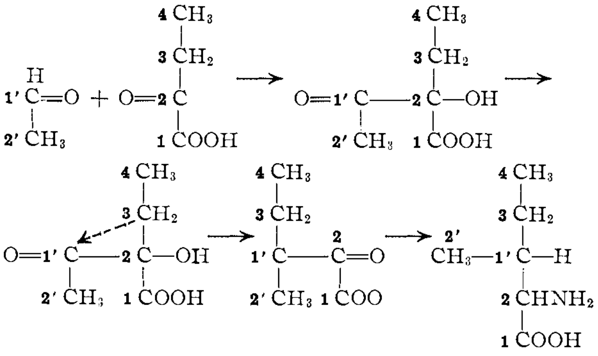
that a similar intramolecular migration occurs in the biosynthesis of isoleucine isolated from the same experiments. The postulated sequence of events, shown in the figure, is a condensation of acetaldehyde with α-ketobutyric acid to yield α-aceto-α-hydroxybutyrate, followed by migration of the ethyl group from carbon 2 of the butyrate moiety to carbon 1′ of the acetaldehyde moiety.



Postulated mechanism of isoleucine biosynthesis from acetaldehyde and α-ketobutyrate

On the assumption that aspartic acid, derived from 4-carbon acids of the citric acid cycle, provides the carbon chain of α-ketobutyrate (presumably via homoserine and threonine[3]), it is possible to calculate from previously outlined considerations[4] that isoleucine synthesized in the presence of labeled acetates by the reaction sequence shown in the figure would have the distribution of acetate methyl and carboxyl carbon shown in the table.

Distribution of Acetate Carbons in Isoleucine

Values are in per cent. of total radioactivity present

	Isoleucine carbon number					
	5	4	3	6	2	1
	CH_3—	CH_2—	CH—	(CH_3)—	$CHNH_2$—	COOH
Acetate						
Methyl Calculated	17	33	0	0	33	17
Methyl Observed	18	19	4	3	39	17
Acetate						
Carboxyl Calculated	50	0	0	0	0	50
Carboxyl Observed	46	0	3	3	1	47

Pure isoleucine, isolated from the yeast hydrolysates by chromatography on Dowex-50, was degraded chemically and the activities of each individual carbon were determined. The remarkable similarity between the observed and calculated distribution patterns shown in the table is regarded as strong evidence of the essential correctness of the mechanism shown in the figure. Distributions of lactate carboxyl, α and β carbons in isoleucine were also in accord with this postulation, based on known mechanisms of conversion of lactate to acetate, acetaldehyde and oxalacetate. These findings are in complete accord with those of Adelberg published in an accompanying report.[5]

Though intramolecular migrations of the type required by this formulation have not hitherto been observed in biological systems, this reaction is plausible from an organic chemical standpoint, being similar to the pinacol rearrangement. It is conceivable that alkyl group migration may play an important role generally in the biosynthesis of branched carbon chains.

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EFFECTS OF RING SIZE ON ELECTRON DISTRIBUTION IN SATURATED HETEROCYCLIC COMPOUNDS[1]

Sir:

Measurements of the basicities of cyclic imines toward trimethylboron,[2] of cyclic ethers toward chloroform and methanol-*d*,[3,4] and of cyclic sulfides toward boron trifluoride,[5] have shown that the basicity changes with ring size in the order: 4 > 5 > 6 > 3-membered rings. Two differing interpretations of these observations have been suggested.

An interpretation based on steric factors was proposed by Brown and Gerstein[2] to account for the dissociation of the addition compounds of the cyclic imines with trimethylboron. According to this view the observed order of basicity results from a combination of F-strain which is more pronounced for the larger rings, and I-strain which is most important in the 3-membered ring. These strains are considered to be steric interactions which occur because of the association between donor and acceptor molecules.

On the other hand, steric factors alone do not account adequately for the results of the hydrogen bonding studies with cyclic ethers[3,4] nor are they a likely explanation for the interaction of cyclic sulfides with boron trifluoride.[5] It was suggested that the basicity differences were due rather to differences in electron availability caused *inherently* by the different sizes of the rings—that is, the electron distribution is altered by ring size.

Direct physical evidence that the electron distribution does depend significantly on ring size has now been obtained by observing the chemical shifts in the proton magnetic resonance[6] of the cyclic imines, ethers and sulfides. These shifts are a sensitive measure of differences in the electronic environment of nuclei. The δ-values[6] observed for the cyclic compounds are given in Table I, and it is seen that there are relatively large variations with ring size for the hydrogens in both the α and β CH_2 groups.

In each series of cyclic compounds, the δ-values of the 3-membered rings are consistently among

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[1] This work was supported by the Office of Naval Research and by a Grant-in-Aid from E. I. du Pont de Nemours and Company.

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TABLE I

PROTON MAGNETIC RESONANCE SHIFTS IN SATURATED HETEROCYCLIC COMPOUNDS

Compound	δ-Value[a] α-CH_2	β-CH_2
$(CH_2)_2O$	−0.26	
$(CH_2)_3O$	− .06	−0.25
$(CH_2)_4O$	− .17	− .34
$(CH_2)_5O$	− .16	− .39
$(CH_2)S$	− .23	
$(CH_2)_3S$	− .19	− .19
$(CH_2)_4S$	− .29	− .29
$(CH_2)_5S$	− .29	− .34
$(CH_2)_2NH$	− .37	
$(CH_2)_3NH$	− .23	− .16
$(CH_2)_4NH$	− .19	− .30
$(CH_2)_5NH$	− .25	− .36

[a] The assignments of lines to the α- and β-CH_2 groups usually could be made from their relative intensities. There are some uncertainties in values for the cyclic imines because the N–H proton resonance was not always resolved from the CH_2's.

the most negative while the α-CH_2's in the 4-membered rings are among the most positive. It has been established[6] that more positive δ-values correspond to lower electron densities about the proton. Also, a low electron density on the CH_2 groups must be compensated for by a high electron density on the hetero atom. So we conclude that the hetero atom has a low electron density in the 3-membered ring and high in the 4, which agrees with the observed order of basicity.

It is also noteworthy that the changes in electron distribution with ring size appear to be more systematic at the β-CH_2 group than at the α. As the ring size increases, the δ-value for the β-CH_2 group approaches monotonically the value −0.39 observed in cyclohexane.[6]

Further study of variations in electron distribution with ring size is planned with these and other systems. More detailed data and interpretations will be presented.

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RECEIVED JULY 30, 1954

THE MECHANISM OF EXCHANGE OF HYDROGEN BETWEEN NITROGEN AND OXYGEN ATOMS

Sir:

In 1950 Brodskii and Sulima[1] reported that deuterium exchange between ammonium salts and water is slow in strongly acid solution. A very recent communication by Kaplan and Wilzbach[2] prompts us to report some results of a program we have been carrying on since 1951 in this field.

The rate of deuterium exchange between 0.3–0.5 M ammonium bromide and 0.1–1.2 M methanol in dimethylformamide solution containing 0.0013–0.13 M hydrogen bromide at 0° is $k[\text{salt}][\text{methanol}][\text{acid}]^{-1}$. The equilibrium constant is 1.0 since identical rates are obtained with the label in either the salt or the methanol. The half-life with 0.3 M salt, 0.1 M methanol and 0.013 M acid is 15 ± 2 min.

The rate usually increases with acidity of the cation or number of substituents. For example, relative rates for 0.1 M unsubstituted, ethyl-, diethyl-, triethyl-, trimethyl- and phenyl-ammonium chloride in methanol (0.06 M HCl, 0°) were 1.0:0.07:0.10:0.5:9:>100. However, guanidinium was unexpectedly >100.

There was a negative salt effect (30% decrease in k from 0.05 to 0.4 M $(C_2H_5)_3NH^+$, CH_3OH, 0.2 M HCl).

The rate usually decreases with increasing polarity of the solvent. Toluene (0.1 M methanol) was immeasurably fast, ethanol was faster than methanol, and ethylene glycol was slow (half-life of one hour). However, acetic and formic acid were immeasurably fast and addition of 0.1 M water increased the rate for 0.9 M triethylammonium chloride (CH_3OH, 0.4 M HCl, 0°) from 2 to 8 × 10^{-4} M sec.$^{-1}$. At 25° this rate (without water) was 5 × 10^{-3} M sec.$^{-1}$, and was unchanged by replacing all chloride by p-toluenesulfonate.

Tritium exchange with 0.2 M triethylammonium chloride (CH_3OH, 0.2 M HCl, 0°) was 0.8 as fast as deuterium exchange.

The proposed[3,4] mechanism is

$$R_3NH^+ + ROD + \text{Solvent} \underset{k_3}{\overset{k_2}{\rightleftharpoons}} R_3N\cdot\cdot H\cdot\cdot OR + \text{Solvent } D^+$$

$$R_3N\cdot\cdot H\cdot\cdot OR \underset{k_5}{\overset{k_4}{\rightleftharpoons}} R_3N + ROH$$

and reversal through similar steps to R_3ND^+, with k_3 [Solvent D^+] > k_4. The hydrogen-bonded complex may be between amine and alcohol (transition state in first step) or between ammonium and alkoxide ions (transition state in second step). The mechanism

$$R_3NH^+ + RO^- \rightleftharpoons R_3N + ROH$$

is excluded for the exchange with ethanol at least, because the calculated ratio $[C_2H_5O^-]$/[transition state] is 10^{-5}. The mechanism

$$NH_4^+ + \text{Solvent} \rightleftharpoons NH_3 + \text{Solvent } H^+$$
$$NH_3 + ROD \rightleftharpoons NH_2D + ROH$$

is possible for some cations but not for a tertiary ammonium ion.

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RECEIVED JUNE 10, 1954

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