uct (BSX) was obtained as colorless plates or leaflets; m. p. 154–155°.

Anal. Found: C, 26.4; H, 3.7; N, 24.8; molecular weight in acetone (Menzies' method), about 350.

The compound is readily decomposed by hot 70% nitric acid (fume-off) and by hot aqueous ammonia. A different product was obtained when propionic anhydride was substituted for the acetic anhydride.

Summary

A new synthesis of the high explosive cyclotrimethylenetrinitramine (RDX) is described. From one mole of hexamethylenetetramine it is possible to obtain two moles of RDX by carrying out the nitrolysis at 75° in acetic anhydride in the presence of ammonium nitrate.

Two new nitrolysis products of hexamethylenetetramine were discovered. One (HMX) is formed in the RDX reaction; the other (BSX) is produced when the reagents are mixed cold and the temperature is raised slowly.

ANN ARBOR, MICHIGAN RECEIVED APRIL 15, 1949

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF WAYNE UNIVERSITY]

Chemical Effects of Steric Strains. I. The Effect of Structure upon the Hydrolysis of Tertiary Aliphatic Chlorides[1]

BY HERBERT C. BROWN[2] AND ROSYLN SILBER FLETCHER[2,3]

The introduction of one or two alkyl groups into the ammonia molecule leads to a marked increase in base strength. The introduction of a third alkyl group has the opposite effect. This peculiar weakness of aliphatic tertiary amines has been attributed to a steric effect, termed B-strain. It was suggested that the steric requirements of the three alkyl groups attached to the nitrogen atom are so large as to set up a condition of strain which resists the conversion of the free tertiary amine into the trialkylammonium ion.[4]

If three alkyl groups attached to nitrogen constitute a center of strain, it follows from the similarity in atomic dimensions of nitrogen and carbon that three alkyl groups attached to carbon should also be a center of strain. It is therefore of interest to examine the reactions of highly branched carbon compounds to ascertain whether the steric strain hypothesis has anything to contribute to an understanding of the behavior of these compounds.[5]

It has long been recognized that the chemistry of the branched-chain aliphatic compounds differs significantly from that of the corresponding straight-chain compounds. Several outstanding points of difference may be mentioned.[6]

1. **Tertiary vs. Primary Alcohols.**—The ease with which tertiary alcohols undergo dehydration is in marked contrast to the behavior of primary alcohols.[7] Moreover tertiary alcohols react exceedingly rapidly with the halogen acids at low temperatures; primary alcohols react with difficulty at elevated temperatures.[8]

2. **Tertiary vs. Primary Halides.**—Tertiary halides hydrolyze relatively rapidly in aqueous solvents by a unimolecular mechanism; the rate of hydrolysis is independent of the hydroxide ion concentration. On the other hand, primary halides hydrolyze predominantly by a bimolecular mechanism and the rate of hydrolysis is dependent upon the hydroxide ion concentration.[9]

3. **Rearrangements.**—Highly-branched aliphatic compounds are especially prone toward rearrangements. For example, the replacement of the hydroxyl group in straight-chain primary alcohols proceeds normally, whereas similar reactions involving primary alcohols with a single or double branch in the beta position proceed with rearrangement.[10]

4. **Bond Rupture.**—Reactions involving rupture of the carbon chain usually proceed with

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(1) Studies in Stereochemistry. XV.

(2) Present address: Department of Chemistry, Purdue University.

(3) Parke, Davis and Co. Fellow at Wayne University, 1945–1947.

(4) Brown, Bartholomay and Taylor, THIS JOURNAL, **66**, 435 (1944).

(5) Spitzer and Pitzer [*ibid.*, **70**, 1261 (1948)] have attempted a calculation of the steric strain involved in the conversion of the trimethylamine molecule into the trimethylammonium ion. They estimate that the deformation of trimethylamine from a molecule with C–N–C bond angles of 112° to a molecule with tetrahedral angles should require slightly less than 500 calories. They assume that the strain involved in converting the free amine into the trimethylammonium ion should be of the same magnitude and therefore that B-strain cannot be an important factor in the weakness of trimethylamine as a base. No alternative explanation is advanced. Moreover, they state, "B-strain may become important when groups much larger than methyl are attached to the central atom because both the angles of distortion and the angle force constant will increase."

The senior author of the present apper (H. C. B.) believes that the quantity calculated by Spitzer and Pitzer is not identical with the steric strain involved in the conversion of trimethylamine into its ion. However, without more experimental data than are now available, it would be pointless to argue the question. Such data are now being gathered. It is hoped that a full and detailed discussion of the importance of B-strain in trimethylamine and related tertiary amines will be possible in the near future.

In any case, the exact magnitude and importance of B-strain in trimethylamine does not affect the present discussion of the effect of steric strain upon the behavior of highly branched carbon compounds in general and upon the hydrolysis of tertiary aliphatic chlorides in particular.

(6) A preliminary communication outlining the utility of the B-strain hypothesis in correlating the behavior of highly branched carbon compounds was published in *Science*, **103**, 385 (1946).

(7) Hibbert, THIS JOURNAL, **37**, 1748 (1915).

(8) Lucas, *ibid.*, **52**, 802 (1930).

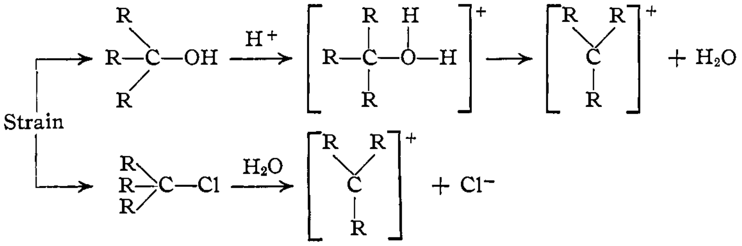
(9) Hughes, *Trans. Faraday Soc.*, **37**, 603 (1941); Bateman, Cooper, Hughes and Ingold, *J. Chem. Soc.*, 925 (1940).

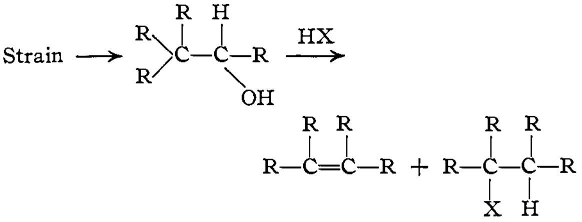
(10) Whitmore and Rothrock, THIS JOURNAL, **54**, 3431 (1932).

considerable difficulty in the case of straight-chain compounds. Similar reactions involving highly branched-chain carbon compounds proceed much more readily. For example, Kalischev reports that hexamethyltrimethylene glycol smoothly breaks down into tetramethylethylene and acetone at room temperature in the presence of acids.[11]

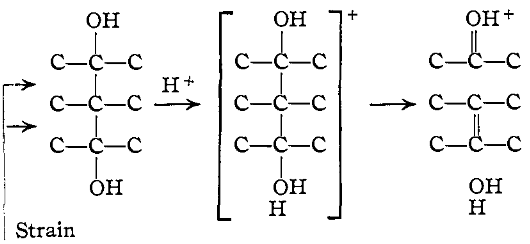
It is possible to account for the peculiar behavior of branched-chain compounds in terms of the strain introduced by the presence of three or four alkyl groups on a single carbon atom. According to this interpretation, the ready reaction of tertiary alcohols and halides by carbonium ion mechanisms would be facilitated by the relief of strain during the conversion of the parent strained molecule into the presumably strain-free planar carbonium ion.

Similarly, the molecular rearrangements frequently observed in the reactions of branched-chain compounds would be facilitated by the strain at the branch. This strain would have a marked labilization effect upon the groups attached to that center.

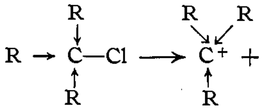




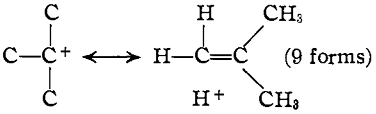
The remarkable bond rupture observed by Kalischev could also be a result of the high strain in the molecule.



Although the steric strain hypothesis appears to be capable of accounting for the major qualitative differences between branched-chain and straight-chain compounds, it should be recalled that alternative interpretations have been advanced. For example, the ready hydrolysis of tertiary chlorides by the unimolecular mechanism has been attributed by Hughes and Ingold to the cumulative inductive effects (+I) of the three alkyl groups. The increase in electron density on the carbon atom holding the halogen atom facilitates the ionization of the latter.[12]



On the other hand, Polanyi and his co-workers have attributed the ready hydrolysis of tertiary chlorides to the stabilization of the carbonium ion by hyperconjugation.[13]



As mentioned earlier, certain of the qualitative differences between straight-chain and branched-chain carbon compounds are readily interpretable in terms of the steric strain hypothesis. However, before inflicting upon chemists a third effect of alkyl groups, it seemed desirable to examine quantitative data on the reactions of highly-branched carbon compounds in order to ascertain whether the effects of structural changes in such compounds may be interpretable in terms of the hyperconjugative and inductive effects alone.

Unfortunately, such quantitative data are either meager or completely lacking. For example, of the reactions of highly branched compounds which have been studied quantitatively, only the hydrolysis of tertiary chlorides has received much attention. Even in this case there are available in the literature rate data for only three saturated tertiary chlorides, namely, *t*-butyl chloride,[14] *t*-amyl chloride,[15] and diethyl-*t*-butylcarbinyl chloride.[16]

Obviously the desired test of the steric strain hypothesis could not be based upon such meager data. Accordingly, twelve different tertiary chlorides were synthesized and their rates of hydrolysis in "80% aqueous alcohol" determined.[17]

The results obtained in these investigations would be exceedingly difficult, if not impossible,

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(11) Kalischev, *J. Russ. Phys.-Chem. Soc.*, **46**, 427 (1914); *Chem. Zentr.* **85**, II, 1261 (1914).

(12) For a recent summary of the views of Hughes and Ingold on the factors governing the reactions of alkyl halides, see Hughes, *J. Chem. Soc.*, 968 (1946).

(13) For a recent summary of the views of Polanyi and his school, see A. G. Evans, "The Reactions of Organic Halides in Solution," The Manchester University Press, 1946.

(14) Cooper, Hughes and Ingold, *J. Chem. Soc.*, 1280 (1937).

(15) Hughes and MacNulty, *ibid.*, 1283 (1937).

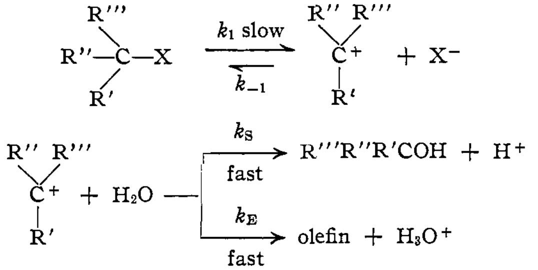
(16) Bartlett and Knox, THIS JOURNAL, **61**, 3184 (1939).

(17) Since the rate constants are markedly affected by relatively small changes in the aqueous content of the solvent, it was decided to include in the present study the three tertiary chlorides mentioned above in order to have a consistent body of data obtained with a single solvent.

to interpret without the assistance of the steric strain concept.

Results

It has been well established by Hughes and Ingold and their co-workers that the hydrolysis of tertiary halides proceeds by the following mechanism.[12,15,18]

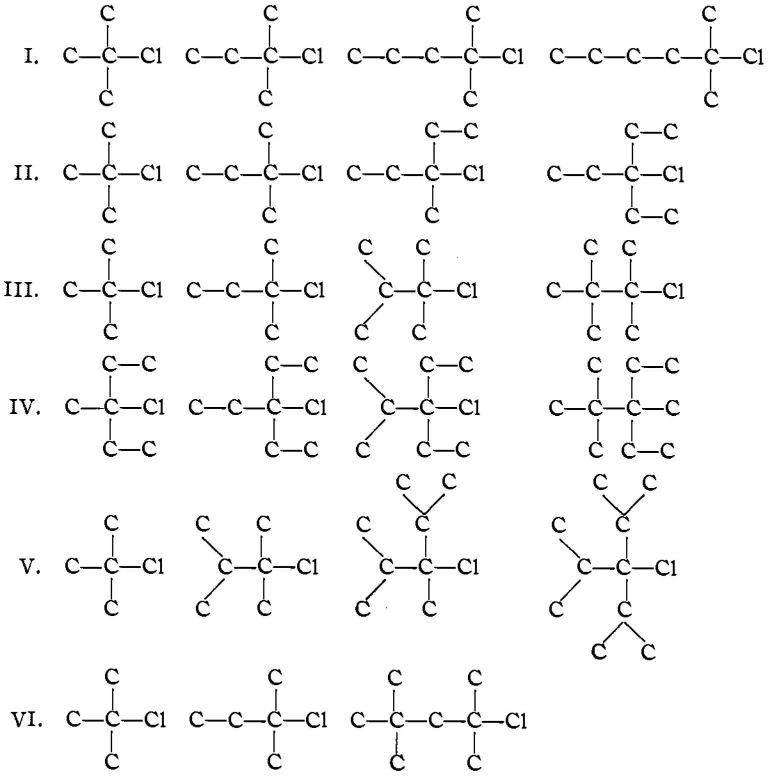


The rate-determining step is the unimolecular ionization of the chloride (k_1), yielding a carbonium ion. This ion can then undergo either a fast substitution reaction with the solvent (k_S), forming the alcohol or the ether, or a fast elimination of a proton (k_E), forming the olefin.

The rates of hydrolysis of the tertiary chlorides were determined in the usual manner by following the hydrogen ions produced. Thus, titration of aliquots of the reaction mixture at suitable intervals of time with standard alkali yields the number of millimoles of tertiary chloride hydrolyzed.

The results permit consideration of the effects of a number of systematic changes in structure. These series are indicated in the chart.

I. Effect of Chain-lengthening in the Series RMe_2CCl.—The unimolecular rate constant increases from 0.033 hr.$^{-1}$ to 0.055 as the group R is changed from methyl to ethyl. An increase in the length of the alkyl group to *n*-propyl and to *n*-butyl brings about relatively minor changes in the rate constant to 0.052 and 0.047, respectively.



SERIES OF TERTIARY ALKYL CHLORIDES STUDIED.

II. Effect of Replacement of Methyl by Ethyl Groups in the Series $Me_{3-x}Et_xCCl$.—As has been noted, the replacement of one methyl group in *t*-butyl chloride by an ethyl group increases the rate constant from 0.033 to 0.055. A second ethyl group in methyldiethylcarbinyl chloride[19] increases the rate constant further to 0.086, and the third ethyl group in triethylcarbinyl chloride raises the rate constant still further to 0.099.

Thus, whatever the cause of the greater effectiveness of an ethyl group over a methyl group in facilitating ionization of the alkyl chloride, the second and third such ethyl groups produce effects similar to those produced by the first. This observation is of particular interest when compared with the opposite effects produced by one isopropyl group and by two and three such groups (*vide post*).

III. Effect of Chain-branching in the Series, RMe_2CCl.—The increase in rate constant as the group R in RMe_2CCl is changed from methyl to ethyl, 0.033 to 0.055, is followed by a sharp decrease as R becomes isopropyl, k_1 = 0.029. It is possible to account for this behavior in terms of a judicious combination of the hyperconjugative and inductive effects. However, it does not appear possible in this way to account for the increase produced by the *t*-butyl group in dimethyl-*t*-butylcarbinyl chloride with k_1 = 0.040.

IV. Effect of Chain-branching in the Series, REt_2CCl.—The effect of chain-branching in the group R in the series REt_2CCl is identical to that observed in the series RMe_2CCl, but is considerably more marked. Thus the rate constant for the

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(18) Hughes and Ingold, *Trans. Faraday Soc.*, **37**, 657 (1941).

(19) With the exception of the two simplest alkyl chlorides for which the common names, *t*-butyl and *t*-amyl chlorides are adequate, the "carbinyl" system of nomenclature has been adopted for referring to the higher tertiary chlorides studied.

hydrolysis increases from 0.086 for the first member of the series, methyldiethylcarbinyl chloride, to 0.099 for triethylcarbinyl chloride. The rate constant decreases to a value in the neighborhood of 0.057–0.066 for diethylisopropylcarbinyl chloride, and finally increases sharply to a value of either 0.40 to 1.60 for diethyl-*t*-butylcarbinyl chloride.

The indefinite values for the rate constants assigned to diethylisopropylcarbinyl chloride and diethyl-*t*-butylcarbinyl chloride are the result of certain unexpected phenomena which were observed in the course of the present investigation. These will be discussed in more detail later. However, it may be mentioned here that the data strongly indicate that the conversion of these highly branched tertiary carbinols into the corresponding tertiary chlorides is accompanied, even under the mildest possible conditions, by considerable rearrangement.

V. Effect of Replacement of Methyl Groups by Isopropyl Groups in the Series, $Me_{3-x}i\text{-}Pr_xCCl$.—It was previously pointed out that in series II the replacement of one, two or three methyl groups in *t*-butyl chloride by a corresponding number of ethyl groups leads to a regular increase in reaction rate. In the present series, such regularity is not observed. Whereas the one isopropyl group in dimethylisopropylcarbinyl chloride, with $k_1 = 0.029$, produces a decrease in rate over the parent compound, *t*-butyl chloride, the second isopropyl group in methyldiisopropylcarbinyl chloride, with $k_1 = 0.45$, results in a very marked increase in rate. The rate constant for the hydrolysis of triisopropylcarbinyl chloride is even greater.[20]

VI. Effect of the Neopentyl Group in Diisobutylene Hydrochloride (Dimethylneopentylcarbinyl Chloride).—It was of interest to compare the effects of replacing one of the hydrogen atoms in *t*-butyl chloride by a small alkyl group, such as methyl and ethyl, and by a large alkyl group, such as *t*-butyl. Methyl produces a relatively moderate increase in rate constant as indicated by the values of 0.033 and 0.055 for *t*-butyl and *t*-amyl chlorides, respectively. The introduction of longer groups, such as ethyl or *n*-propyl in place of the methyl group, is no more effective. On the other hand, the similar replacement of the hydrogen atom in *t*-butyl chloride by a bulky *t*-butyl group is accompanied by a very marked increase in rate constant, as shown by the observed value of 0.74 for dimethylneopentylcarbinyl chloride.

Discussion

Inductive and Hyperconjugative Effects of Alkyl Groups.—The present state of knowledge of the polar effects of alkyl groups leaves much to be desired. It was originally suggested by Ingold[21] that alkyl groups exert a positive inductive effect and increase the electron density at the atom to which the groups are attached. It was proposed that this inductive effect would increase with the size of the alkyl group, so that the predicted order for increasing inductive effect is Me < Et < *i*-Pr < *t*-Bu. This order has been observed in a number of instances.[22,23]

More recently hyperconjugation has been considered to be an important factor in alkyl groups.[24] It is proposed that the ability of alkyl groups to effect electron release through hyperconjugation will decrease in the order Me > Et > *i*-Pr > *t*-Bu.[25] This order is precisely opposite to that predicted for inductive effect and has been observed in the unimolecular hydrolysis of *p*-alkylbenzhydryl chlorides.[26]

Finally, instances have been observed where neither order is obtained.[23] In these cases it is considered that the observed orders are the result of a superposition of hyperconjugative and inductive effects, neither of which is predominant.

The situation may perhaps be clarified by reference to Fig. 1. In a reaction which is facilitated by electron accession to the reaction center, the rate constant could either increase or decrease monotonically with the series Me, Et, *i*-Pr, *t*-Bu (curves A or D), depending upon whether the inductive effect or the hyperconjugative effect were predominant. Combinations of the two effects could produce the sequences represented by curves B and C.

The Steric Factor in the Unimolecular Hydrolysis.—For convenience in following the discussion the experimental results are summarized in Table I.

TABLE I

RATE DATA FOR THE FIRST ORDER HYDROLYSIS OF TERTIARY ALKYL CHLORIDES AT 25° IN "80%" AQUEOUS ETHANOL[a]

	Alkyl chloride, R'R''R'''CCl	R'	R''	R'''	k_1 (hr.$^{-1}$)
1	*t*-Butyl	Me	Me	Me	0.033
2	*t*-Amyl	Me	Me	Et	.055
3	Dimethyl-*n*-propylcarbinyl	Me	Me	*n*-Pr	.052
4	Dimethylisopropylcarbinyl	Me	Me	*i*-Pr	.029
5	Dimethyl-*n*-butylcarbinyl	Me	Me	*n*-Bu	.047
6	Dimethyl-*t*-butylcarbinyl	Me	Me	*t*-Bu	.040
7	Dimethylneopentylcarbinyl	Me	Me	neo-C_5	.74
8	Methyldiethylcarbinyl	Me	Et	Et	.086
9	Triethylcarbinyl	Et	Et	Et	.099
10	Diethylisopropylcarbinyl[b]	Et	Et	*i*-Pr	.057–0.066
11	Diethyl-*t*-butylcarbinyl[b]	Et	Et	*t*-Bu	1.60 0.40
12	Methyldiisopropylcarbinyl[b]	Me	*i*-Pr	*i*-Pr	0.45 0.031

[a] Density d^{25}_4 0.8496. [b] The peculiarities of these compounds are discussed in the section on rearrangements.

The increase in rate from *t*-butyl chloride to *t*-amyl chloride might be attributed to the increased

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(20) Private communication from Professor Paul D. Bartlett. Triisopropylcarbinyl chloride and other more highly branched tertiary chlorides were not included in the present study, since it was learned that Professor Bartlett was interested in this particular phase of the problem.

(21) Ingold, *Chem. Reviews*, **15**, 225 (1934).

(22) Bateman and Hughes, *J. Chem. Soc.*, 945 (1940).

(23) Baker, Dippy and Page, *ibid.*, 1774 (1937).

(24) Mulliken, Rieke and Brown, THIS JOURNAL, **63**, 41 (1941).

(25) Baker and Nathan, *J. Chem. Soc.*, 1844 (1935).

(26) Hughes, Ingold and Taher, *ibid.*, 949 (1940).

inductive effect of the ethyl substituent in *t*-amyl chloride over the corresponding methyl substituent in *t*-butyl chloride. The fact that the rate of hydrolysis does not change appreciably as the length of the chain is increased may be reconciled on the basis that increase of the chain beyond two carbon atoms should not appreciably increase the inductive effect of the group and that the possibilities for hyperconjugation, involving the alpha hydrogen atoms, are not affected by the process of lengthening the chain.

The introduction of an isopropyl group in place of the ethyl group in *t*-amyl chloride brings about a sharp decrease in rate. Obviously, if this observation is to be accounted for in terms of the inductive and hyperconjugative effects, it can only be the result of a combination of the two effects with neither predominant, such as is indicated by curve C of Fig. 1.

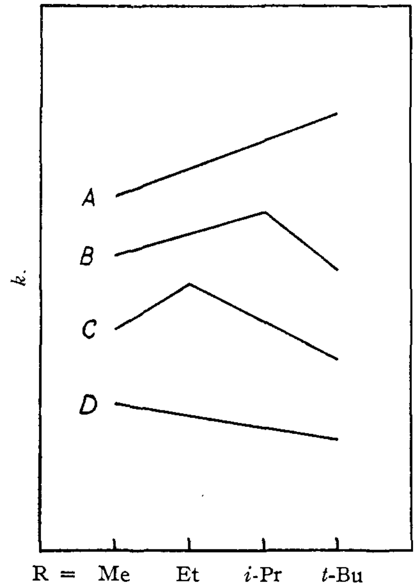

Fig. 1.—Influence of the inductive and hyperconjugative effects of alkyl groups on rate or equilibrium constants.

However, instead of a further decrease as the isopropyl group is converted to a *t*-butyl group, corresponding to curve C, there is observed an increase in rate constant (Fig. 2). To the knowledge of the authors, such behavior has not been observed in cases where the alkyl group is systematically varied from methyl to *t*-butyl in a position which is remote from the reaction center. In the present instance the change occurs at the reaction center and it is reasonable to ascribe the peculiar behavior to this fact. It is therefore suggested that the increase in rate is to be attributed to an increase in steric strain which is relieved in the planar carbonium ion. This strain therefore contributes to the driving force facilitating ionization of the alkyl chloride.

The increase in rate is relatively small and there may be some hesitation in calling in a new effect to explain an increase of this order of magnitude. It should be pointed out, however, that there are a number of factors which would be expected to affect adversely the rate of hydrolysis of a tertiary chloride with a large bulky substituent. Thus, the ionization must be preceded by solvation of the chlorine atom. The presence of the bulky *t*-butyl group would be expected to hinder such solvation. Solvation of the carbonium ion is also considered to contribute to the ease of ionization. Solvation energy is large for a small ion and decreases for larger ions. In this respect the presence of the bulky *t*-butyl group should again be unfavorable. Further, there is some opinion that the ionization is facilitated by the approach of solvent molecules to the rear of the central carbon atom. Accompanying the "pull" of solvation of chloride ion there is a "push" by the solvent molecule becoming attached to carbon.[27] Whatever the importance of this effect in solvents of high dielectric constant, it also should be minimized by the presence of a large bulky group at the reaction center.

All of these effects predict a decrease in rate for the change of the substituent from isopropyl to *t*-butyl. It may well be that these effects tend to minimize the increase caused by the steric strain factor.

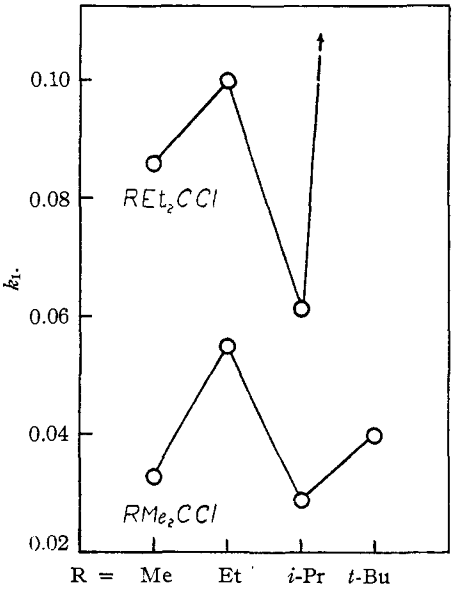

Fig. 2.—Rate constants for the hydrolysis of RMe_2CCl and REt_2CCl.

The argument in favor of steric strain is strengthened by a consideration of the results obtained in the series REt_2CCl. Here again there is observed an increase as R is altered from methyl to ethyl, and a decrease with change of the group to isopropyl. Introduction of a tertiary butyl group produces a marked increase in rate, some twenty-fold in magnitude (Fig. 2).

An even stronger argument is furnished by

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[27] Swain, THIS JOURNAL, **70**, 1119 (1948).

consideration of the different behavior of the two series, $Me_{3-x}Et_xCCl$ and $Me_{3-x}i\text{-}Pr_xCCl$. In the former series, the increase observed with one ethyl group is continued by the second, and by the third such group. In the case of the second series, the replacement of a methyl by an isopropyl group causes a decrease in rate. However, the second isopropyl group produces the opposite effect, a sharp increase in rate. A third isopropyl group causes a still further increase[20] (Fig. 3).

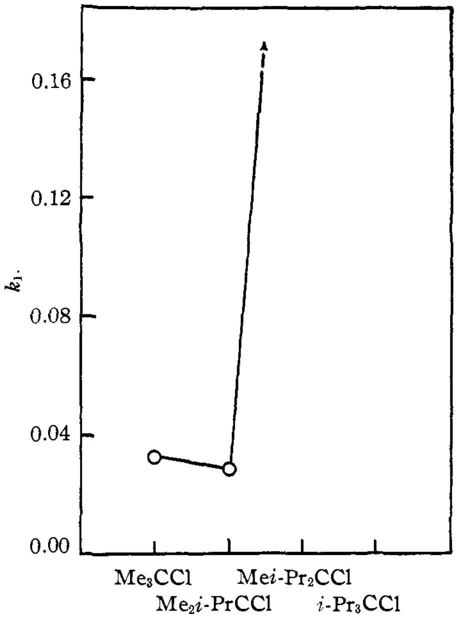
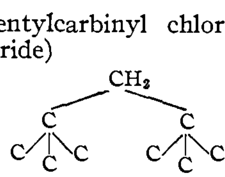


Fig. 3.—Rate constants for the hydrolysis of the tertiary chlorides, $i\text{-}Pr_{3-x}Me_xCCl$.

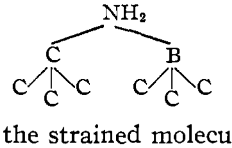
In view of the regularity of the increase with the ethyl derivatives, it would have been anticipated that the effect of one, two and three isopropyl groups should be regular. Regardless of the exact nature of the effect which causes the monoisopropyl derivative to hydrolyze at a slower rate than *t*-butyl chloride, a second isopropyl group should have a similar effect, and so should the third. The only simple explanation available for the observed reversal is steric strain. The accumulation of two bulky isopropyl groups results in a crowding at the reaction center which facilitates ionization. A third isopropyl group is even more effective.

Finally, consider the effect of replacing the R group in the series $R\text{-}CH_2CMe_2Cl$ by a small alkyl group, such as methyl and ethyl, and by a large alkyl group, such as *t*-butyl. The *t*-butyl group has a tremendous effect compared to the methyl and ethyl groups. Since in all cases the two secondary hydrogen atoms are unchanged and the structural changes are relatively remote from the reaction center, neither the inductive effect nor hyperconjugation appears capable of accounting for the large increase.

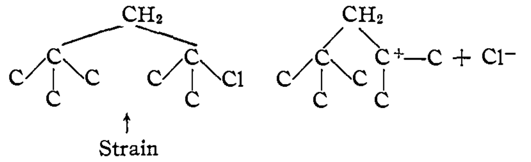
Examination of the *t*-butyl derivative, that is, dimethylneopentylcarbinyl chloride (diisobutylene hydrochloride)



reveals that the molecule has essentially the molecular configuration of di-*t*-butylmethane. This molecule has been postulated to be under considerable strain as a result of earlier studies in the dissociation of its isostere, *t*-butylamine-trimethylboron.[28]



Ionization of the strained molecule, diisobutylene hydrochloride, would relieve the strain because of the planar arrangement postulated for the carbonium ion.



Although further work along these lines is desirable, these results strongly support the suggestion of steric strain as a factor in the reactions of highly branched carbon compounds. Without steric strain, the results could not be easily interpreted in terms of present theories. With the aid of the steric strain concept, the marked increases observed with the introduction of bulky alkyl groups are readily interpretable.

Molecular Rearrangements in the Preparation of Tertiary Chlorides.—Earlier in the paper it was suggested that the relative ease with which branched chain compounds undergo molecular rearrangement might in part be the result of strain at the branch center. Such strain would be expected to labilize the groups attached to that center and facilitate their rearrangement. Certain of the results obtained in the present study lend support to this view and indicate that such rearrangements must be far more common than is ordinarily considered to be the case.

In the present investigation the tertiary alcohols were synthesized by the Grignard reaction using reactants which should cause a minimum of side reaction. The tertiary alcohols were purified by distillation. No difficulty was encountered in isolating fractions of high purity as evidenced by constancy of physical properties and agreement with previously reported values for such properties. The alcohols were then converted to the tertiary chloride by mixing the alcohol with an excess of concentrated hydrochloric acid at room temperature. After the two substances had been

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(28) Brown and Barbaras, *J. Chem. Phys.*, **14**, 114 (1946).

in contact for approximately one hour, the tertiary chloride was separated, dried, and distilled under reduced pressure. Constant boiling products were obtained; these were utilized in the rate studies.

In most cases the calculated first order rate constants (k_1) were sensibly constant or showed a slight increase with time. Such an increase has been previously observed and has been attributed to a "salt effect." The accumulation of ions (from the hydrochloric acid) in the reaction medium increases its ionizing properties and increases the rate of hydrolysis of the tertiary chloride. This effect may be minimized by studying the rate of hydrolysis only during the initial stages. However, in aqueous ethanol the effect is relatively small and does not offer any difficulty with the tertiary chlorides studied in the present investigation. Another, more serious, phenomenon was observed in the hydrolysis of two of the tertiary chlorides, diethyl-*t*-butylcarbinyl chloride and methyldiisopropylcarbinyl chloride. In these cases the calculated first order rate constants showed a marked *decrease* with time.

A typical set of experimental results for diethyl-*t*-butylcarbinyl chloride is illustrated in Fig. 4. Ordinarily a plot of the logarithm of the concentration of unhydrolyzed alkyl chloride *versus* time yields a straight line, from the slope of which the rate constant may be determined. However, the points in Fig. 4 obviously do not define a straight line.

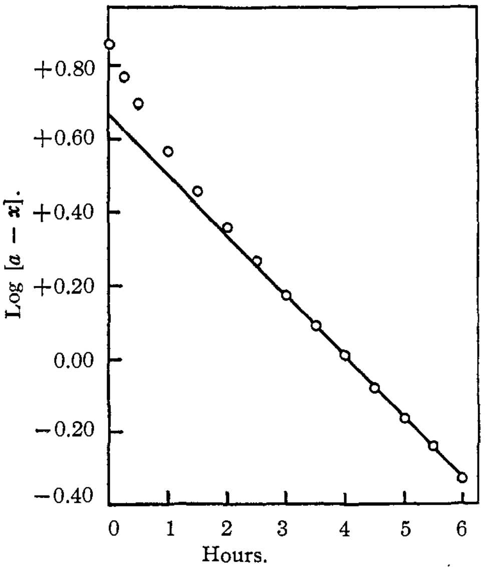

Fig. 4.—Hydrolysis of diethyl-*t*-butylcarbinyl chloride.

It was noted that the individual points after three hours do define a straight line. This observation suggested that the peculiar data were the result of two simultaneous first order reactions. Such data could arise if the alkyl chloride used was actually a mixture of two alkyl chlorides, one of which hydrolyzed relatively rapidly and was essentially completely hydrolyzed by the end of the three-hour period, while the other hydrolyzed at a considerably slower rate. According to this hypothesis, the slope of the line defined by the experimental points after three hours gives the first order constant for the less reactive of the two halides, $k_1^\beta = 0.38$ hr.$^{-1}$. By correcting the experimental results for the hydrochloric acid contributed by this tertiary chloride (beta), a new set of data is obtained (Fig. 5). These data permit calculation of the first order rate constant for the more reactive of the two halides ($k_1^\alpha = 1.58$ hr.$^{-1}$).[29] The data also indicate that the more reactive of the two halides, alpha, is present to the extent of 35% in the original chloride and the less reactive halide, beta, to the extent of 65%.

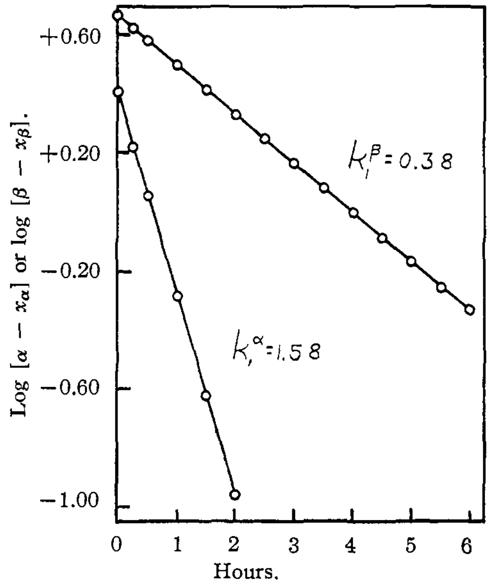

Fig. 5.—Separation of data from hydrolysis of "diethyl-*t*-butylcarbinyl chloride" into two simultaneous first order reactions.

The hydrolysis of diethyl-*t*-butylcarbinyl chloride had been previously studied by Bartlett and Knox.[16] These authors reported a rate constant of 0.42 hr.$^{-1}$. Their alkyl chloride had been prepared by treatment of the alcohol at 0° with dry hydrogen chloride. It was first thought that the difference in results might be due to differences in the preparative methods. However, examination of the data of Bartlett and Knox, data which were generously made available by Professor Bartlett, revealed that these data also could be analyzed into two rate constants in excellent agreement with the values obtained in the present study. Moreover, the data indicated the presence of the two alkyl chlorides in approximately the same mole ratio as that reported above.

Similarly, the experimental results obtained

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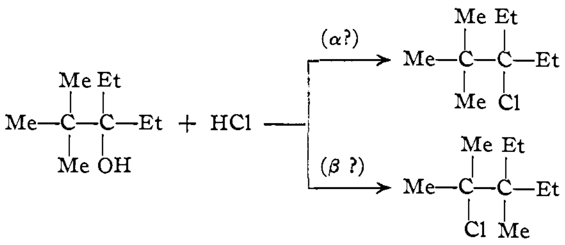
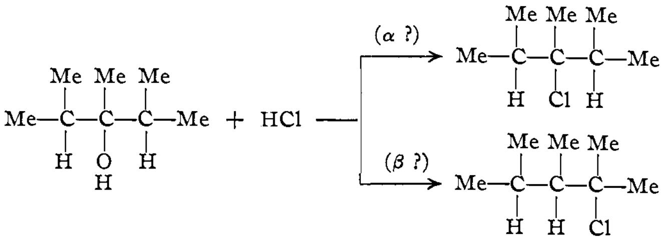
(29) The results reported in Table I differ slightly from these figures; the values there reported represent the mean of several determinations.

with methyldiisopropylcarbinyl chloride could be analyzed into two first order rate constants, $k_1^{\alpha} = 0.46$ and $k_1^{\beta} = 0.032$.[29] These data indicate that in this instance also the more reactive halide was present in lesser amount, the ratio being alpha: beta = 28:72.

It is believed that these unusual results are due to an exceedingly facile rearrangement during the preparation of the tertiary chloride. It is suggested that the following structural changes occur in the course of the reaction.





It is not yet possible to state with certainty which of the structures corresponds to the alpha component of the tertiary chloride and which to the beta. However, from the information gained in the present study as to the effects of structure upon rate of hydrolysis, it is possible to make a tentative assignment of structure. It is proposed that the faster hydrolyzing component in each case (the alpha component) corresponds to the unrearranged product, whereas the slower hydrolyzing component (the beta derivative) corresponds to the rearranged product. An investigation is now underway seeking to separate and isolate the individual components and to establish their structures with greater certainty.

It is believed that the conversion of the tertiary alcohol into the chloride involves the formation of a carbonium ion as an intermediate and the rearrangement proceeds within this carbonium ion by transfer of a methyl group or a hydrogen atom with their electron pair. Such rearrangements are, of course, well recognized and have been thoroughly investigated in the case of primary and secondary alcohols containing one or two branches on the carbon atom next to the carbinol group.[30] However it appears to have been assumed by Whitmore and others that the very ready conversion of aliphatic tertiary alcohols with a branch in the position next to the carbinol group to the corresponding tertiary halides is not complicated by rearrangement.[31]

It was somewhat puzzling that the tertiary chloride obtained from diethylisopropylcarbinol did not exhibit similar behavior. Here also the structure appeared favorable for the formation of two tertiary chlorides. However, a plot of the experimental results satisfactorily defined a single straight line. It seemed possible that this result might be due not to the absence of any rearranged chloride in the product, but rather to a close similarity in the rate at which the two chlorides hydrolyzed. Under this condition the procedure applied to diethyl-*t*-butylcarbinyl chloride would fail.

Another procedure was therefore adopted. The tertiary chloride was distilled through a Viggreux column under reduced pressure and three fractions collected. Each fraction was then separately hydrolyzed under identical conditions, and the rate determined. The observed rate constant changed from 0.066 for the first fraction, to 0.062 for the second, to 0.057 for the third. Such a variation is far greater than the experimental error and points to the presence in the tertiary chloride of at least two components which are partially separated in the course of distillation.

These results indicate that rearrangements of this kind must be quite common. They suggest that the properties attributed to highly branched tertiary halides and the structures they have been assigned should be accepted with considerable reservation. Indeed, it is quite probable that with the exception of a few unusual cases where the rearranged and unrearranged derivatives are identical, *e. g.*, dimethylisopropylcarbinyl chloride, no pure tertiary chlorides derived from alcohols with a branch in the beta position have ever been isolated.

This phenomenon is being studied further. The importance of the steric factor in labilizing the groups at the chain branch is also under investigation.

Experimental Part

Materials.—The solvent used for the hydrolysis studies was an ethanol–water mixture of approximately 80%

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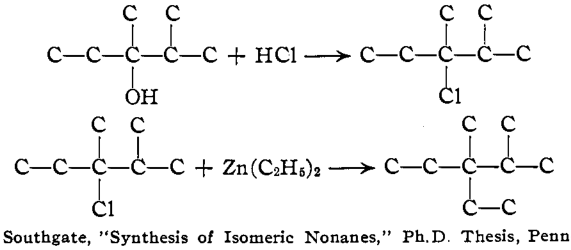
(30) Whitmore, THIS JOURNAL, **54**, 3274 (1932); Whitmore and Church, *ibid.*, **55**, 1119 (1933); Whitmore and Meunier, *ibid.*, **55**, 3721 (1933); Whitmore and Laughlin, *ibid.*, **55**, 3732 (1933).

(31) For example, Southgate reports the preparation of "pure" 2,3-dimethyl-3-ethylpentane by the series of reactions



Southgate, "Synthesis of Isomeric Nonanes," Ph.D. Thesis, Pennsylvania State College, 1940.

The product boiled over a considerable range and at low temperatures solidified to a glass. It is probable that the formation of the tertiary chloride involved rearrangement to dimethyl-*sec.*-butylcarbinyl chloride, so that the final product contained 2,2,3-trimethylhexane, as well as the desired nonane.

ethanol by volume. It was prepared by mixing eight volumes of absolute ethanol with two volumes of water. The density of the solution, as determined with a Geissler pycnometer, was d^{25}_4 0.8496 g./ml.

The tertiary alcohols used were prepared by the Grignard reaction with the exception of *t*-butyl and *t*-amyl alcohols. These were obtained by fractionation of the commercial products. In general the preparation of the tertiary alcohols followed standard procedures with yields of 60–75%. The products were isolated and purified by distillation under vacuum.

The tertiary chlorides (with the exception of diisobutylene hydrochloride) were prepared from these alcohols by placing in a separatory funnel one mole of the tertiary alcohol with approximately five moles of concentrated hydrochloric acid. The mixture was shaken vigorously several times during the course of an hour. At that time the lower layer was withdrawn and discarded and a fresh portion of concentrated hydrochloric acid added. The mixture was alternately shaken vigorously and permitted to stand at room temperature for another hour. The upper layer was separated, dried over anhydrous calcium chloride, and distilled under reduced pressure using a Vigreux column and all-glass distillation equipment. Diisobutylene hydrochloride was prepared by the addition of hydrogen chloride to the olefin. The physical constants of the tertiary chlorides thus obtained and used in the rate studies are listed in Table II.

TABLE II

PHYSICAL CONSTANTS OF TERTIARY CHLORIDES

Chloride obtained from the carbinol, R′R″R‴COH			B. p., °C.	Pressure, mm.	Refractive index n^{25}_D
R′	R″	R‴			
Me	Me	Me	50.5–51.0	753	
Me	Me	Et	56.4–56.6	300	1.4023
Me	Me	*n*-Pr	56.8–57.2	119	1.4113
Me	Me	*i*-Pr	67.6–70.0	108	1.4162
Me	Me	*n*-Bu	76.2–76.4	103	1.4185
Me	Me	*t*-Bu	M. p. 129–130°		
Me	Me	neo-C_5	59.0–60.0	26	1.4286
Me	Et	Et	56.2–56.6	82	1.4190
Et	Et	Et	88.5–88.6	97	1.4308
Et	Et	*i*-Pr	98.6–100.4	98	1.4405
Et	Et	*t*-Bu	53.0–54.0	6	1.4528
Me	*i*-Pr	*i*-Pr	54.0	16	1.4390

Kinetic Measurements.—The procedure used for the determination of the first order hydrolysis constants and the olefin fractions is a modification of that used by Hughes and Ingold and their co-workers.[15]

In a round-bottomed long-necked flask was placed 100 ml. of the "80%" ethanol solvent. The flask was immersed in a constant temperature bath maintained at 25.0 ± 0.03°. When temperature equilibrium had been attained, approximately 1 ml. of the tertiary chloride was added to the flask and the contents were rapidly mixed by swirling. At definite time intervals, 5-ml. samples of the solution were pipetted out and run into 100 ml. of absolute ethanol at 0° in order to halt the reaction. The hydrochloric acid formed in the course of the hydrolysis was determined by titration with standard (approximately 0.04 *N*) sodium hydroxide solution. Methyl red was used as indicator. The original concentration of the halide was determined by passing a 5-ml. sample of the reaction mixture into either water or a dilute alcohol–water mixture and allowing the mixture to stand for a sufficient interval (usually overnight) to attain complete hydrolysis. The hydrochloric acid formed by the completely hydrolyzed sample was determined in the usual manner.

From the data thus obtained, the first order rate constants, k_1, were calculated for the individual chlorides using the expression

$$k_1 = \frac{2.303}{t} \log \frac{a}{a - x}$$

where t is the time in hours, a is the original concentration of the alkyl chloride and $a - x$ is the concentration of the alkyl chloride at the time t. Since this is a first order reaction, the concentrations may be conveniently expressed in terms of the ml. of the standard sodium hydroxide solution required for the titration of the 5-ml. aliquots of the reaction mixture. The mean value of k_1 for each chloride is determined by taking the average of the individual values of k_1 until the alkyl chloride is 40–50% hydrolyzed. In this way the "salt effect" is minimized.

Rate Data.—Each determination was run at least in triplicate in order to have a measure of the precision of the results. In general the values of k_1 agreed to within 1%. Space will not permit reproducing the experimental data in THIS JOURNAL. Complete data are contained in a thesis by Roslyn Silber on deposit in the library of Wayne University.

Rate Data for "Diethylisopropylcarbinyl Chloride."—In the hydrolysis of three different fractions collected in the distillation of the product obtained by treating diethylisopropylcarbinol with hydrochloric acid, the first order rate constant k_1 shows a steady decrease. Although the change is relatively small for each separate fraction, the over-all decrease which is observed is some 15%. This is highly reproducible and far beyond the experimental uncertainty.

The tertiary chloride which had been previously distilled was slowly fractionated with a Vigreux column. Three fractions were collected as follows. Fraction I distilled at 98.6–99.5 at 98 mm., n^{25}_D 1.4400; fraction II distilled at 99.5–99.9 at 98 mm., n^{25}_D 1.4405; fraction III distilled at 99.9–100.4 at 98 mm., n^{25}_D 1.4410. These fractions yielded rate constants (k_1, hr.$^{-1}$) as follows: I, 0.066; II, 0.062; III, 0.057.

Rate Data for "Diethyl-*t*-butylcarbinyl Chloride."—Data for a typical study of the hydrolysis of the chloride obtained from diethyl-*t*-butylcarbinol are illustrated in Fig. 4. The first order rate constant changes from 0.739 at 0.50 hour to 0.576 at 2.00 hours, to 0.470 at 5.00 hours. From the slope of the line defined by the points with $t <$ 2.5 hours (slope $= -0.167$), a value for $k_1{}^\beta$ is calculated of 0.38 hr.$^{-1}$. Extrapolation of the curve to $t = 0$, indicates that the beta component requires 4.68 ml. of the standard alkali solution.

The contribution of the hydrochloric acid produced by the beta component may now be calculated and the rate data corrected for this contribution. The results are listed in Table III.

TABLE III

RATE DATA FOR THE HYDROLYSIS OF THE *alpha* COMPONENT OF "DIETHYL-*t*-BUTYLCARBINYL CHLORIDE"

t, hr.	$x_\alpha + x_\beta = x$	$\beta - x_\beta$	log $(\beta - x_\beta)$	x_α	$\alpha - x_\alpha$	log $(\alpha - x_\alpha)$
0	0	4.68 = β	0.670	0	2.56 = α	0.408
0.25	1.82	4.25	.628	0.89	1.67	.223
0.50	2.24	3.86	.587	1.42	1.14	.057
1.00	3.54	3.18	.502	2.04	0.52	−.284
1.50	4.37	2.63	.420	2.32	.24	−.620
2.00	4.96	2.17	.336	2.45	.11	−.959
2.50	5.39	1.79	.253	2.50		
3.00	5.75	1.48	.170	2.55		
3.50	6.02	1.22	.086	2.56		
4.00	6.22	1.00	.00	2.54		
5.00	6.56	0.68	−0.168	2.56		
6.00	6.78	0.47	−0.328	2.57		
∞	7.25					

The data are plotted in Fig. 5. From the slope of the line (−0.687) a value for the rate constant for the alpha component of 1.58 hr.$^{-1}$ may be calculated. The limiting value of x_α in Table III is 2.56, so that the mole ratio of the two components is alpha:beta = 2.56:4.68.

It was suggested that the results might be due to the accumulation of hydrogen ion in the reaction medium. Conceivably, such an accumulation could repress a simultaneous bimolecular elimination reaction by either ethoxide or hydroxide ion. However, the addition of sufficient hydrogen chloride to the reaction medium to make it 0.05 *N* in hydrogen ion (equivalent to the acidity of a completely hydrolyzed solution of the tertiary chloride) did not noticeably alter the results. Nor did decreasing the initial concentration of the tertiary chloride to one-half the usual value affect the results. In both experiments the data could be analyzed into two first order rate constants in good agreement with the data in Table III.

Rate Data for "Methyldiisopropylcarbinyl Chloride."—The tertiary chloride obtained from methyldiisopropylcarbinol also hydrolyzes at a rate which appears to decrease with time. The calculated first order rate constant decreases from the value 0.143 at 0.50 hour, to 0.90 at 5.00 hours, to 0.045 at 25.00 hours. These data were analyzed in a manner identical with that described for "diethyl-*t*-butylcarbinyl chloride" into $k_1^\alpha = 0.46$ and $k_1^\beta = 0.032$.

Acknowledgment.—The authors wish to express their debt to Mr. Rolf B. Johannesen, who in 1945 carried out a preliminary investigation of the problem with the aid of financial assistance from Grants 710 and 776 of the Penrose Fund of the American Philosophical Society. The assistance afforded by two graduate fellowships supported by Parke, Davis and Company in 1945 and 1946 is also gratefully acknowledged.

Summary

1. It is suggested that the peculiar behavior of the highly branched carbon compounds is to be attributed in part to a steric effect. The attachment of three or four alkyl groups to a single carbon atom introduces a center of strain. This strain facilitates reactions which involve the formation of less strained carbonium ions, the rearrangement of atoms or groups of atoms located at the strained center, or the rupture of carbon-to-carbon bonds at this center.

2. The need for quantitative data to test the proposal led to an investigation of the rate of hydrolysis of twelve tertiary alkyl chlorides in 80% ethanol at 25°. The effect of structural changes on the rate of hydrolysis cannot be explained on the basis of polar effects alone. With the aid of the steric strain hypothesis, a satisfactory interpretation of the observed facts is possible.

3. Certain peculiarities in the experimental data obtained with chlorides prepared from diethyl-*t*-butylcarbinol, methyldiisopropylcarbinol, and diethylisopropylcarbinol are explained in terms of a facile rearrangement accompanying the reaction of these carbinols with hydrochloric acid. It is suggested that no tertiary chloride containing a branch in the beta position has ever been prepared in pure form from the corresponding alcohol, with the exception of those few cases where the rearranged product is identical with the original structure.

LAFAYETTE, IND. RECEIVED OCTOBER 4, 1948

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF MERCK & CO., INC.]

Vitamin B_{12}. IV.[1] Further Characterization of Vitamin B_{12}

BY NORMAN G. BRINK, DONALD E. WOLF, EDWARD KACZKA, EDWARD L. RICKES, FRANK R. KONIUSZY, THOMAS R. WOOD AND KARL FOLKERS

Some chemical, physical and biological properties of crystalline vitamine B_{12} from liver[1a] and from a culture broth[1c] of a grisein-producing strain of *Streptomyces griseus* have been reported. The finding that vitamin B_{12} is a cobalt coördination complex which also contains nitrogen and phosphorus was described.[1b] Further observations on the physical and chemical characterization of this extremely biologically active vitamin are described herein.

Samples of crystalline vitamin B_{12} have had a cobalt content of about 4.5%, corresponding to an approximate minimum molecular weight of 1300. An ebullioscopic determination of the molecular weight carried out in methanol solution gave a value of 1490 ± 150, showing that the molecule contains one atom of cobalt.

The analytical data indicate that vitamin B_{12} has a composition typified by but not necessarily limited to $C_{61-64}H_{86-92}N_{14}O_{13}PCo$. Numerically, the formulas $C_{62}H_{86-90}N_{14}O_{13}PCo$ and $C_{63}H_{88-92}N_{14}O_{13}PCo$ agree excellently with the analytical results.

Vitamin B_{12} is optically active. The intense red color of its aqueous solutions made observations difficult, but working in dilute solution at the red end of the spectrum, a specific rotation of $[\alpha]^{23}_{6563} = -59 \pm 9°$ was observed. Vitamin B_{12} is a polyacidic base, as revealed by potentiometric titration in glacial acetic acid solution. The basic groups are quite weak, however, and were not detected when the compound was titrated in aqueous solution.

It is of considerable initial interest to determine the type or class of organic structure to which vitamin B_{12} belongs. Prior to its isolation in crystalline form, some investigators have reported the presence of amino acids in acid hydrolyzates of concentrates of the antipernicious anemia factor at progressing stages in the purification,[2] and the association of activity with a polypeptide was

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[1] Three previous papers have contained the initial information on the properties of vitamin B_{12}: (a) I, Rickes, Brink, Koniuszy, Wood and Folkers, *Science*, **107**, 396 (1948); (b) II, *ibid.*, **108**, 134 (1948); (c) III, *ibid.*, **108**, 634 (1948).

[2] For a review by SubbaRow, Hastings and Elkin on earlier investigations, see "Vitamins and Hormones," Vol. III, 257, Academic Press, Inc., New York, N. Y., 1945.