. of nitrobenzene) and in acetophenone (0.9 g. *rac.* acid and 0.47 cc. of glycine ester in 9 cc. of acetophenone) and gave $k_{d,l} \times 10^5$ (nitrobenzene) = 185.0; $k_{d,l} \times 10^5$ (acetophenone) = 170.0. In nitrobenzene constant k values up to decomposition of about 70% were obtained; in acetophenone only up to about 30%.

The bases were always taken in amounts equivalent to those of the acid, using 0.8–1 g. of acid within 16–20 cc. of nitrobenzene.

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PAVIA, ITALY

(9) J. W. Brühl, *Ber.*, **36**, 1305 (1903).

(10) D. Pitré and F. Luchetti, *Il Farmaco*, **5**, 148 (1950).

(11) E. Fischer, *Ber.*, **34**, 433 (1901).

(12) We thank Dr. K. Vogler, Hoffmann–La Roche, Basel (Switzerland), who kindly gave us a sample of this compound.

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