Study of the Tautomerization of Benzylidene Benzylamine Labelled With C^{14}

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MADRID, 1957
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BENZYLIDENE BENZYLAMINE LABELLED WITH C

by

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In order to gain a more through knowledge of the mechanism of S2' synchronic prototropy reactions, we have done a series of researches on the influence of alkyl substituents on the equilibrium and rate constants of such reactions. The system chosen was the methylene-azomethine

\[
\begin{align*}
\text{I} & : \quad \text{C}_6\text{H}_5^-\text{CH} = \text{CH}-\text{C}_6\text{H}_5 \\
\text{II} & : \quad \text{C}_6\text{H}_5^+\text{C} = \text{N} = \text{CH}_2-\text{C}_6\text{H}_5
\end{align*}
\]

which has a suitable mobility to be kinetically studied when reacting in a basic medium. The rates of direct and reverse reaction for this system when \( R = \text{Me}, \text{Et}, \text{Pr}, \text{Bu} \) have been studied (1) (2).

In view of the interest now displayed in the study and comparison of the so called Arrhenius parameters in connection with the determination of the relative magnitude of the various polar and steric effects in a reacting system in which the substituents are changed, the study of the aforesaid system has been pursued and the activation energies and frequency factors of the reactions in question have been calculated (3).

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It seems obvious the importance of undertaking the study of the tautomerization of the simplest methylene azomethine system when R = H, for this H is the term of comparison that is normally considered when studying relative magnitudes of the different effects induced by the series of substituents under study. Furthermore, if we observe the prototropic reaction I \[ \rightleftharpoons \] II we see that the tautomerization of the benzylidene-benzylamine can be taken as a term of comparison, both for direct and inverse reactions.

The evaluation of Arrhenius parameters in the tautomerization of benzylidene-benzylamine entails the determination of various temperatures, of the kinetic constants of the reaction, bearing in mind that in this case, the two-direct and inverse-are equal. Of all the methods so far employed for the kinetic study of prototropy, only the deuteration is applicable to our case. However, it implies an extrapolation to know the initial rate of hydrogen exchange between system and medium, since benzylidene-benzylamine has three hydrogens which are replaceable by deuterium. For this reason we have applied radio tracer technique using azomethine labelled with C-14 in the methylene group.

In the reaction
\[ C_6H_5 - ^{14}CH_2 - N = CH - C_6H_5 \xrightleftharpoons[k]{k} C_6H_5 - ^{14}CH = N - CH_2 - C_6H_5 \]
every tautomerization act transfers the radioactivity from the methylenic carbon to the methinic one or vice-versa. If we start with a benzylidene-benzylamine of a given specific activity and we hydrolyze it at different reaction times, as the reaction progresses, the specific activity of the benzylamine obtained in the hydrolysis (which at zero time will be identical to that of the original azomethine), will decrease and, accordingly, that of the benzaldehyde (which is nil at zero time) will increase. The specific rate of approach to the equilibrium will, as we have said, be identical to that of the decrease of activity in the benzylamine-and to that of the increase in the benzaldehyde, and two fold the specific rates of the direct and inverse reactions which are equal, so that the latter can be deduced from the aforesaid variations of activity.

We have calculated the reaction rate simultaneously from the loss of activity of the amine and the gain of activity of the benzaldehyde. We were thereby able to ascertain, furthermore, that the total sum of the specific activities of the products of hydrolysis, for each kinetic experiment, is constant and equal to the specific activity of the original azomethine. This constancy is a proof that the isolation and purification of radioactive products and other experimental operations were properly carried out.

Once the benzyliden-benzylamine of \[ \alpha - ^{14}C \], subjected to reaction during various lengths of time, in the experimental conditions previously used, had been hydrolyzed, the resulting products were transformed into solid derivatives: benzoyl-benzylamine and benzal-semi carbazone, which makes purification by crystallization easy. The carbon dioxide produced by the combustion of each
sample of these products, was precipitated in the form of barium carbonate. As we had available a sufficient quantity of barium carbonate, we always prepared samples at infinite thickness, thus obtaining activity values proportional to the specific activities.

The combustion of organic products and collection of CO₂ was done by standard methods (4) and the samples of barium carbonate were prepared after suspension in methyl alcohol, by filtration.

Counting was done by ordinary thin window Geiger counter and also with flow counter operating as Geiger.

The benzylidene-benzylamine - α¹⁴C was synthesis from benzoic acid carboxyl-¹⁴C according to the following scheme:

\[
\begin{align*}
\text{C}_6\text{H}_5^{-14}\text{CO}_2\text{H} & \xrightarrow{\text{Cl}_2\text{SO}} \text{C}_6\text{H}_5^{14}\text{CO} \xrightarrow{\text{NH}_3} \text{C}_6\text{H}_5^{-14}\text{CONH}_2 \xrightarrow{\text{AlCl}_3\text{NaCl}} \\
\text{C}_6\text{H}_5^{-14}\text{CN} & \xrightarrow{\text{H}_4\text{LiAl}} \text{C}_6\text{H}_5^{-14}\text{CH}_2^{-\text{NH}_2} & \text{C}_6\text{H}_5^{-14}\text{CH}_2^{-\text{N}} = \text{CH-CH}_2\text{N} \\
\end{align*}
\]

All the steps of this process were tested with ordinary products until satisfactory yields were reached. At first we attempted a direct reduction of benzamide to benzylamine with lithium aluminium hydride, without satisfactory results, for which reason we dehydrated the amide with sodium aluminium chloride (5) and the resulting benzonitrile was reduced to amine with lithium aluminium hydride (6).

The radio-chemical purity of the products of the synthesis was checked by the correspondence between the activities at infinite thickness of samples of barium carbonate coming from the combustion of the original benzoic acid, of benzamide and of benzoyl-benzylamine, prepared from radioactive benzylamine. The benzyliden-benzylamine subjected to several distillations gave by combustion barium carbonate which always showed the same activity. The constant value of the sum of activities of the products of hydrolysis, in each kinetic experiment, is also a check of purity. To make sure that all the activity of the azomethine was in the methylenic carbon, we measured the activity of the products of hydrolysis of the azomethine before subjecting this to the prototropy reaction, and it was confirmed that it was so. This last fact has again been confirmed after keeping the radioactive azomethine stored during one year; which proves that for prototropy changes to take place there must necessarily be present a catalyst.

To calculate the activation energy and frequency factor, we determined the kinetic constant of this reaction, at four different temperatures. The catalytic solution used was prepared, in all cases, according to the process previously described in another paper (1).
The experimental procedure is the following: We introduce into the thermostat in two tubes with stoppers, a known amount of azomethine and a volume in excess of catalytic solution. After they have reached the thermostat temperature, we measure, by means of a pipette, provided with a special suction device, as many milliliters of catalytic solution as are needed to get the azomethine solution of concentration 0.4 molar. This is rapidly poured into the tube containing the azomethine, and the time at which this is done is taken as the initial time of the experiment. At different intervals of time, samples of the reacting solution are sucked by means of different pipettes and poured onto cold water in which the azomethine precipitates, thus stopping the reaction. We next extract with ether, separate, and hydrolyze with hydrochloric acid; the benzaldehyde is extracted with ether and precipitated as semicarbazone. The benzylamine contained in the acid extract is benzoyled and both products are purified by crystallization.

Weighed samples of semicarbazone and benzoyled derivative are burned in a combustion tube; the barium carbonate is collected and weighed, to check the chemical purity of the compound burned.

With every portion of barium carbonate we prepare two samples at infinite thickness to measure their radioactivity. The difference between the average value and that of the samples has never exceeded 2.5%.

The activity at infinite thickness of benzylidene-benzylamine, $A_Z$, and that of benzoyl-benzylamine, $A_B$, are directly comparable; that of benzal-semicarbazone multiplied by $4/7$ gives the values represented by $A_S$ which are comparable too.

As the rate of loss of activity in benzylamine and that of gain of activity in benzaldehyde are expressed, respectively, by:

$$\frac{d}{dt} A_B = k (A_S - A_B)$$
$$\frac{d}{dt} A_S = k (A_B - A_S)$$

and

$$A_B + A_S = A_Z,$$

we deduce that:

$$k = \frac{\log \left( \frac{2A_B}{A_Z} - 1 \right)}{0.868 \ t}$$
$$k = \frac{\log \left( \frac{A_S}{A_Z} \right)}{0.868 \ t}$$

To calculate $k$, by either formula, we can take as the value of $A_B$, the average of the sums $A_B + A_S$, including the value obtained in the direct combustion of the azomethine, or the value $A_B + A_S$ corresponding to each determination. Whether we use one or the other of these values or one formula or another for
the calculation, we obtain four values for \( k \) which, naturally, are either equal or very close to one another.

As an example of the calculation of a kinetic constant we will give a table-summary of the experiments carried out at 28°C.

**TABLE I**

Kinetics of the tautomerization of benzylidene-β-benzylamine - \( \alpha \text{-} ^{14} \text{C} \) to benzyliden-\( \alpha \text{-} ^{14} \text{C} \)-benzylamine.

At 28°C, in the ethyl alcohol -(60%)-dioxane (40%), in the presence of sodium ethylate 1.3 N. Azomethine concentration 0.4 M.

<table>
<thead>
<tr>
<th>Time (sec.)</th>
<th>( A_B )</th>
<th>( A_S )</th>
<th>( A_B + A_S )</th>
<th>( k \times 10^4 \text{ seg}^{-1} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>3520</td>
<td>1971</td>
<td>361</td>
<td>2332</td>
<td>0.523</td>
</tr>
<tr>
<td>5995</td>
<td>1782</td>
<td>551</td>
<td>2333</td>
<td>0.530</td>
</tr>
<tr>
<td>10263</td>
<td>1603</td>
<td>756</td>
<td>2359</td>
<td>0.503</td>
</tr>
<tr>
<td>14698</td>
<td>1442</td>
<td>914</td>
<td>2356</td>
<td>0.512</td>
</tr>
</tbody>
</table>

**Average values**: 2345, 0.516

\( A_B, A_S \) are expressed in counts/minute

We have to bear in mind that the first of the values mentioned above was found in a test experiment independent of the others, carried out to determine the approximate value of the kinetic constant, which would enable us to calculate the most favourable reaction times for the errors to be minimal. However, we see, that the value obtained in a single test agrees very well with the average of those in a different series, and this is a proof of the reproducibility of the method followed.

The results of kinetics experiments carried out at different temperatures are plotted in fig. 1.

Fig. 2 represents log \( k \) against \( 1/T \) and proves that Arrhenius’ equation is fulfilled.

We give below the values of the kinetic constants, at different temperatures, and the values deduced from the for the activation energy and frequency factor.
Fig. 1

Fig. 2
Temperatures, °K: 

<table>
<thead>
<tr>
<th>Temperature</th>
<th>301.1</th>
<th>308.8</th>
<th>315.2</th>
<th>322.4</th>
</tr>
</thead>
</table>

k. $10^4$ sec$^{-1}$: 

<table>
<thead>
<tr>
<th>Temperature</th>
<th>0.517</th>
<th>1.150</th>
<th>2.252</th>
<th>4.730</th>
</tr>
</thead>
</table>

Activation energy: $= 20.0$ Kcal/mol

Frequency factor = 10.3

In a previous paper (7) (8) we discussed, by comparing the kinetic constants of the direct and inverse tautomerization reactions of the alkyl derivatives of benzylidene-benzylamine, the different polar and steric influences exerted by those substituents on the course of the reaction, and came to the conclusion that the polar effects, and among them the inductive one, play a preponderant part in the reaction. However, the data now at our disposal in relation to Arrhenius' parameters, in this series of compounds, lead us to think that we may have to modify our first point of view, and that the steric effects are more largely responsible for the reaction rate variation than was formerly thought. We are now working out an interpretation in accordance with these data, and it would, therefore, be premature to state any new conclusions.