Recovery of I from Solutions in Concentrated Sulfuric Acid.—2,4-Dinitrobenzenesulfenyl chloride (I), 0.10 g., m.p. 96–97° was finely-ground and added to 20 ml. of 96% sulfuric acid. The mixture was let stand, and stirred occasionally, for one hr. This was filtered through a sintered-glass funnel, the filtrate poured on 50 g. of crushed ice, and the latter mixture was extracted with 50 ml. of carbon tetrachloride. Evaporation of the solvent, from the extract, gave 5 mg. of unchanged I (m.p. and m.m.p. with authentic I, 95–96°).

LOS ANGELES, CALIFORNIA

NOTES

5-Thiol-7-hydroxy-1-γ-triazolo[d]pyrimidine[1,2]

BY CARL TABB BAHNER AND DOROTHY ELLIS BILANCIO

RECEIVED AUGUST 7, 1953

5-Thiol-7-amino-1-γ-triazolo[d]pyrimidine has been reported to be a strong inhibitor of the growth of *Streptococcus faecalis* R.[3] but not of *Adenocarcinoma* 755.[4] The closely related compound having an hydroxy group in place of the 7-amino group has been prepared as described below. It produces a 65% reduction in the growth of *L. casei* at a concentration of 0.005 mg./ml.[5] The effect can be reversed by pteroylglutamic acid or adenine. The results of screening against various tumors are to be published elsewhere.

A solution of 7.0 g. of sodium nitrite in the minimum volume of water was added slowly to a solution of 15.0 g. of 2-thiol-4,5-diamino-6-hydroxypyrimidine[6,7] in one liter of 2 *N* H_2SO_4 at 40°. Stirring was continued 15 minutes after all the sodium nitrite had been added. The solution was chilled for two hours and the solid product was recovered by filtration. It was suspended in boiling water and dissolved by addition of ammonia. The resulting solution was chilled and the crystals which formed were dissolved in boiling water. The hot solution was treated with activated charcoal, filtered hot, acidified with acetic acid and chilled. The crystals which formed were recrystallized from acetone; they then decomposed sharply at 265°. In sodium bicarbonate-buffered solution, the product reacted with iodine in the ratio of 4 atoms of iodine to 1 molecule of product. Grynberg[8] reported similar results with xanthine and guanine. However 8-azaguanine does not behave in the same way. Ultraviolet absorption data for this compound are shown in Table I. The sample for carbon and hydrogen analysis was dried at 110° and 0.1 mm. before analysis, but the analysis indicated the presence of one molecule of water. Roblin,[9] *et al.*, observed that the corresponding dihydroxy compound also was obtained as the monohydrate in spite of careful drying. *Anal.* Calcd. for $C_4H_5N_5O_2S$: C, 25.64; H, 2.69. Found: C, 25.85; H, 2.60.

TABLE I

ULTRAVIOLET ABSORPTION SPECTRA

*p*H	$\lambda_{max.}$	$\lambda_{min.}$
1	242	255
	270	278
	294	
6.5	238	219
	288	253
10	232	252
	276	
11	277	250

We are indebted to Gertrude Elion and George H. Hitchings of the Wellcome Research Laboratories and Lee Bennett, Jr., of the Southern Research Institute for ultraviolet absorption data and to Galbraith Analytical Laboratories for carbon and hydrogen determination.

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[1] This research was supported in part by a grant from the Damon Runyan Memorial Fund for Cancer Research and in part by a research grant from the National Institutes of Health, U. S. Public Health Service.

[2] Presented in part at the Southeastern Regional Meeting of the American Chemical Society, Auburn, Ala., October 24, 1952.

[3] C. T. Bahner, H. A. Rutter, Jr., and J. R. Totter, *J. Tenn. Acad. Sci.*, **27**, 179 (1952).

[4] G. W. Kidder, V. C. Dewey, R. E. Parks, Jr., and G. L. Woodside, *Cancer Research*, **11**, 204 (1951).

[5] Gertrude Elion and George H. Hitchings, private communication.

[6] W. Traube, *Ann.*, **331**, 71 (1904).

[7] A. Albert, D. J. Brown and G. Cheeseman, *J. Chem. Soc.*, 474 (1951).

[8] M. Z. Grynberg, *Biochem. Z.*, **253**, 143 (1932).

[9] R. O. Roblin, Jr., J. O. Lampen, J. P. English, Q. P. Cole and J. R. Vaughan, Jr., THIS JOURNAL, **67**, 290 (1945).

On Competition between the Clarke–Eschweiler and Pictet–Spengler Reactions

BY RICHARD BALTZLY

RECEIVED JULY 28, 1953

Some years ago in these laboratories Dr. J. S. Buck and the author observed that the attempt to produce dimethylhomoveratrylamine from homoveratrylamine or N-methylhomoveratrylamine by the Clarke–Eschweiler reaction[1] gave mainly 2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline. Similar results were obtained with N-benzylhomoveratrylamine[2] and an attempt to methylate β-(2,5-dimethoxyphenyl)-propylamine by this procedure afforded a compound that was not the corresponding dimethylamine and whose hydrochloride gave analyses consistent with the composition $C_{13}H_{20}ClNO_2$.[3] In this latter case the authors were reluctant to ascribe to this substance the structure of a tetrahydroisoquinoline since there was no activating group in the parent phenethylamine para to the point of prospective ring closure.

More recently Castrillon[4] has reported the cycli-

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[1] H. T. Clarke, H. B. Gillespie and S. Z. Weisshaus, THIS JOURNAL, **55**, 4571 (1933).

[2] J. S. Buck and R. Baltzly, *ibid.*, **64**, 2263 (1942).

[3] R. Baltzly and J. S. Buck, *ibid.*, **62**, 161 (1940).

[4] J. C. Castrillon, *ibid.*, **74**, 558 (1952).

zation of mescaline to 2-methyl-6,7,8-trimethoxy-1,2,3,4-tetrahydroisoquinoline as a result of attempts to prepare N,N-dimethylmescaline by the Clarke–Eschweiler procedure.

While the Pictet–Spengler[5,6] method of cyclization of phenethylamines to tetrahydroisoquinolines usually employs mineral acid, the conditions of acidity are not far removed from those in the usual Clarke–Eschweiler, especially if, as is often convenient with small quantities, the excess of formic acid is not minimized.

Since up to the present, the Pictet–Spengler had not been observed in the absence of strong acid except with phenolic amines[7] and a recent study of the Wallach reaction (of which the Clarke–Eschweiler is a special case) has shown that acidity is not required for it[8] the probability seemed high that homoveratrylamine could be methylated by formalin and formic acid if acidity were avoided.

In an application of the above argument homoveratrylamine was heated with formalin while the *p*H was kept close to 7 by addition of formic acid. Toward the end of the operation enough acid was admitted to give a *p*H of 5. Despite these precautions, the yield of N,N-dimethylhomoveratrylamine was only 44%. In addition there was obtained a 14% yield of 2-methyl-6,7-dimethoxytetrahydroisoquinoline and a small amount of a substance apparently isomeric with the latter.

It appears consequently that the Pictet–Spengler cyclization is considerably more facile than has previously been supposed and that when the structural peculiarities of a phenethylamine are favorable for this cyclization the Clarke–Eschweiler reaction cannot be manipulated to avoid the cyclization completely. To some extent this can be rationalized if one assumes that both reactions proceed through an alkylolamine intermediate which must become cationic for either reaction to proceed. Such an assumption is generally made for the Pictet–Spengler reaction and is not unreasonable for the Wallach reaction.

$$\mathrm{RNHCH_2OH} \xrightarrow[\mathrm{H_3O^+}]{}$$

$$\underset{\mathrm{I}}{\mathrm{RN\overset{+}{H}_2CH_2OH}} \rightleftarrows \underset{\mathrm{II}}{\mathrm{R\overset{+}{N}H{=}CH_2} \longleftrightarrow \mathrm{RNH{-}\overset{+}{C}H_2}}$$

Two obvious cationic forms, I and the resonance hybrid II, can be written and the equilibrium between them might well be *p*H dependent. Thus, in the present instances, the essentially neutral medium may have minimized the tendency of I to pass into II without preventing it completely.

Experimental

Ten cc. of formalin was added to 9.1 g. (50 mmoles) of homoveratrylamine in a 3-necked conical flask set in a steam-bath and equipped with a stirrer, thermometer and dropping funnel. After the admission of 2.4 cc. of 90% formic acid the stirrer was started and the flask was heated to about 87°. The evolution of gas commenced at about 50°. Further quantities of 90% formic acid were added to maintain a *p*H of about 7. After three hours a total of 5 cc. of formic acid had been added. Five cc. more formalin was then run in and the reaction continued, 3 cc. more formic acid being added in the next 1.5 hour. The *p*H was then 5 and was unaltered by 1.5 hours further heating. The solution was evaporated *in vacuo*, 7 cc. of concentrated hydrochloric acid was added (change of color from brown to green) and the mixture was again taken down *in vacuo*. The residue was dissolved in absolute ethanol, ethyl acetate was added and the solution was seeded with N,N-dimethylhomoveratrylamine hydrochloride. The solid obtained, however, was not this expected salt since it melted at 204–208°. On recrystallization the melting point rose to 213–215° and was not depressed by admixture of authentic 2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride. The weight of this pure fraction was 1.7 g. (7 mmoles).

The mother liquors were evaporated and the bases were liberated and distilled *in vacuo* (below 1 mm.). The more volatile material (boiling below 120°) afforded, after crystallization of the hydrochlorides, 22 mmoles of pure N,N-dimethylhomoveratrylamine hydrochloride. The undistilled bases (*ca.* 3 g.) were dissolved in hot hexane, a small amount of tar was removed, and attempts were made to crystallize the bases. As these were unsuccessful the material was reconverted to the hydrochlorides and 0.8 g. of a solid melting at 224–225° was obtained. Recrystallization from ethanol–ether mixture raised this melting point to 229–230° dec. Higher decomposition points could be obtained if the bath was heated rapidly (242°, 239°), but all these were decomposition points and none were so high as those reported for 6,7-dimethoxytetrahydroisoquinoline hydrochloride (253°, 262°)[9] which is said to melt without obvious decomposition.

Anal. Calcd. for $C_{12}H_{18}ClNO_2$: C, 59.1; H, 7.4. Found: C, 59.3; H, 7.4.

The composition is thus consistent with this substance being a dimethoxy-N-methyltetrahydroisoquinoline hydrochloride. Permanganate oxidation yielded an acid whose identity is as yet uncertain.

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(5) *Cf.* "Organic Reactions," Edited by Roger Adams, Vol. VI, John Wiley and Sons, Inc., New York, N. Y., 1951, p. 151.

(6) J. S. Buck, THIS JOURNAL, **56**, 1769 (1934).

(7) C. Schöpf and H. Bayerle, *Ann.*, **513**, 190 (1934). Actually a considerable gap exists between the conditions of Schöpf (dilute neutral solution and room temperature) and those customary in the synthetic reaction (high acidity, relatively high concentration and steam-bath temperatures). So far as the cyclization is concerned, concentration should affect only the formation of the methylolamine intermediate.

(8) E. Staple and E. C. Wagner, *J. Org. Chem.*, **14**, 559 (1949).

(9) J. S. Buck, THIS JOURNAL, **56**, 1769 (1934); R. Forsyth, C. I. Kelly and F. L. Pyman, *J. Chem. Soc.*, **127**, 1659 (1925).

THE WELLCOME RESEARCH LABORATORIES
TUCKAHOE 7, NEW YORK

Identification Derivatives of 2-Aminofluorene and of 2-Aminofluorenone

BY C. W. BENNETT AND W. W. MUELDER[1]

RECEIVED JUNE 26, 1953

The following new derivatives of 2-aminofluorene have been prepared and characterized.

2-Fluorenyl Phenyl Thiourea.—A solution of 1 g. of 2-aminofluorene in 50 ml. of ethanol and 2 g. of phenyl isothiocyanate was heated to boiling. Upon cooling, white needles separated. After recrystallization from ethanol, the m.p. was 179–180° uncor.

Calcd.[2] for $C_{20}H_{16}SN_2$: N, 8.86. Found: N, 9.40.

N-(2-Fluorenyl)-3-nitrophthalimide.—A mixture of 1 g. of 2-aminofluorene, 1.5 g. of 3-nitrophthalic anhydride and 15 ml. of dimethylaniline (solvent) was refluxed for 2 hours at the b.p. While still hot, 100 ml. of 95% ethanol was added. Shiny, golden flakes amounting to 0.4 g. when recrystallized from benzene of m.p. of 255.6° uncor. were obtained.

Calcd. for $C_{21}H_{12}O_4N_2$: N, 7.86. Found: N, 7.94.

New Derivatives of 2-Amino-9-fluorenone. N-2-(9-Oxo)-fluorenyl-4-nitrobenzamide.—A mixture of 0.5 g. of 2-aminofluorenone, 0.5 g. of *p*-nitrobenzoyl chloride and 10 ml. of pyridine was brought to the boiling point. While still hot, the mixture was filtered, diluted with 50 ml. of

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(1) Abstracted from the M.S. thesis of W. W. Muelder.

(2) Analyses were performed by Dr. Carl Tiedcke of Teaneck, N. J.

ethanol and allowed to cool. Orange-yellow crystals were obtained which after recrystallization from ethanol did not melt under 340°.

Calcd. for $C_{20}H_{12}N_2O_4$: N, 8.14. Found: N, 8.16.

N-2-(9-Oxo)-fluorenylbenzamide.—A mixture of 0.5 g. of 2-aminofluorenone, 0.36 g. of benzoyl chloride and 10 ml. of pyridine was heated to boiling. While still hot, the solution was filtered, diluted with 50 ml. of ethanol and allowed to cool. Vermillion crystals were obtained which after recrystallization from ethanol melted at 242° uncor.

Calcd. for $C_{20}H_{13}NO_2$: N, 4.68. Found: N, 4.89.

2-(9-Oxo)-fluorenylphenylurea.—A mixture of 0.5 g. of 2-aminofluorenone, 0.6 g. of phenyl isocyanate and 50 ml. of absolute ethanol was heated slowly to boiling. Crystals formed immediately but the mixture was allowed to cool. After three recrystallizations from ethanol the bright orange needles melted at 268°, resolidified and remelted at 323–324° (all uncor.).

Calcd. for $C_{20}H_{14}N_2O_2$: N, 8.92. Found: N, 9.18.

2-(9-Oxo)-fluorenylphenylthiourea.—A mixture of 0.5 g. of 2-aminofluorenone, 0.4 g. of phenyl isothiocyanate and 50 ml. of ethanol was brought to the boiling point and then allowed to cool. After 3 recrystallizations from dilute ethanol, the yellow-orange crystals melted at 185°.

Calcd. for $C_{20}H_{14}N_2SO$: N, 8.49. Found: N, 8.40.

2-Aminofluorenone oxime, prepared in the usual way and recrystallized from dilute ethanol, separated as orange yellow needles melting at 216–217° uncor.

Calcd. for $C_{13}H_{10}N_2O$: N, 13.33. Found: N, 13.29.

2-Aminofluorenone semicarbazone, prepared in the usual way, did not melt under 325° when repeatedly crystallized from ethanol.

Calcd. for $C_{14}H_{12}ON_4$: N, 22.22. Found: N, 21.69.

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DEPARTMENT OF CHEMISTRY
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The Role of Water Vapor on the Stoichiometric Reactions of Solid Proteins with Polar Gases[1]

BY SIDNEY W. BENSON, ROBERT L. ALTMAN,[2] RYDEN L. RICHARDSON[2] AND JERROLD M. SEEHOF[2]

RECEIVED JULY 28, 1953

In a very interesting paper,[3] Czarnetsky and Schmidt (henceforth C. and S.) reported the reversible addition of acidic and basic gases such as CO_2, H_2S, NH_3 to proteins in the solid state. Such results, if verified, would have great importance both as an analytical tool in establishing the number and type of functional groups in the protein molecule and as a structural tool in clarifying the configuration, thermodynamic properties and spatial availability of these groups in the protein molecule.

C. and S. reported that on measuring the sorption isotherms of the above gases on solid proteins, isobaric regions were observed (*i.e.*, regions in which the proteins adsorbed the gases at constant partial pressures). Such isobaric regions of adsorption can be interpreted by means of the phase rule as corresponding to the formation of new, pure, solid phases and the amount of gas adsorbed would then correspond quantitatively to the amount of the new phase, in short, a stoichiometric, gas phase titration.

These results are, however, in contradiction to the results obtained in our own[4,5] and other laboratories.[6–8] The discrepancies may be summarized as follows: 1. The vapor pressures of the isobaric regions reported by C. and S. are in general different from those found in our own[4,5] and other laboratories.[6,7] 2. Only one pressure flat is found by C. and S. and this is ascribed to chemical combinations of some 5 or more different components of the protein (*e.g.*, arginine, lysine, etc.). One would expect each hydrochloride to be formed at a different equilibrium pressure. 3. An anomalous type of hysteresis is found by C. and S. in the adsorption of HCl on gelatin. 4. C. and S. find completely reversible sorption of HCl on gelatin. This is again in direct conflict with the previous findings of ourselves and others.[4–7]

Because of the above inconsistencies it was decided to repeat the experiments with gelatin and dry HCl gas. For these purposes a conventional apparatus similar to the one used by C. and S. was employed with certain modifications which have been described elsewhere.[4] The results which were obtained were consistent with those we had obtained previously with other proteins. There was no region of stable, reproducible[9] isobaric sorption. The desorption curve lay considerably above the sorption curve and was typical of hysteresis found with other proteins. Finally the desorption did not continue to zero HCl pressure but was completed (at 10^{-6} mm. pressure) at an amount of HCl sorbed, quantitatively equal to the sum of the arginine, histidine and lysine residues present in the gelatin sample.

These experiments, however, differed in one important respect from those reported by C. and S. The latter reported that in order to obtain reproducible results it was necessary to have catalytic traces of water vapor present. To achieve this they attached a side arm to their sorption buret containing $Na_2SO_4 \cdot 10H_2O$–Na_2SO_4 mixtures. At constant temperature this would provide a constant vapor pressure of water in the system. While they gave none of the specific details of the procedure followed they did mention having to then correct their pressure readings by a constant amount (*ca.* 1 mm.),[10] presumably that due to the water vapor thus introduced. They did not say whether or not the side arm with the $Na_2SO_4 \cdot 10H_2O$ was left open to the system during the sorption runs, although this seems implied by some of their subsequent discussion.

To check on these presumed effects of water

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[1] This work has been supported by a Grant (G-3541) from the United States Public Health Service.

[2] Graduate Research Fellows on United States Public Health Service Grant (G-3541).

[3] E. Czarnetsky and D. Schmidt. *J. Biol. Chem.*, **105**, 301 (1934).

[4] S. W. Benson and J. Seehof, THIS JOURNAL, **73**, 5053 (1951).

[5] Benson and Seehof, *ibid.*, **75**, 2427 (1953).

[6] W. D. Bancroft and C. J. Barnett. *J. Phys. Chem.*, **34**, 449 (1930).

[7] B. Belden, *ibid.*, **35**, 2164 (1931).

[8] R. Green, *Trans. Proc. Roy. Soc. New Zealand*, **78**, 291 (1950).

[9] Transient isobaric regions have been found which disappear if sufficient time is allowed to elapse to reach equilibrium.[4,5]

[10] This vapor pressure correction is rather mysterious since it does not correspond to any vapor pressure of the decahydrate easily accessible under laboratory conditions.

vapor we made two different types of measurements. In the first we measured the sorption of HCl gas on a $Na_2SO_4 \cdot 10H_2O$–Na_2SO_4 mixture in the absence of protein.[11] We found in these experiments that the decahydrate reacted stoichiometrically and irreversibly at 25° with HCl and the sorption curves could be interpreted as corresponding to the consecutive reactions[12]

$$HCl(g) + Na_2SO_4 \cdot 10H_2O(s) \longrightarrow NaCl(s) + NaHSO_4(s) + 10H_2O(g) \quad (1)$$

$$HCl(g) + NaHSO_4(s) \longrightarrow NaCl \cdot H_2SO_4 \text{ (solid solution)} \quad (2)$$

The first reaction occurs at constant pressure indicating the formation of a new phase, while the second takes place with rising pressure indicating solid solution. The region of constant-pressure sorption is very close to the pressure observed by C. and S. and it seems reasonable to thus interpret their results as arising from the reaction of HCl with the decahydrate rather than with the protein. This conclusion is not certain since C. and S. nowhere state their experimental method explicitly.

In order to then check further we performed an experiment in which the gelatin was first allowed to come to equilibrium with a constant vapor pressure of water. The side arm with decahydrate was then closed off and the sorption of HCl measured directly on this sample. The results of this experiment were similar to those found in the absence of H_2O and showed none of the characteristics reported by C. and S.

While the above experiments do not explain all of the features of the sorption processes observed by C. and S., in particular the results obtained with CO_2 and H_2S (similar to HCl) or the lengths of the isobars (with all gases) they do indicate that their results with HCl and gelatin are inconsistent with results obtained in these and other laboratories, and they indicate a probable source of the anomalies: namely, the reaction of HCl with the $Na_2SO_4 \cdot 10H_2O$–Na_2SO_4 mixtures introduced into the system to maintain constant vapor pressure of water.

(11) These experiments were done by weighing the sample *in situ* using as a balance a helical quartz spring.

(12) The H_2O in reaction 1 may be displaced as a vapor as indicated or may under some conditions be partially bound in the form of hydrates of the NaCl and/or $NaHSO_4$.

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Dielectric Measurement of Heptacosafluorotributylamine

BY FIELDING BROWN

RECEIVED JUNE 22, 1953

The dielectric constant and loss tangent of heptacosafluorotributylamine, $C_{12}F_{27}N$, has been measured over the temperature range of 140 to −52°. The measurements were carried out at frequencies of 60 cycles, 1000 cycles, 15 kc., 30 kc., 60 kc. and 100 kc., and the results are shown in the accompanying graph.

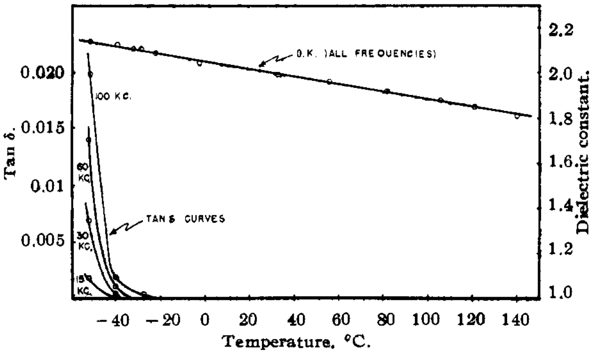

Fig. 1.—Dielectric properties of $C_{12}F_{27}N$.

The liquid was measured in a cell originally described by Horsch and Berberich[1] and the values of capacity and power factor were determined by means of a General Radio 716-C bridge using generators and detectors appropriate to the frequencies in question. A General Radio 716-P2 guard circuit also was employed to balance the guard ring of the measuring cell.

The points on the dielectric constant curve are accurate to ±4% and those of the tan δ curve to ±0.00007. As can be seen, the losses in the liquid are extremely small above −20° but rise sharply below that temperature. The values shown on the graph are further in approximate agreement with those given earlier.[2] Unfortunately it was not possible to carry the measurements low enough in temperature to calculate the electric moment of the molecule. Various members of this laboratory have assisted in performing the measurements.

(1) W. G. Horsch and L. J. Berberich, *Rev. Sci. Instr.*, **5**, 194 (1934).

(2) Technical Report No. 57, Laboratory for Insulation Research, M. I. T.

THE SPRAGUE ELECTRIC CO.
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Reaction of Methyl *p*-Nitrobenzoate with Phenylmagnesium Bromide

BY DAVID Y. CURTIN AND JAMES C. KAUER

RECEIVED JULY 6, 1953

Phenylmagnesium bromide has been shown to react readily with nitrobenzene to give diphenylamine as the principal product.[1]

$$4C_6H_5MgBr + C_6H_5NO_2 \longrightarrow (C_6H_5)_2NH + C_6H_5C_6H_5 + C_6H_5OH$$

Newman and Smith,[2] however, have found that at −70° the reaction of *m*-nitrobenzaldehyde with phenylmagnesium bromide occurs preferentially at the carbonyl group to give *m*-nitrobenzhydrol in 77% yield.

In connection with other work, we have had occasion to examine the reaction of phenylmagnesium bromide with methyl *p*-nitrobenzoate at −70° and found it leads to *p*-carbomethoxydiphenylamine in a yield of 45% (based on Grignard reagent). None of the product to be expected from reaction at the ester carbonyl could be isolated.

(1) H. Gilman and R. McCracken, THIS JOURNAL, **51**, 821 (1929).

(2) M. S. Newman and A. S. Smith, *J. Org. Chem.*, **13**, 592 (1948).

Our work, together with that of Newman and Smith, suggests the following order of reactivity of groups toward phenylmagnesium bromide at $-70°$: $\text{-CH=O} > \text{-NO}_2 > \text{-COOCH}_3$

Experimental[3]

Phenylmagnesium bromide prepared from 35.3 g. (0.195 mole) of redistilled bromobenzene and 6.5 g. of magnesium turnings in 100 ml. of dry ether was added dropwise over a period of 5 hours to 12.5 g. (0.069 mole) of methyl *p*-nitrobenzoate, m.p. 95–96°, in 175 ml. of dry toluene and 40 ml. of dry ether. The reaction mixture was continuously agitated and maintained at $-70°$ under a nitrogen atmosphere. The product was hydrolyzed at $-70°$ by addition of 30 ml. of saturated aqueous ammonium chloride. After removal of the solvent the product was dissolved in 200 ml. of ether, washed with 10% sulfuric acid, 10% sodium carbonate and water. It was then dried over calcium chloride and passed through a separatory funnel containing 300 g. of activated alumina (Harshaw A1-0109P) with 500 ml. of ether. Evaporation of the solvent followed by recrystallization from hexane produced 5 g. (45%) of brown crystals, m.p. 106–112°. Recrystallization from 95% methanol raised the m.p. to 114–116°. Purification by chromatography on an alumina column (with benzene as the eluant) gave white crystals of *p*-carbomethoxydiphenylamine, m.p. 115.8–116.5° (lit.[4] 115°). The structure was confirmed by infrared analysis (ester carbonyl at 1720 cm.$^{-1}$) and by hydrolysis with 2% sodium hydroxide in quantitative yield to *p*-carboxydiphenylamine which had m.p. 159.3–159.8° (lit.[4] 156°) after recrystallization from a benzene–hexane mixture.

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(3) Melting points are corrected. We are indebted to Miss Helen Miklas for the infrared spectrum.

(4) H. Gilman and G. E. Brown. This Journal, **62**, 3208 (1940).

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The Half-Wave Potential of Lithium

By Walter E. Clark

Received July 27, 1953

An accurate determination of the half-wave potential of aqueous lithium ion recently has been made in this Laboratory. When the dropping electrode assembly is carefully damped to eliminate all vibration, it is possible to obtain a regular, well-defined lithium wave having the theoretical slope for a one-electron reversible reduction. The point of inflection corresponding to $E_{1/2}$ is not sharply defined, however, since $E_{1/2}$ could not be accurately determined by means of Muller's oscillographic technique.[1] As expected, the half-wave potential was found to be independent of concentration, of mercury height, and of the capillary employed. The average experimental value of the half-wave potential, corrected for cell resistance, was found to be -2.331 ± 0.003 v. *vs.* the S.C.E.

$E_{1/2}$ for the anodic wave obtained by using dilute (approx. 1×10^{-3} *M*) lithium amalgam as the dropping electrode agreed approximately with the value obtained by conventional electrolysis. Very accurate data could not be obtained from the dropping amalgam electrode due to frequent plugging of the capillary.

Even with the utmost precautions it was not possible to obtain a constant value for $i_d/Cm^{2/3}t^{1/6}$ at any concentration. The polarographic waves were well-defined except that when the concentration of lithium was greater than about 2×10^{-3} *M* the diffusion current became increasingly ill-defined; below about 1×10^{-4} *M* the residual current of the supporting electrolyte became inconveniently large compared to the height of the lithium wave.

Experimental

The polarograph employed was the high sensitivity visual recording instrument described by Kelley and Miller.[2] The supporting electrolyte was 0.1 *M* tetra-*n*-butylammonium hydroxide obtained by diluting the 1 *M* product supplied commercially by Southwestern Analytical Chemicals, Austin, Texas. The discharge potential of this electrolyte is about -2.8 v. *vs.* the S.C.E. which makes it preferable to the corresponding tetraethyl or tetramethyl compound. Occasionally a wave was observed in the supporting electrolyte which appeared to be due to some impurity as reported by Zlotowski and Kolthoff.[3] In 0.1 *M* solution this wave was usually negligible and in any event its effect was eliminated by determining the residual current before adding the lithium compound. The latter was hydroxide from a specially purified stock solution.

Half-wave values were determined from the plot of *E vs.* log $i/i_d - i$, which allows the $E_{1/2}$ value to be read to a precision greater than the accuracy of the experimental data. The limiting factor in the accuracy of the method appears to be the determination of the diffusion current. It was found advantageous to employ an undamped circuit in this determination.

The values of *E* used in the log plots were determined in the conventional way by interpolation on the polarogram between points the potentials of which were accurately determined with a potentiometer. In the course of the investigation several different calomel electrodes were employed. These were checked against each other prior to making a run and the maximum variation observed was 0.2 millivolt.

The polarographic cell employed was of the "H" type described by Lingane and Laitinen.[4] Instead of housing the reference anode in the second arm of the cell, this arm was filled with a solution of the supporting electrolyte and used as a salt bridge to make connection with a separate calomel electrode. As further insurance against diffusion of potassium ion into the polarographic cell, an agar plug containing 0.1 *M* tetra-*n*-butylammonium chloride was inserted next to the fritted disc in the salt bridge arm of the cell. The cell was immersed in a water-bath thermostatically controlled to a temperature of $25 \pm 0.1°$.

The author wishes to acknowledge his indebtedness to Dr. W. B. Schaap and to Dr. D. J. Fisher for helpful suggestions on experimental technique and on instrumentation, respectively.

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(1) R. H. Muller, R. L. Garman, M. E. Droz and J. Petras, *Ind. Eng. Chem., Anal. Ed.*, **10**, 339 (1938).

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The Leuckart Reaction of Some 1,5-Diketones

By Francis Chubb, Allan S. Hay and Reuben B. Sandin

Received July 20, 1953

In an attempt to prepare some 1,5-diamines it was decided to examine the behavior of some 1,5-diketones toward the ammonium formate–formamide reagent, described by Ingersoll and co-workers in their investigation of the Leuckart reaction.[1]

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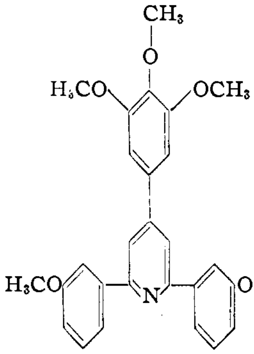
(1) A. W. Ingersoll. J. H. Brown. C. K. Kim, W. D. Beauchamp and G. Jennings. This Journal, **58**, 1808 (1936).

We have found that when a mixture of benzaldiacetophenone and an excess of the formate–formamide reagent is heated for 5 hours at 180–185°, 2,4,6-triphenylpyridine (31%) and 2,4,6-triphenylpiperidine (47%) are formed. Similarly, 3,4,5-trimethoxybenzal-di-(3-methoxyacetophenone) affords 2,6-di-(3-methoxyphenyl)-4-(3,4,5-trimethoxyphenyl)-pyridine (I) (35%) and the corresponding piperidine derivative (II) (45%).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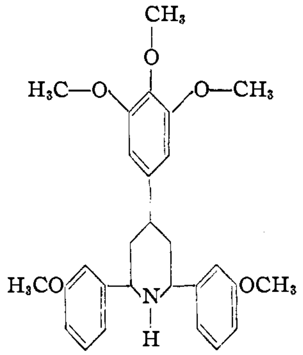
II

Apparently under the conditions of the Leuckart reaction[2] the 1,5-diketones are converted into 1,5-diamines which then cyclize to form piperidine derivatives.[3] Also under the same conditions the pyridine compounds can be accounted for on the basis of a reaction between ammonia and the 1,5-diketones. Dihydropyridines are formed and these compounds are known to disproportionate to form pyridine and piperidine derivatives.[4] In our work the yield of piperidines is too high to account for their formation solely on the basis of the disproportionation of the corresponding dihydropyridines. It seems likely that the direct cyclization of the 1,5-diamines is also an important reaction.[5]

Experimental

3,4,5-Trimethoxybenzaldi-(3-methoxyacetophenone) (III).—A mixture of 3-methoxyacetophenone (4.5 g.), 3,4,5-trimethoxybenzaldehyde (1.96 g.), alcohol (10 ml.) and 40% sodium hydroxide solution (2.0 ml.) was heated on a steam-bath for 15 minutes and then poured into cold water. The mixture was extracted with ether, the ether solution was washed with dilute hydrochloric acid and water and then dried over sodium sulfate. Evaporation of the ether gave 3.0 g. (62.7%) of 3,4,5-trimethoxybenzaldi-(3-methoxyacetophenone), colorless needles, m.p. 97–99°. An analytical sample, recrystallized from alcohol, melted at 100–101°.

Anal. Calcd. for $C_{28}H_{30}O_7$: C, 70.28; H, 6.32; mol. wt., 478. Found: C, 69.81; H, 6.39; mol. wt., 492.

Leuckart Reaction of 3,4,5-Trimethoxybenzaldi-(3-methoxyacetophenone).—A mixture of 12 g. of III and 24 g. of ammonium formate–formamide reagent was heated in an oil-bath for 5 hours at 180–185°. After cooling and the addition of alcohol (80 ml.) and concentrated hydrochloric acid (80 ml.), the mixture was refluxed for 1 hour. The solution was cooled and made basic by the addition of excess sodium hydroxide solution. The reaction mixture was extracted with ether and the ether solution was dried over sodium sulfate. After evaporation of the solvent, the residue was dissolved in boiling alcohol and on cooling afforded 4.1 g. of I (35%), colorless crystals, m.p. 102–105°. An analytical sample crystallized from alcohol melted at 105–106°.

Anal. Calcd. for $C_{28}H_{27}NO_5$: C, 73.50; H, 5.95. Found: C, 73.38; H, 6.26.

The picrate was prepared from a solution of the amine in alcohol and picric acid. It was crystallized from alcohol, m.p. 166–168°.

Anal. Calcd. for $C_{34}H_{30}N_4O_{12}$: C, 59.47; H, 4.40. Found: C, 59.75; H, 4.42.

The filtrate from the separation of I was diluted with water and treated with concentrated hydrochloric acid. On standing, the solution deposited 5.2 g. (45%) of the colorless hydrochloride of II, m.p. 140–143° dec. The salt was crystallized from dilute alcohol and it then melted at 150° with considerable preliminary decomposition.

Anal. Calcd. for $C_{28}H_{34}NO_5Cl$: Cl, 7.10. Found: Cl, 6.89.

The hydrochloride was decomposed with dilute sodium hydroxide, and extracted with ether. The ether solution was dried over sodium sulfate. Evaporation of the solvent afforded the amine (II), colorless needles from alcohol, m.p. 107–108°.

Anal. Calcd. for $C_{28}H_{33}NO_5$: C, 72.54; H, 7.17; mole of active H, 1.00. Found: C, 72.76; H, 7.48; moles of active H, 1.04.[6]

The picrate was prepared by treating a solution of the amine in alcohol, with excess picric acid. It was crystallized from alcohol, m.p. 215–216°.

Anal. Calcd. for $C_{34}H_{36}N_4O_{12}$: C, 58.95; H, 5.24. Found: C, 59.32; H, 5.19.

The melting point of a mixture of I and II showed a depression. Moreover, a solution of I in hydrochloric acid was colored yellow, whereas II in hydrochloric acid showed no coloration.

Leuckart Reaction of Benzaldiacetophenone.—Thirty grams of benzaldiacetophenone was treated with the ammonium formate–formamide reagent (80 g.) as previously described. The amine reaction mixture was dissolved in alcohol and afforded 15 g. (31%) of the picrate of triphenylpyridine, m.p. 189–192°. According to Pictet and Stehelin[7] the m.p. is 192°. The picrate was decomposed with 2% ethanolamine and there was obtained 6.5 g. of 2,4,6-triphenylpyridine, m.p. 137–138°. The m.p. of this compound[5] has been given as 137°. The filtrate from the above picrate was evaporated and the residue was treated with excess of ethanolamine solution and extracted with ether. The ether solution was dried over sodium sulfate. Removal of the solvent left an oily residue which was dissolved in absolute alcohol and treated with dry hydrogen chloride. This afforded 15 g. (47%) of 2,4,6-triphenylpiperidine hydrochloride, colorless needles, m.p. 292–300° dec.

Anal. Calcd. for $C_{23}H_{24}NCl$: Cl, 10.15. Found: Cl, 10.36.

The free amine was obtained by decomposing the hydrochloride with sodium hydroxide and extracting with ether. The amine formed colorless needles from alcohol and melted at 83–85°. Active hydrogen was determined at 100° as

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(2) For a review of the Leuckart reaction see M. L. Moore in R. Adams, "Organic Reactions," Vol. V, John Wiley and Sons, New York, N. Y., 1949, p. 301. For some recent work see J. F. Bunnett and J. L. Marks, This Journal, **71**, 1587 (1949); P. A. S. Smith and A. J. Macdonald, *ibid.*, **72**, 1037 (1950); J. H. Burckhalter and S. H. Johnson, *ibid.*, **73**, 4830 (1951); D. S. Noyce and F. W. Bachelor, *ibid.*, **74**, 4577 (1952).

(3) H. S. Mosher in R. C. Elderfield's "Heterocyclic Compounds," Vol. I, John Wiley and Sons, New York, N. Y., 1950, p. 650.

(4) M. Scholtz, *Ber.*, **30**, 2295 (1897); E. Knoevenagel and J. Fuchs, *ibid.*, **35**, 1788 (1902); K. W. Merz and H. Richter, *Arch. Pharm.*, **275**, 294 (1937).

(5) M. Weiss, This Journal, **74**, 200 (1952), in some careful studies on the Chichibabin pyridine synthesis has shown that when a mixture of benzaldehyde, acetophenone, ammonium acetate and acetic acid is refluxed, triphenylpyridine and benzylacetophenone are formed. In this case the sequence of reactions involves an aldol condensation, followed by the formation of the 1,5-diketone which then condenses with ammonia to form the dihydropyridine. The latter then undergoes dehydrogenation by transfer of hydrogen to benzalacetophenone. We have found that when a mixture of benzaldiacetophenone (9.8 g.), ammonium acetate (30 g.) and acetic acid (75 ml.) is refluxed under the above conditions, triphenylpyridine (6.1 g.) and triphenylpiperidine (2.7 g.) isolated as the hydrochloric acid salt, are formed.

(6) Active hydrogen was determined at 100° and in the apparatus described by P. M. Maginnity and J. B. Cloke, *Anal. Chem.*, **20**, 978 (1948). At 26° the amine showed 0.03 mole of active hydrogen.

(7) A. Pictet and P. Stehelin, *Compt. rend.*, **162**, 876 (1916).

previously described. At 28° there was no indication of active hydrogen.

Anal. Calcd. for $C_{23}H_{23}N$: C, 88.34; H, 7.40; mole of active H, 1.00. Found: C, 88.26; H, 7.45; moles of active H, 1.05.

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Dielectric Constant and Refractive Index from 20 to 35° and Density at 25° for the System Tetrahydrofuran–Water[1]

BY FRANK E. CRITCHFIELD,[2] JOHN A. GIBSON, JR., AND JAMES L. HALL[3]

RECEIVED JUNE 15, 1953

For studies of conductance, activities and rates of reaction in solution it is desirable to have available solvent mixtures which may be made up to any specified dielectric constant within a wide range of dielectric constant values. To know to what extent the effects measured are functions of the dielectric constant only, and not of the specific solvent mixture used, it is necessary to use different mixtures to cover the same range of dielectric constant. Dioxane–water, methanol–water and other mixtures have been used for such studies. The system tetrahydrofuran–water is proposed as an alternate solvent system for these studies. The dielectric constant of tetrahydrofuran is relatively low and it is miscible with water in all proportions. Tetrahydrofuran of high purity is now available commercially. For the tetrahydrofuran–water system we report here the dielectric constants and refractive indices from 20 to 35° and the densities at 25°.

Experimental

Materials.—The water used in these measurements was prepared as described previously.[4] The fraction retained had a specific conductance of 1×10^{-6} ohm^{-1} cm.$^{-1}$. The tetrahydrofuran, from the Electrochemicals Department of E. I. du Pont de Nemours and Co., contained hydroquinone as an inhibitor. The tetrahydrofuran was separated by distillation after being mixed with an equal volume of heavy mineral oil to prevent an accumulation of concentrated peroxides in the still. For the product thus obtained, time–temperature cooling curves were determined using an N.B.S. calibrated platinum resistance thermometer and a Leeds and Northrup Co. Mueller Bridge. The freezing point was found to be −109.238° and the purity, as determined from the shape of the curves by the method of Rossini,[5] was found to be not less than 99.87%. This purity was adequate for the present purpose and so no further purification was attempted.

Method.—The measurements of dielectric constant were made with the apparatus previously described[4] except that a larger inner electrode was used in the cell. The cell was calibrated at each temperature used, since the cell capacitance was relatively large and small changes in the dimensions of the cell with temperature variations caused slight variations in cell capacitance. For calibration of the cell, the dielectric constant of water at the various temperatures was assumed to be as reported by Wyman[6] and Albright.[7]

Table I lists for the various temperatures the capacitance of the cell containing water, the dielectric constant of water with the corresponding literature reference, the calculated cell capacitance, d*ε*/d*c*, and the lead capacitance.

TABLE I

CALIBRATION DATA FOR NON-INDUCTIVE TYPE CELL

Temp., °C.	Cell capacitance with water	Dielectric constant of water	Cell capacitance	Lead capacitance
20	390.13	80.38	4.836	1.41
25	381.66	78.48	4.846	1.35
30	372.76	76.75	4.839	1.37
35	363.05	74.95	4.825	1.42

In order to check this calibration, the dielectric constants of methanol and acetone were determined at 25°. The value, 20.74, which was obtained for acetone agrees exactly with the value given by Albright,[7] and the value, 32.66, which was obtained for methanol is in exact agreement with the value of Albright and Gosting.[8]

A Bausch and Lomb Abbé refractometer was used for the refractive index measurements. The density determinations were made by the usual method using a 50-ml. Leach specific gravity bottle, fitted with a thermometer by means of a ground glass joint. This pycnometer was filled and the liquid level was adjusted in a constant temperature-bath which was controlled within 0.01°. All density calculations were based upon the density of water at 25°.

Results

The dielectric constants for the system tetrahydrofuran–water from 20 to 35° are shown in Table II. These data are believed to be accurate to about one part in 1000 in the low range of dielectric constant and one part in 2000 at the higher range.

TABLE II

DIELECTRIC CONSTANT FOR THE TETRAHYDROFURAN–WATER SYSTEM

	Temperature, °C.			
THF, wt. %	20	25	30	35
0.00	80.37	78.48	76.75	74.95
10.00	73.73	71.76	70.15	68.68
20.00	66.46	64.60	63.02	61.64
30.00	58.42	56.59	55.24	53.88
40.00	49.77	48.22	46.91	45.65
50.00	41.21	39.96	38.77	37.75
60.00	33.04	31.97	31.04	30.24
70.00	25.45	24.62	24.08	23.39
80.00	18.75	18.25	17.77	17.38
90.00	12.90	12.59	12.36	12.05
95.00	10.24	9.97	9.74	9.58
100.00	7.58	7.39	7.25	7.16

Table III shows the refractive indices for the system tetrahydrofuran–water over the temperature range 20 to 35°.

The absolute densities of the tetrahydrofuran–water system were determined at 25°. The density of water was taken as 0.9970 and the density of the tetrahydrofuran was measured to be 0.8811 at this temperature. The intermediate densities may be calculated by the equation

$$d = 0.9970 - 2.582 \times 10^{-4}P - 1.074 \times 10^{-5}P^2 + 1.73 \times 10^{-8}P^3$$

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[1] Presented before the Division of Physical and Inorganic Chemistry, 124th National Meeting of the American Chemical Society, Chicago, Ill., September 6–11, 1953.

[2] The data upon which this report is based are included in the Ph.D. Dissertation of Frank E. Critchfield, West Virginia University, 1953.

[3] Please address communications to James L. Hall.

[4] F. E. Critchfield, J. A. Gibson, Jr., and J. L. Hall, THIS JOURNAL, **75**, 1991 (1953).

[5] B. J. Mair, A. R. Glasgow and F. D. Rossini, *J. Research Natl. Bur. Standards*, **26**, 591 (1941).

[6] J. Wyman, Jr., *Phys. Rev.*, **35**, 623 (1930).

[7] P. S. Albright, THIS JOURNAL, **59**, 2098 (1937).

[8] P. S. Albright and L. J. Gosting, *ibid.*, **68**, 1061 (1946).

Table III

Refractive Index for the Tetrahydrofuran–Water System

THF. wt. %	Temperature, °C. 20	25	30	35
0.00	1.3330	1.3324	1.3320	1.3314
10.00	1.3433	1.3427	1.3419	1.3412
20.00	1.3537	1.3527	1.3519	1.3510
30.00	1.3637	1.3622	1.3611	1.3600
40.00	1.3724	1.3711	1.3695	1.3683
50.00	1.3801	1.3788	1.3769	1.3753
60.00	1.3872	1.3854	1.3837	1.3819
70.00	1.3934	1.3915	1.3896	1.3878
80.00	1.3987	1.3967	1.3949	1.3938
90.00	1.4033	1.4011	1.3989	1.3967
95.00	1.4050	1.4028	1.4008	1.3986
100.00	1.4068	1.4045	1.4022	1.4000

where d is the density and P is the weight % of tetrahydrofuran. Densities calculated using this equation agree with the experimental values within 2 parts in 10,000.

Acknowledgment.—This work was a joint undertaking of the Department of Chemistry of West Virginia University and the Office of Ordnance Research, U. S. Army. Appreciation is expressed to the Electrochemicals Department of E. I. du Pont de Nemours and Company for the tetrahydrofuran used in this work, and to James B. Hickman for assistance in determination and analysis of the time–temperature cooling curves.

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The Heats of Neutralization of Acid Clays and Cation-exchange Resins[1]

By N. T. Coleman and M. E. Harward

Received June 1, 1953

A note of considerable interest to soil scientists and others concerned with the chemical reactions of clays and other ion-exchange materials was recently published.[2] The author reported the heats evolved when acid bentonites prepared by electrodialysis and by passage through a column of H-sulfonic acid exchange resin were neutralized with NaOH. Also presented were potentiometric titration curves of clays prepared by the two procedures. Up to about 80% base saturation the freshly-columned clay gave a titration curve of strong acid character, similar to that of H-sulfonic acid exchange resins. At this point a sharp inflection was followed by a short region of buffering in the *p*H range 6–7, and then a second inflection. The heat of neutralization in the first portion of the titration curve was about -13.5 kcal. per mole, again indicating strong acid character.

In the case of electrodialyzed clay the initial strong acid portion of the potentiometric titration curve extended to only about 30% base saturation, while the region of buffering between *p*H 6 and 7 was pronounced. The heat of neutralization in the strong-acid portion of the curve was again about -13.5 kcal. per mole. This fell to around -5 kcal. in the *p*H range 6–7. Slabaugh has explained the heats and the course of the titration curves on the basis that two H-ion energy levels exist.

The present authors have made similar observations on a variety of clay and exchange resin systems, and have come to somewhat different conclusions. Clays of the montmorillonite type, of which Slabaugh's Wyoming bentonite is typical, are alumino silicates. It is well established that in slightly acid media such clay minerals decompose with the liberation of ionic aluminum.[3] Such ionic aluminum appears to be strongly adsorbed by the clay, with the result that acid clays prepared by electrodialysis, by dilute acid leaching, or by natural depletion of such cations as Ca and Mg in nature, contain both H and Al as exchangeable cations with the latter usually predominating.[3–5]

It is possible, however, as Slabaugh[2] has pointed out, to prepare acid clays which differ greatly from those obtained by more conventional means. Columning with H-exchange resin is one method by which this may be done. Rapid leaching with 1 *N* HCl also results in a clay with the electrochemical and thermochemical properties of columned clay. For the reasons outlined below, the present authors believe columned clay and 1 *N* HCl-leached clay to be H-clays, while electrodialyzed and dilute acid leached clays are H-Al-clays.

Figure 1 shows potentiometric titration curves of H- and Al-Amberlite IR-120, acid bentonite prepared by leaching with 0.1 *N* HCl, and acid bentonite prepared by leaching with 1 *N* HCl. Figure 2 compares the curve for acid bentonite prepared by leaching with 1 *N* HCl with those for bentonite leached first with 1 *N* HCl and then with $AlCl_3$, and bentonite leached with 1 *N* HCl and treated with an amount of $AlCl_3$ equivalent to one-half the exchange capacity. In all cases free electrolyte was removed by washing with water before the titrations were performed. The similarity between the curves for Al-resin, dilute acid-leached clay, and $AlCl_3$-leached clay is striking. Also very similar are the curves for H-resin and 1 *N* HCl-leached clay. The 1 *N* HCl-leached clay treated with $^1/_2$ symmetry concentration of $AlCl_3$ shows the features of both H- and Al-exchangers, with the H being neutralized first.

Heats of neutralization of several clay and exchange resin systems are presented in Table I. They were measured with an apparatus which has been described previously.[6] The heats reported in Table I are integral rather than the summation of differential heats as measured by Slabaugh,[2] and refer in all cases to the amount of NaOH consumed in the reaction. Heats of neutralization of H-exchange resins and of columned or 1 *N* HCl-leached bentonite were about -13.5 kcal., which is close to the heat of formation of water from the ions. Heats of neutralization of the Al-resin and

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(1) Journal Series #467. North Carolina Agricultural Experiment Station.

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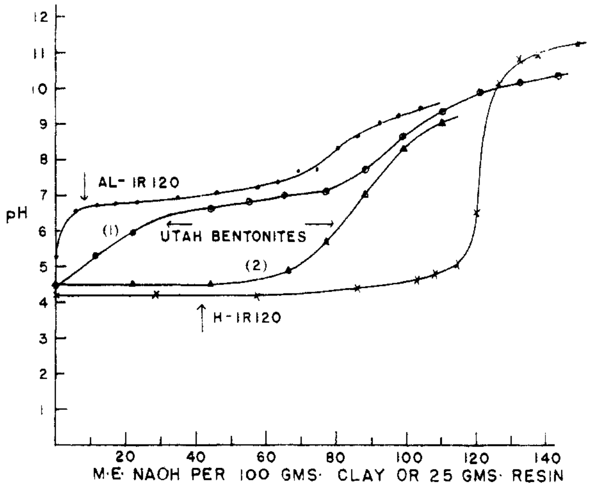

Fig. 1.—Potentiometric titration curves of H- and Al-Amberlite IR-120 and of acid Utah bentonites prepared by (1) leaching with 0.1 N HCl and (2) leaching with 1 *N* HCl.

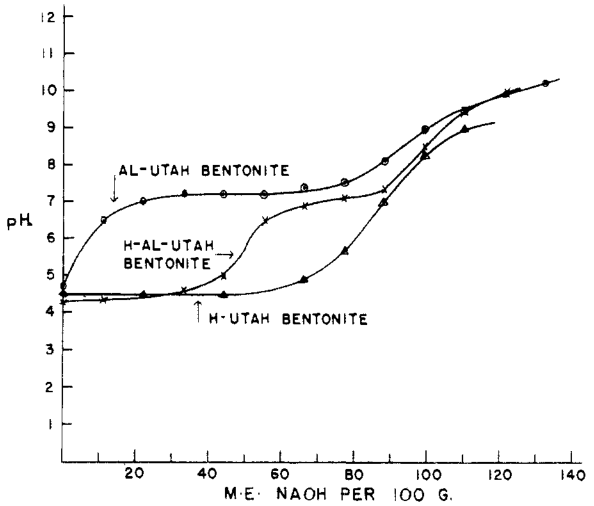

Fig. 2.—Potentiometric titration curves of H-Utah bentonite prepared by leaching with 1 *N* HCl, Al-Utah bentonite prepared by leaching first with 1 *N* HCl and then with $AlCl_3$, and of H-Al-Utah bentonite prepared by leaching with 1 *N* HCl and then treating with an amount of $AlCl_3$ equivalent to one-half the exchange capacity.

the $AlCl_3$-leached clay, as well as of the 0.05 *N* HCl-leached and of electrodialyzed clay, varied between −5.4 and −6.4 kcal. per mole of NaOH consumed.

TABLE I

HEATS OF NEUTRALIZATION (KCAL. PER EQUIVALENT) OF ACID CLAYS AND EXCHANGE RESINS

	Method of preparation				
Material	Electrodialyzed	Leached with 0.05 *N* HCl	Leached with 1 *N* HCl	Columned	Leached with $AlCl_3$
Wyoming bentonite	−5.8	...	....	−13.4	
Utah bentonite	−6.4	−6.2	−13.5	−13.5	−5.4
IR-120	...	...	−13.6	....	−5.7

Exchangeable Al and exchangeable H can be replaced from clays and other cation exchangers by exhaustive leaching with neutral salt solutions.[3,4] The clays studied here were leached with *N* KCl and H and Al were determined in the leachate. For electrodialyzed bentonite, 0.05 or 0.1 *N* HCl-leached bentonite, and $AlCl_3$-leached bentonite, 95–100% of the titratable acidity in the KCl leachate was Al. For *N* HCl-leached bentonite and for columned bentonite, 90–100% of the titratable acidity was H. On storage of the latter two clays, a gradual increase in exchangeable Al and decrease in exchangeable H was observed.

The authors conclude from this that Slabaugh worked with H-Al clays, rather than with clays containing exchangeable H in different energy states.

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The Reactivity of Primary Alkyl Halides with Sodium Thiocyanate

BY THOMAS I. CROWELL

RECEIVED JULY 2, 1953

Many examples of the reactivity of the straight-chain alkyl halides in displacement reactions indicate a minimum in rate for the *n*-butyl derivative; further lengthening of the molecule increases the reaction rate.[1] Although the equilibrium counterpart of this interesting kinetic phenomenon has been investigated by Brown, Taylor and Sujishi,[2] no series of rate constants sufficiently accurate to establish its existence or magnitude can be found.

A convenient reagent for such a comparison is the nucleophilic thiocyanate ion.[3] The reaction of sodium thiocyanate with alkyl bromides, described in this paper, is easily followed at constant ionic

$$RBr + NaSCN \longrightarrow RSCN + NaBr$$

strength and is homogeneous in alcoholic solution owing to the moderate solubility of sodium bromide.

Table I shows one of the runs made with *n*-hexyl bromide. All the results are summarized in Table

TABLE I

SAMPLE DATA FOR *n*-HEXYL BROMIDE[a]

t, min.	KIO_3, ml.	10^5 *k*, l./mole-sec.
0	20.89[b]	..
1355	19.20	1.18
3057	17.49	1.24
4317	16.60	1.22
5688	15.78	1.22
8826	14.39	1.22
11500	13.60	1.21
14184	13.09	1.17

[a] Initially 0.0960 *M*. [b] Corresponds to 0.2002 *M* NaSCN in sample.

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TABLE II

RATE OF REACTION OF RBr WITH 0.2 *M* NaSCN

R	Purity, %	No. of runs	$10^5 k$, l./mole-sec.
Ethyl	..	3	1.67
n-Propyl	99.5	2	1.15
n-Butyl	99.8	3	1.14
n-Amyl	99.6	3	1.20
n-Hexyl	99.8	2	1.22
n-Heptyl	99.4	2	1.24
n-Octyl	99.0	6	1.27
n-Decyl	98.6	2	1.23
Cetyl	98.3	3	1.20
Isobutyl	99.4	1	0.05
Isoamyl	..	1	0.73
Isohexyl	98.7	2	1.23

II. The average deviation from the mean *k* was less than 1% for each of the alkyl halides except *n*-amyl bromide, for which it was 1.3%, and isobutyl and isoamyl bromides, where only one run was made. There can be no doubt that *n*-amyl bromide is considerably more reactive than *n*-butyl bromide and that the reactivity increases with increasing chain length so that *k* for *n*-octyl bromide is 11% higher than for *n*-butyl bromide. The reactivity of the 10- and 16-carbon bromides appears to be slightly lower, though the lower degree of purity of these compounds causes some uncertainty in the value of *k*.

The data of Table II refer to an initial molarity of alkyl bromide of about 0.09. Because of the considerable differences in molecular weight, however, the percentage by weight of alkyl halide varied from 1.0 to 3.6. That this slight change in the medium was not entirely responsible for the variation in Table II was demonstrated by five experiments in which the molarity of *n*-octyl bromide ranged from 0.05 to 0.14. The extreme values of *k* differed by only 2% and moreover indicated the usual decrease in rate with increasing alkyl bromide concentration.[4]

It is difficult to formulate any simple effect of the alkyl group which would lead to greater reactivity with increasing chain length. An inductive effect should reduce the rate by increasing the electron density at the reaction center. Steric hindrance of the attacking reagent by the longer chain, as proposed by Brown, Taylor and Sujishi,[2] to explain the comparatively low basicity of *n*-propylamine in aqueous solution, would also decrease the rate here. The most satisfactory explanation, however, lies in the fact that the C–Br bond energy gradually decreases from 68.5 to 63.5 kcal./mole as the series is ascended from methyl to butyl bromide,[5] and probably decreases somewhat further in the higher derivatives. Although the small differences in activation energy corresponding to these rate differences would be difficult to measure experimentally, the activation energies of several displacement reactions have been found to decrease slightly when the halide is changed from ethyl to *n*-propyl, though an entropy effect decreases the rate.[4]

Table II also shows that although isobutyl and isoamyl bromides react more slowly than their straight-chain isomers, the branching of the chain in isohexyl bromide is too far from the reaction center to affect the rate.

Experimental

Materials.—Commercially available alkyl bromides were shaken with H_2SO_4, washed with water, dried over K_2CO_3 and fractionated. The purity given in Table II was estimated by Volhard titration for bromide after hydrolysis in a sealed tube. Isohexyl bromide (1-bromo-4-methylpentane) was prepared from formaldehyde and isoamyl alcohol by the Grignard reaction.[6] Eimer and Amend C.P. sodium thiocyanate, dried at 130° for 24 hours, assay (Volhard) 99.8°, was used. The solvent was 95% ethanol (d^4_{25} 0.8004–0.8010).

Procedure.—The kinetic runs were started by weighing the alkyl bromide into a 100-ml. volumetric flask containing 25 ml. of solvent, adding 50 ml. of 0.4 *M* NaSCN (alcoholic) and diluting to the mark at 25.00°. Five-milliliter samples were withdrawn at one- or two-day intervals and added to 30 ml. of water. After adding 7 ml. of 0.5 *M* KCN and 50 ml. of 3 *M* HCl, the sample was titrated for thiocyanate with standard KIO_3 and starch indicator.[7] The Volhard titer of the reaction mixture remained constant, and 99% of the theoretical quantity of thiocyanate ion was consumed after two months. This procedure parallels the standard preparation of alkyl thiocyanates.

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[4] T. I. Crowell and L. P. Hammett, THIS JOURNAL, 70, 3444 (1948); W. F. Johnson and I. M. Kolthoff, *ibid.*, 74, 22 (1952).

[5] E. W. R. Steacie, "Atomic and Free Radical Reactions," Reinhold Publ. Corp., New York, N. Y., 1946, pp. 77–79.

[6] S. C. J. Olivier, *Rec. trav. chim.*, 55, 1027 (1936).

[7] W. C. Oesper, "Newer Methods of Volumetric Analysis," D. Van Nostrand Co., Inc., New York, N. Y., 1938, p. 85.

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The Preparation of Acyl Trifluoroacetates from Trifluoroacetic Anhydride

BY WILLIAM D. EMMONS, KEITH S. MCCALLUM AND ARTHUR F. FERRIS

RECEIVED AUGUST 3, 1953

Recently the preparation of acyl trifluoroacetates from silver trifluoroacetate and acyl halides in ether has been reported.[1] It has now been established that acyl trifluoroacetates may be obtained in good yields from equimolar quantities of trifluoroacetic anhydride and carboxylic acids. Satisfactory procedures have been worked out for the preparation of benzoyl trifluoroacetate (55% yield), lauroyl trifluoroacetate (59% yield), furoyl trifluoroacetate (63% yield) and phenylacetyl trifluoroacetate (53% yield). Thus the hypothesis that the high order of reactivity of trifluoroacetic anhydride–carboxylic acid mixtures in acylation reactions is due to the *in situ* formation of the acyl trifluoroacetate is probably correct.[2]

$$RCOOH + CF_3COOCOCF_3 \longrightarrow RCOOCOCF_3 + CF_3COOH$$

We were originally interested in examination of the equilibrium between trifluoroacetic anhydride and carboxylic acids. The availability of pure samples of acyl trifluoroacetates made possible the development of an infrared procedure for following this reaction. Accordingly, the reaction between benzoic acid and trifluoroacetic anhydride was studied in *n*-butyl ether and in acetonitrile. Each of

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[1] A. F. Ferris and W. D. Emmons, THIS JOURNAL, 75, 232 (1953).

[2] E. J. Bourne, M. Stacey, J. C. Tatlow and J. M. Tedder, *J. Chem. Soc.*, 2976 (1949).

the four components of the equilibrium mixture was determined quantitatively. In both solvents it was found that equilibrium was established immediately and that within the accuracy of the analytical method (estimated at 5%) benzoyl trifluoroacetate was formed quantitatively. Furthermore, equimolar solutions of trifluoroacetic anhydride with lauric, furoic and phenylacetic acids had infrared spectra which indicated that only the acyl trifluoroacetate and trifluoroacetic acid were present, *i.e.*, the reaction was quantitative with these acids too. Therefore, the isolation of the acyl trifluoroacetates was undertaken and was easily effected by previously described techniques.[1]

Experimental

Benzoyl Trifluoroacetate.—To 525 g. (2.5 moles) of trifluoroacetic anhydride was added 244 g. (2.0 moles) of benzoic acid. This mixture was then stirred and heated under reflux for 30 minutes. The trifluoroacetic anhydride and acid were distilled *in vacuo* and the benzoyl trifluoroacetate flash distilled at 100° (0.5 mm.), yield 240 g. (55%). The infrared spectrum of this material was identical to that prepared from silver trifluoroacetate and benzoyl chloride.[1]

Lauroyl Trifluoroacetate.—To a solution of 20.0 g. (0.1 mole) of lauric acid in 100 ml. of dry methylene chloride was added 21.0 g. (0.1 mole) of trifluoroacetic anhydride. The methylene chloride was immediately distilled *in vacuo* and the lauroyl trifluoroacetate flash distilled at 160° (0.4 mm.), yield 17.1 g. (59%). The infrared spectrum of this preparation was identical with that of an authentic sample.

Reaction of Carboxylic Acids and Trifluoroacetic Anhydride.—Solutions of benzoic, furoic, lauric and phenylacetic acid were prepared in purified *n*-butyl ether.[3] Aliquots of each acid and trifluoroacetic anhydride were made up to volume to give equimolar concentrations of each at the 0.1 *M* level. Infrared spectra were obtained on a Perkin-Elmer Model 21 spectrophotometer. The strong trifluoroacetic anhydride band at 1873 cm.$^{-1}$ was absent from the spectrum of each mixture. In its place were the following acyl trifluoroacetate carbonyl bands: benzoyl trifluoroacetate, 1835 cm.$^{-1}$; furoyl trifluoroacetate, 1835 cm.$^{-1}$; phenylacetyl trifluoroacetate, 1850 cm.$^{-1}$; lauroyl trifluoroacetate, 1850 cm.$^{-1}$. These frequencies are in reasonable agreement with those previously reported for capillary layers of the mixed anhydrides.[1]

Reaction of Benzoic Acid and Trifluoroacetic Anhydride.—Mixtures were analyzed for each component in both acetonitrile and *n*-butyl ether for the system benzoic acid–trifluoroacetic anhydride. All measurements were made at 25–28°. Working curves were prepared from solutions of the pure components. Band intensities were measured for each solution at each analysis frequency to obtain corrections for mutual interference. Curvature of these optical density *vs.* concentration plots was too great to permit use of simultaneous equation solutions based on Beer's law. The method of successive graphical approximations was, therefore, used for determination of the concentrations of each of the components. The data obtained are summarized in Table I. The fact that an excess of trifluoroacetic acid over benzoyl trifluoroacetate was obtained is accounted for by some hydrolysis of trifluoroacetic anhydride by water introduced into the system while the solutions were processed; accordingly, one-half of the excess trifluoroacetic acid found over benzoyl trifluoroacetate (Table I) represents the molar quantity of water introduced into the system. If this correction is taken into account, 0.109 mole of product was accounted for in acetonitrile out of 0.107 mole originally introduced. Similarly in *n*-butyl ether the analytical procedure accounted for 0.086 mole out of 0.084 mole introduced. It should also be mentioned that there was no evidence of disproportionation of benzoyl trifluoroacetate during any of these experiments.

TABLE I

REACTION OF BENZOIC ACID AND TRIFLUOROACETIC ANHYDRIDE

Compound	Analysis bands, cm.$^{-1}$ Acetonitrile	Analysis bands, cm.$^{-1}$ *n*-Butyl ether	Moles added Acetonitrile	Moles added *n*-Butyl ether	Moles found Acetonitrile	Moles found *n*-Butyl ether
$CF_3COOCOCF_3$	1872	1873	0.035	0.057	None	0.028
C_6H_5COOH	714	708	0.066	0.025	0.036	None
$C_6H_5COOCOCF_3$	1832	1835	None	None	.030	.027
CF_3COOH	688	695	None	None	.043	.031
H_2O			0.006	0.002		
Total moles			0.107	0.084	.109	.086

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[3] A. T. Blomquist and A. F. Ferris, THIS JOURNAL, 73, 7412 (1951).

Further Studies on the Enzymatic Phosphorylation of Riboflavin[1]

BY SASHA ENGLARD[2]

RECEIVED JULY 13, 1953

In a previous communication,[3] ADP[4] was found to participate in the flavokinase reaction which catalyzes the phosphorylation of riboflavin to yield FMN. The inability to detect myokinase which catalyzes the reaction 2 ADP $\rightleftarrows$ ATP + AMP, in the enzyme preparations, plus the fact that the relative efficiencies of ATP and ADP in FMN synthesis are the same throughout purification, led to the conclusion that ADP participated directly in the synthesis of FMN. In view of the widespread acceptance that in most transphosphorylation reactions involving the adenylic acid system only the terminal phosphate of ATP can be directly transferred,[5] the problem was reinvestigated, and myokinase activity was detected even in the purest flavokinase preparations. The finding of such a contaminant in the flavokinase preparations sug-

TABLE I

Each tube contained approximately 7.5 μM. of a preparation derived from Sigma Ba-ADP which consisted of 1.11 μM. AMP, 5.51 μM. ADP, and 0.66 μM. ATP; 1 mg. of flavokinase at an activity of 213, 375 μM. of tris-(hydroxymethyl)-aminomethane buffer at *p*H 7.41 and 1×10^{-3} *M* $MgSO_4$ or 6×10^{-4} *M* $ZnSO_4$. The final volume of the reaction mixture was 5.0 ml. The tubes were incubated for 2 hr. at 33.5°, after which time they were immersed in a boiling water-bath for 5 min. prior to filtration through Whatman No. 2. A 3-ml. aliquot of each filtrate was diluted to 25 ml. with water and these solutions passed through Dowex-1 anion exchange columns according to the method of Cohn and Carter [THIS JOURNAL, **72**, 4273 (1950)]. Results are recalculated on the basis of the 5.0-ml. final volume of the original reaction mixture.

	Mg^{++} and boiled enzyme, μM.	Mg^{++} and enzyme, μM.	Zn^{++} and enzyme, μM.
ΔAMP	+1.44	+1.65	+0.03
ΔADP	−2.96	−3.11	+ .14
ΔATP	+1.53	+1.58	+ .03

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[1] Supported in part by a grant from the Prentiss Fund of Western Reserve University.

[2] U. S. Public Health Pre-doctoral Fellow of the National Institute of Arthritis and Metabolic Diseases. Now at McCollum–Pratt Institute, Baltimore 18, Md.

[3] E. B. Kearney and S. Englard, *J. Biol. Chem.*, **193**, 821 (1951).

[4] The following abbreviations are used: AMP = adenosine monophosphate; ADP = adenosine diphosphate; ATP = adenosine triphosphate; IMP = inosine monophosphate; FMN = flavin mononucleotide.

[5] S. P. Colowick, in Summer and Myrback, "The Enzymes," Vol. II, Part I, Academic Press, Inc., New York, N. Y., 1951, p. 114.

TABLE II

Expt. no.	Conditions	mμ M. FMN[a] synthesized in 2 hr.
1	1×10^{-3} *M* MgSO$_4$, 1.8×10^{-3} *M* ATP	230.2
	1×10^{-3} *M* MgSO$_4$, 1.6×10^{-4} *M* ADP	104.8
	6×10^{-4} *M* ZnSO$_4$. 1.8×10^{-3} *M* ATP	328.3
	6×10^{-4} *M* ZnSO$_4$, 1.6×10^{-4} *M* ADP	0.0
2	1×10^{-3} *M* MgSO$_4$, 2.8×10^{-4} *M* ATP	153.3
	1×10^{-3} *M* MgSO$_4$, 2.8×10^{-4} *M* ATP, 4.5×10^{-4} *M* AMP	82.9
	1×10^{-3} *M* MgSO$_4$, 2.8×10^{-4} *M* ATP, 4.8×10^{-4} *M* IMP	142.3
	6×10^{-4} *M* ZnSO$_4$, 2.8×10^{-4} *M* ATP	57.7[b]
	6×10^{-4} *M* ZnSO$_4$, 2.8×10^{-4} *M* ATP, 4.5×10^{-4} *M* AMP	51.9
	6×10^{-4} *M* ZnSO$_4$, 2.8×10^{-4} *M* ATP, 4.8×10^{-4} *M* IMP	63.5
3	1×10^{-3} *M* MgSO$_4$. 2.0×10^{-4} *M* ATP	146.9
	1×10^{-3} *M* MgSO$_4$, 2.0×10^{-4} *M* ATP, 4.5×10^{-4} *M* AMP	68.5
	1×10^{-3} *M* MgSO$_4$, 2.0×10^{-4} *M* ATP, 6.0×10^{-4} *M* adenosine	144.0
4	6×10^{-4} *M* ZnSO$_4$, 3.0×10^{-4} *M* ATP	38.7
	6×10^{-4} *M* ZnSO$_4$, 3.0×10^{-4} *M* ATP, 4.5×10^{-4} *M* AMP	41.6
	6×10^{-4} *M* ZnSO$_4$, 3.0×10^{-4} *M* ATP, 6.0×10^{-4} *M* adenosine	39.0

[a] Standard assay conditions and analytical determination of FMN as previously described,[1] except that the reaction was run at *p*H 7.41 and at 33.5°. [b] The lower synthesis in the presence of Zn^{++} is due to the fact that in the presence of Zn^{++} the saturation level for ATP is increased. At higher concentrations of ATP, Zn^{++} is more efficient than Mg^{++} (expt. 1 and unpublished data).

gested that ADP probably participated in the reaction by prior conversion to ATP. Moreover, the previously observed inhibitory effect of AMP[1] which was interpreted as suggesting a competition with ATP for the active site on the enzyme surface by virtue of its NH$_2$ group on the 6-position of the purine ring, could be re-evaluated as a competition for ATP to form inactive ADP and thus lowering the effective concentration of the phosphate donor for the synthesis of FMN. To determine whether or not ADP participated directly in the reaction and also in order to elucidate the mechanism of the AMP inhibition it was necessary to obtain a system devoid of myokinase activity. In the presence of Zn^{++} which can replace Mg^{++} as an activator of the flavokinase reaction,[1] the myokinase contaminant is virtually inactive as indicated in Table I.

The effect of Zn^{++} on the myokinase activity is probably inhibitory in nature, since in other experiments it has been shown that the myokinase is still active in the absence of added metal, although this activity can be increased by the addition of Mg^{++}. Table I also shows that the boiled control in the presence of Mg^{++} reached the same equilibrium over the 2-hr. incubation period, as the unheated sample. Similar reports on the resistance of myokinase to boiling have appeared previously.[6,7] The inability to detect myokinase with the method previously used can be attributed to the unusual resistance of myokinase to treatments which generally denature most proteins. The method previously used was based on the quantitative determination of AMP with Schmidt deaminase[8] which catalyzes the specific deamination of AMP to IMP. It was ascertained by measuring the AMP content, of what was thought to be a protein-free filtrate, that preincubation of AMP and ATP with a flavokinase preparation did not result in a loss of AMP which would have occurred had myokinase been present. It is now probable in view of the unusual high resistance of myokinase to denaturating treatments, that the so-called protein-free filtrate was contaminated with myokinase. Hence, the previously established equilibrium, which resulted from incubating ATP and AMP with a flavokinase preparation contaminated with myokinase, probably reverted back to the initially added concentration of components by virtue of the irreversibility of Schmidt deaminase

$$\mathrm{IMP} \xleftarrow{\text{Schmidt deaminase}} \mathrm{AMP} + \mathrm{ATP} \underset{}{\overset{\text{Myokinase}}{\rightleftarrows}} 2\mathrm{ADP}$$

Using a highly active preparation of flavokinase, the ability of ADP to act as a phosphate donor was re-examined both in the presence of Mg^{++} and Zn^{++}. The results obtained are outlined in Table II, exp. 1.

It is clear from this experiment that in the presence of Mg^{++}, ADP was about 45% as effective as ATP, in the presence of Zn^{++} ADP was inactive as a phosphate donor in the synthesis of FMN. Moreover, whereas in the presence of Mg^{++} AMP as previously reported exerted a 46% inhibition, no such inhibitory effect was detected in the presence of Zn^{++} (Table II, expt. 2). IMP, for which no enzymatic transphosphorylation from ATP has as yet been reported, does not inhibit the synthesis of FMN even in the presence of Mg^{++} (Table II, expt. 2). It could be argued, however, that Mg^{++} may be required for the binding of AMP to the ATP site on the flavokinase surface and actually as previously suggested this binding through the 6-NH$_2$ group of the purine ring is an essential part of the mechanism of its inhibition. A similar mechanism of inhibition has been proposed to explain the inhibitory effects of adenine and its derivatives in contrast to compounds of the inosine series, on the phosphorylation of pyridoxal.[9]

If such a mechanism were involved, adenosine

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(6) S. P. Colowick and H. M. Kalckar. *J. Biol. Chem.*, **148**, 117 (1943).

(7) A. Kornberg and W. E. Pricer, Jr., *ibid.*, **193**, 481 (1951).

(8) H. M. Kalckar, *J. Biol. Chem.*, **167**, 461 (1947).

(9) J. Hurwitz, *Biochim. Biophys. Acta*, **9**, 496 (1952).

which does not participate in the myokinase reaction would be expected nonetheless to inhibit the phosphorylation of riboflavin in the presence of Mg^{++}. However, as can be seen from Table II, expt. 3, whereas AMP inhibited the synthesis of FMN by 53.5%, no inhibition by adenosine was observed. Thus, on the basis of this analogy, it appears less likely that the absence of Mg^{++} is responsible for the loss of AMP inhibition in the presence of Zn^{++}. The higher AMP inhibition noted here as compared to expt. 2 is due to the slightly lower relative ATP concentration and to the use of unpurified ATP solutions which probably already contain some AMP. As expected neither AMP nor adenosine inhibited in the presence of Zn^{++} (Table II, expt. 4).

The experimental results outlined here are highly suggestive that the observed activity of ADP as a phosphate donor in the presence of Mg^{++} is due to contaminating myokinase activity. The remote possibility that ADP acts as a direct phosphorylating agent only in the presence of Mg^{++} has not been excluded. The competitive inhibition of AMP observed in the presence of Mg^{++} can be attributed to a competition with riboflavin for ATP to form ADP which in itself cannot donate phosphate, thus lowering the effective ATP concentration of the reaction mixture.

Although the maximal velocity with ADP in the presence of Mg^{++} is about 50% of that with ATP, this does not constitute an unequivocal argument to conclude that the activity of ADP is direct and not due to its prior conversion to ATP by myokinase. A possible inhibitory effect of ADP on the flavokinase reaction may very well lead to such fortuitous results. Neither does the maximal velocity with ADP equal that with AMP in the activation of crude muscle phosphorylase (Dr. S. P. Colowick, personal communication). Yet with purified muscle phosphorylase ADP does not retain its activating effect, suggesting that its stimulatory effect in the crude system was due to its prior conversion to AMP by myokinase.

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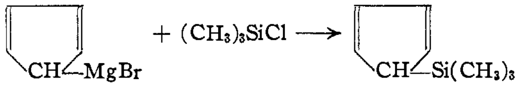
Cyclopentadienylsilane Derivatives

BY KURT C. FRISCH*

RECEIVED JUNE 19, 1953

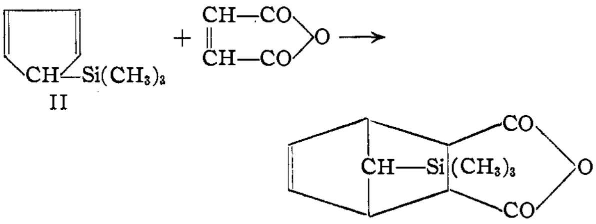
Cyclopentadienylsilane derivatives have hitherto not been reported in the literature. Several routes are possible for the preparation of these derivatives, among them the use of alkali metals to form the corresponding salts which then could react further with chlorosilanes. However, some of these salts are spontaneously inflammable on exposure to air.[1]

The Grignard method offered a convenient and safe way to arrive at these compounds. Cyclopentadienylmagnesium bromide (I) was prepared according to the method of Grignard and Courtot[2] using an exchange reaction between cyclopentadiene and ethylmagnesium bromide. This Grignard compound I then was treated with various chlorosilanes. The reaction of I with trimethylchlorosilane resulted in the formation of cyclopentadienyltrimethylsilane (II).



I II

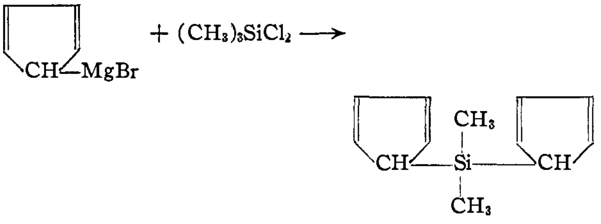
Since a silicon analysis alone was not sufficient to decide between a monomeric or dimeric structure, a molecular weight determination in dioxane indicated the existence of the monomeric form. In addition, a crystalline Diels-Alder adduct III with maleic anhydride gave further proof that the conjugated double bond system in II was still intact



II

III

The reaction of cyclopentadienylmagnesium bromide with dimethyldichlorosilane led to the isolation of two products from which bis-(cyclopentadienyl)-dimethylsilane (IV) was identified.



IV

Another product, distilling at 80–83° at 0.7 mm., was obtained in a yield of 11%. It had a silicon content of 16.6% and gave a positive chlorine test. However, no definite structure was assigned as yet to this product.

Experimental

Cyclopentadienylmagnesium Bromide (I).—To an ethylmagnesium bromide solution, prepared from 200 g. of ethyl bromide was added 500 cc. of benzene and the ether removed by distillation.

One hundred twenty-one grams of cyclopentadiene, obtained by slow distillation from dicyclopentadiene, was added slowly to the ethylmagnesium bromide solution. It was then added for 1.5 hours at 60°. Ethane evolution occurred during the heating period. Cyclopentadienylmagnesium bromide formed a dark colored, clear solution.

Cyclopentadienyltrimethylsilane (II).—Half of the above Grignard solution was added gradually to a solution of 99.5 g. of trimethylchlorosilane in 150 cc. of benzene. The reaction mixture was then refluxed for 15.5 hours. The inorganic precipitate was filtered off and washed with benzene. The solvent was removed from the filtrate and the residual liquid vacuum distilled. The product distilled at 43–44° at 19 mm. as a colorless liquid which darkened on prolonged exposure to air. The yield was about 45%.

Anal. Calcd. for $C_8H_{14}Si$: Si, 20.3; mol. wt., 138. Found: Si, 19.7; mol. wt. 135.

The 3,6-*endo*-Trimethylsilylmethylene-1,2,3,6-tetrahydrophthalic Anhydride (III).—Two and two-tenths grams of maleic anhydride was added to a solution of 3.1 g. of cyclopentadienyltrimethylsilane in 10 cc. of benzene at room temperature. An instantaneous exothermic reaction set in. The reaction mixture was allowed to stand at room tempera-

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[1] J. Thiele, *Ber.*, **34**, 68 (1901).

[2] V. Grignard and C. Courtot, *Compt. rend.*, **158**, 1763 (1914).

ture for 2 hours. It was then concentrated using an air blower. It was filtered and 4 g. (78.5% of theory) of a colorless, crystalline material was obtained. Recrystallized from glacial acetic acid, it melted at 105° (uncor.).

Anal. Calcd. for $C_{12}H_{16}O_3Si$: Si, 11.86. Found: Si, 11.4.

Bis-(cyclopentadienyl)-dimethylsilane (IV).—Half of the above-described cyclopentadienylmagnesium bromide solution was added gradually to a solution of 207 g. of dimethyldichlorosilane in 250 cc. of benzene. The reaction mixture was refluxed for 15.5 hours. It was filtered and the inorganic precipitate washed with benzene. The solvent was removed and the residual material vacuum distilled. The product, a colorless liquid, distilled at 73° at 25 mm. This material gave a negative chlorine test. The yield was about 40%.

Anal. Calcd. for $C_{12}H_{16}Si$: Si, 14.89. Found: Si, 14.5.

NEW PRODUCTS DEVELOPMENT LABORATORY
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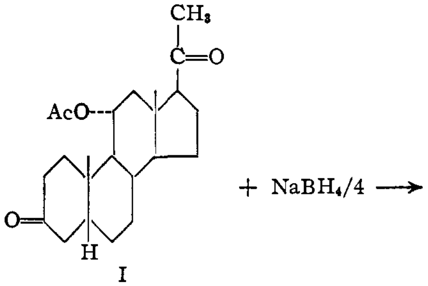
The Kinetics of 20-Keto Reduction in 11α-Acetoxypregnane-3,20-dione by Sodium Borohydride

BY EDWARD R. GARRETT AND DOUGLAS A. LYTTLE

RECEIVED JULY 17, 1953

The selective reduction by sodium borohydride of the 3-keto group of pregnane-3,20-diones to the 3α-hydroxy configuration has been reported.[1-3] In the course of studies on the quantitative rates of selective reduction we have found that the reduction of the 3-keto group of the dione I occurred too rapidly for precise measurement under our experimental conditions. Therefore, we have investigated the kinetics of the reduction of the C-20 carbonyl group. The kinetics of borohydride reduction of 3α-hydroxy-11α-acetoxypregnan-20-one (II) are bimolecular with respect to carbonyl and sodium borohydride concentration. The stoichiometry of the reduction requires one mole of sodium borohydride to four moles of carbonyl.



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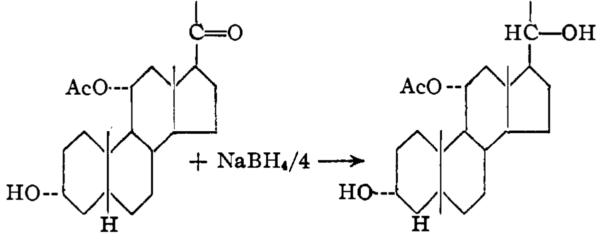

II III

Experimental

Materials.—The $NaBH_4$ (Metal Hydrides, Inc.) was used as received from the manufacturer. The 11α-acetoxypregnane-11,20-dione[4] melted at 149.5–153.5°. The 3α-hydroxy-11α-acetoxypregnan-20-one[1] melted at 145.5–147.0°. The dioxane was freshly distilled over $NaBH_4$.

Borohydride Assay.—The effective borohydride concentration of the solutions used was determined in the following manner: a 5-cc. sample containing up to 15 mg. of $NaBH_4$ was pipetted into a solution of 1 cc. of 2 N NaOH and 25 cc. of 0.1 N KIO_3. To this was added 1 g. of KI, 15 cc. of $CHCl_3$ and 12 cc. of 2 N H_2SO_4. The released I_2 was titrated with 0.1 N $Na_2S_2O_3$ using 1% starch indicator. The equivalent weight of $NaBH_4$ is $^1/_8$ molecular weight.[5]

Rate Studies.—The ketosteroid was dissolved in dioxane and this solution was added to an aqueous solution of sodium borohydride previously assayed and of known alkalinity. The resulting solvent was 68.5% dioxane. Aliquots were removed at timed intervals and titrated by the procedure given above.

The composition of the solutions studied is given in Table I.

TABLE I

THE REACTION CONDITIONS FOR SODIUM BOROHYDRIDE REDUCTIONS OF KETOSTEROIDS IN 68.5% DIOXANE

Run no.[a]	Temp., °C.	$NaBH_4$, M	NaOH, M	k (l. mole^{-1} hr.$^{-1}$)[b] for 20-ketone reduction
1[c]	15 ± 0.5	0.00656	0.0544	..
2	25.5 ± .3	.0502	.0564	0.40
3	56.0 ± .5	.0533	.0552	3.6
4	57.0 ± 1.0	.0533	.0281	3.7
5	56.0 ± 0.5	.0262	.0555	4.2
6	56.5 ± 0.2	.0389	.0552	3.9

[a] Runs 1 through 5 were with 0.0517 M 11α-acetoxypregnane-3,20-dione (I). Run 6 was with 0.0517 M 3α-hydroxy-11α-acetoxypregnan-20-one (II). [b] The bimolecular rate constant, k, is calculated from the product of $2.303/(4A - B)$ and the slope of the linear plot of $\log[(A - x)/(B - 4x)]$ *vs.* time in hours. The initial carbonyl molarity (B) is twice the molarity of the diketosteroid and equal to the molarity of the monoketosteroid. The initial molarity of borohydride is A and x is the calculated consumption of borohydride at time t. [c] 87% of the $NaBH_4$ was consumed within two minutes.

Results and Discussion

The relatively instantaneous reduction of the 3-keto group of 11α-acetoxypregnane-3,20-dione under the mildest conditions studied is shown in run no. 1 at 15° and with no borohydride in stoichiometric excess of the 3-keto group (Table I). In the other runs the consumption of a second stoichiometric equivalent proceeded at a measurable rate. Each molecule of borohydride was equivalent to the reduction of four carbonyls.

This is consistent with the proposed mechanism of Chaikin and Brown[6] of a 1:4 adduct prior to hydrolysis. On the postulate that this adduct is formed in four successive steps, 1:1, 1:2, 1:3 and finally, 1:4, and that the first 1:1 adduct formation is rate determining, the over-all rate expression is

$$dx/dt = k(A - x)(B - 4x)$$

where $A = [NaBH_4]$, the initial molar concentration of sodium borohydride, $B = [R_2C{=}O]$, the molar concentration of reducible carbonyl groups,

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(1) J. A. Hogg, D. A. Lyttle and A. H. Nathan, U. S. Patent 2,647,-134.

(2) O. Mancera, A. Zaffaroni, B. A. Rubin, F. Sondheimer, G. Rosenkranz and C. Djerassi, THIS JOURNAL, **74**, 3711 (1952).

(3) O. Mancera, Howard J. Ringold, C. Djerassi, G. Rosenkranz and F. Sondheimer, *ibid.*, **75**, 1286 (1953).

(4) S. H. Eppstein, D. H. Peterson, H. Marian Leigh, H. C. Murray, A. Weintraub, L. M. Reineke and P. D. Meister, *ibid.*, **75**, 421 (1953).

(5) D. A. Lyttle, E. H. Jensen and W. A. Struck, *Anal. Chem.*, **24**, 1843 (1952).

(6) S. W. Chaikin and W. G. Brown, THIS JOURNAL, **71**, 122 (1949).

and x = amount of borohydride reacted at time t. This expression may be integrated to

$$\log [(A - x)/(B - 4x)] = (4A - B)kt/2.303 - \log (B/A)$$

The typical bimolecular plot for this equation is given in Fig. 1 for the data of run no. 2. The linearity is consistent with this postulated mechanism which is further substantiated by the fact that variation of the initial borohydride concentration does not significantly affect the rate constant (Table I, runs 3 and 5).

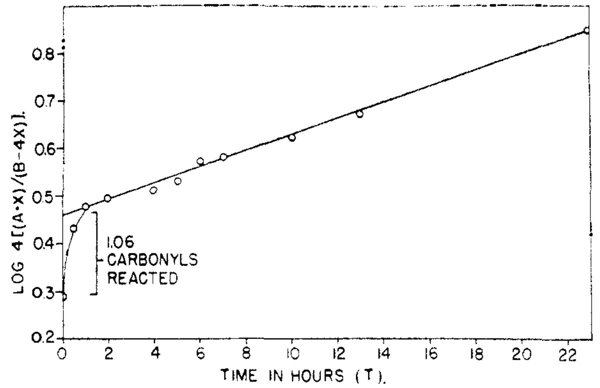

Fig. 1.—Bimolecular plot of log $4[(A - x)/(B - 4x)]$ against time (t) in hours at 25° in 68.5% dioxane for the reduction of the initial reducible carbonyl concentration (B) by the initial sodium borohydride concentration (A), where x is the amount of borohydride reacted at time (t): $A = 0.0502$ M $NaBH_4$; $B/2 = 0.0517$ M 11α-acetoxypregnane-3,20-dione and the initial solution is 0.0564 M in NaOH.

These kinetics are also consistent with an alternative mechanism, one that does not postulate a large tetrasteroid complex with borohydride in aqueous solution or does not necessitate borohydride–steroid adducts reacting with carbonyls at faster rates than borohydride alone. This alternative mechanism would involve the rate-determining formation of a 1:1 steroid–borohydride complex which undergoes hydrolysis to a corresponding carbinol and an oxidized borohydride moiety. This moiety may subsequently react quickly in non-rate-determining steps with other molecules of carbonyl. The presence of alkali may assist in their stabilization. The sequence of equations may be written

$$R_2C{=}O + NaBH_4 \xrightarrow{k_1} (R_2CHO)NaBH_3 \quad (1)$$

$$(R_2CHO)NaBH_3 + HOH \xrightarrow{k_1'} R_2CHOH + NaBH_3(OH) \quad (2)$$

$$R_2C{=}O + NaBH_3(OH) \xrightarrow{k_2} (R_2CHO)NaBH_2OH \quad (3)$$

$$(R_2CHO)NaB(OH)_3 + HOH \xrightarrow{k_4'} R_2CHOH + NaBO_2 + 2HOH \quad (8)$$

where the rate constant k_1 (and/or k_1') is very much smaller than the rate constants k_2, k_3, k_4 and the hydrolysis constants k_2', k_3', k_4'.

The wide discrepancy in reactivities of the 3- and 20-keto groups is shown in Fig. 2 for runs no. 3 and 6. The open circles represent the reduction of the diketo compound, 11α-acetoxypregnane-3,20 dione (I). The solid circles represent the reduction of the monoketo compound, 3α-hydroxy-11α-acetoxypregnan-20-one (II). The conditions at the start of this latter reaction were chosen to be exactly the same as those of the former on the assumption of instantaneous reduction of the 3-keto groups. The agreement of the data with the common line drawn through the points is confirmatory.

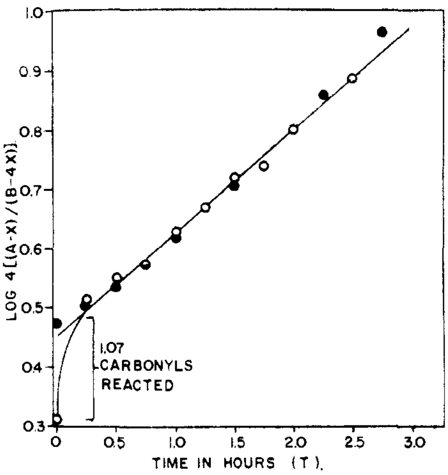

Fig. 2.—Bimolecular plot of log $4[(A - x)/(B - 4x)]$ against time (t) in hours at 56° in 68.5% dioxane for the reduction of the initial carbonyl concentration (B) by the initial sodium borohydride concentration (A), where x is the amount of borohydride reacted at time (t). For the solid circles, $A = 0.0389$ M $NaBH_4$, $B = 0.0517$ M 3α-hydroxy-11α-acetoxypregnan-20-one. For the open circles, $A = 0.0533$ M $NaBH_4$, $B/2 = 0.0517$ M 11α-acetoxypregnane-3,20-dione. Both reaction solutions were initially 0.0552 M in NaOH.

Variation in alkali concentration has no mechanistic effect on the reduction rate as per the rate constants for runs no. 3 and 4. Run no. 4 did show an apparent rate increase near completion of the reduction of the 20-keto group which can readily be accounted for by concomitant decomposition of borohydride in a more acidic media.[5] It is indicated that alkali concentration, above the necessary minimum to stabilize the borohydride, is not kinetically significant.

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Metal–Water Reactions. I. The Reaction between Calcium and Water Vapor*

By Dale S. Gibbs and Harry J. Svec

Received April 20, 1953

During the development of an analytical method for determining the oxygen content of Ca metal, the reaction between water vapor and Ca metal was studied. In the temperature range 177 to 369° a series of distinct reactions was found. In order of occurrence these are

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* Work was performed in the Ames Laboratory of the Atomic Energy Commission.

$$2Ca + H_2O \longrightarrow CaO + CaH_2 \qquad (I)$$

$$CaH_2 + 2H_2O \longrightarrow Ca(OH)_2 + 2H_2 \qquad (II)$$

$$CaO + H_2O \longrightarrow Ca(OH)_2 \qquad (III)$$

Step I takes place exclusively as long as Ca metal is present. An investigation of the reaction shown in step I indicated that the equation correctly describes the stoichiometry involved.

The solid products of the reaction maintained the shape of the original metal specimens with no spalling occurring until hydrogen began to evolve with the onset of step II. Examination of the cross sections of the reaction product specimens showed a definite band structure. When the reaction was stopped before all the Ca was consumed, five bands were observed. The compositions of these as determined by X-ray methods were: (1) pure CaO, (2) mixture of CaO and CaH_2, (3) pure CaH_2, (4) mixture of CaH_2 and Ca, (5) pure Ca. When the reaction was allowed to proceed until all the metal was consumed, bands (4) and (5) disappeared.

This band structure can be explained on the basis of known physicochemical properties of all the substances involved in reaction I. CaO is insoluble or very slightly soluble in Ca metal.[1] As CaO forms in the initial stages of the reaction, it is deposited on the metal surface. Johnson, *et al.*,[2] have shown that CaH_2 is 19 to 35% soluble in γ-Ca and liquid Ca in the temperature range 778–894°. It is impossible to extrapolate these data to the temperature range covered in this paper due to the transition[3] in Ca at 440°: however, it is probable that a limited solubility of CaH_2 in β-Ca exists. Hence any CaH_2 formed in the initial stage of the reaction dissolves in the metal and does not deposit along with CaO until local saturation is reached. The CaO deposited during the time in which saturation of Ca with CaH_2 is occurring constitutes band (1). Band (2) consists of the mixed Ca and CaH_2 and increases in width as the reaction proceeds. As CaH_2 is precipitated from solution in the metal, an extremely thin band, band (3), appears. The boundary between band (4) and the metal is very diffuse. Pilling and Bedworth[4] have shown that the CaO film will be cracked because of the great difference between the molecular volumes of oxide and metal. It is assumed, therefore, that water vapor diffuses through the relatively loose structure of the reaction products and that the reaction between water molecules and Ca takes place on the receding metal surface.

The experimental facts were consistent with the above theory. Band (1) was always thin and of relatively constant thickness in all specimens examined. From a consideration of the dimensions of band (1) the solubility of CaH_2 in Ca at 369° was estimated to be 14.2 ± 4.0%. Band (2) reached its maximum width when all the Ca metal had been consumed in the reaction. Band (3) was so thin that positive identification of its composition as pure CaH_2 was very difficult to determine experimentally. Since the boundary between bonds (4) and (5) was very diffuse, etching with air passed through hot water was required to develop any evidence for its existence.

A detailed consideration of the composition of band (2) is of interest. It might be expected that because of the nature of its boundaries a concentration gradient of CaH_2 should exist. Both X-ray and H_2 evolution experiments supported this contention. The concentration of CaH_2 was greater near the center of the reaction product specimens than near the surface.

Experimental

Apparatus.—The apparatus consisted of a reaction tube, recording manometer,[5] a means of introducing water vapor into the system and appropriate high vacuum equipment to evacuate the entire system thoroughly. By means of a special furnace which could be slid over the reaction tube, the reaction temperature was controlled to ±0.1°. The vacuum tight port through which water was introduced into the apparatus consisted of a serum bottle rubber stopper placed in a constricted tube and covered with mercury. Below this stopper was a well into which liquid water was introduced by means of a hypodermic syringe. Throughout the experiments liquid water always remained in this well and was maintained at 25 ± 1°.

Procedure.—Cylinders of redistilled Ca metal (Ca distilled in the Ames Laboratory) were prepared by machining under sodium-dried turbine oil. The oil-covered cylinders were suspended at two points in a special stainless steel frame. After four rinses in sodium-dried petroleum ether and one rinse in sodium-dried diethyl ether the cylinders and frame were placed in the reaction tube. The entire apparatus was rapidly evacuated and as soon as the pressure was reduced to less than 0.1 μ of Hg the preheated furnace was slid into place. When temperature equilibrium was reached the reaction was initiated by introducing degassed liquid water into the water well.

Great care was taken to prevent manual handling of the Ca metal even under oil. This precaution was necessary to prevent fingerprinting which introduces active centers on the metal surface and obviates a uniform reaction product. Neoprene-tipped forceps or rubber gloves previously dipped in dry oil or solvent were used for handling the metal samples.

During the course of some of the experimental runs a small increase in pressure (about 25 to 35 mm. of Hg partial pressure of H_2) was observed. This H_2 pressure, after rising to a maximum, rapidly diminished, and after two or three hours no detectable amount of H_2 remained in the apparatus. In most runs, however, no initial H_2 pressure was observed nor could H_2 be detected in the apparatus. All gas analyses were made by means of a mass spectrometer having a sensitivity for H_2 of 1 part in 40,000.

Weight Gained by the Sample.—In one representative trial a Ca cylinder weighing 20.718 g. was allowed to react with H_2O vapor until the gas pressure within the apparatus began to rise when H_2 formed. The reaction was stopped, and the weight of the cylinder was found to be 25.210 g. Assuming the product mixture to be CaO and CaH_2 in equimolar quantities, the calculated weight was 25.38 g. A small residual core of metal in the cylinder of reaction products could very easily account for the difference between observed and calculated weights.

Analysis of Solid Reaction Products.—Two types of reaction product specimens were examined. Type A was obtained from experimental runs in which the reaction had consumed about half the Ca. In type B specimens all the Ca was consumed. Longitudinal sections of the specimens were examined by means of a recording X-ray diffractometer. The bands have already been identified above. It is significant, however, that in type B specimens where a more detailed examination of band (2) was made, a reversion of peak heights (due to principal reflections of CaO and CaH_2)

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(1) From experiences in the Ames Laboratory of the Atomic Energy Commission during years of handling Ca. No quantitative data are available at this time.

(2) W. C. Johnson, M. F. Stubbs, A. E. Sidwell and A. Pechukas, THIS JOURNAL, **61**, 318 (1939).

(3) O. Kubaschewski and B. E. Hopkins, "Oxidation of Metals and Alloys," Academic Press, Inc., New York, N. Y., 1953, p. 6.

(4) N. B. Pilling and R. E. Bedworth, *J. Inst. Metals* (*London*), **29**, 529 (1923).

(5) H, J. Svec and D. S. Gibbs, *Rev. Sci. Instruments*, **24**, 202 (1953),

was observed as sections deeper within the specimens were examined. The H_2 evolution experiments corroborated these results. Table I shows the results of some typical experiments on one of the reaction product specimens obtained at 369°.

TABLE I

COMPOSITION OF $CaO–CaH_2$ MIXTURES FROM DIFFERENT REGIONS OF THE REACTION PRODUCT SPECIMENS

Sample no.	Sample description	Wt. of sample, g.	H_2 pressure, cm. of Hg	CaH_2, %[a] calcd.
1	Center	0.4947	30.5	84.5
2	Center	.7228	43.4	82.3
3	Center	.5178	31.2	87.5
4	Center	.7258	47.6	88.7
5[b]	Near outer surface	.8339	34.4	41.8

[a] Volume of apparatus was 1250 ml. [b] Gas evolution experiments were performed at 35 ± 0.02°, except this one which was at 47 ± 02°.

In all the X-ray experiments, peaks due to X-ray reflections were not as sharp as would be expected in well-defined crystalline materials, thus indicating crystallites of short range. Although the gross appearance of the reaction product specimens was solid, the specimens appeared granular when broken to expose their cross sections, indicating that ample paths for the diffusion of water vapor through the reaction product coat were available.

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Heats of Formation of Chromium(III) and Chromium(II) Iodides

BY N. W. GREGORY AND T. R. BURTON

RECEIVED AUGUST 6, 1953

The heat of formation of CrI_3 has not been determined previously; the reported value for CrI_2 (−54.2 kcal./mole)[1] is based on a heat of solution determined by Mosnier[2] and is not consistent with properties observed in this Laboratory. From heats of solution of CrI_3 and CrI_2 and related substances, we find the heats of formation[3] at 25° to be −47.8 and −37.8 kcal./mole, respectively, with an uncertainty of ±3%.

Heats of solution of millimole quantities of $CrCl_2$, $CrCl_3$, CrI_2, CrI_3, KCl and KI in 750 ml. of an aqueous solution 1 molal in KCl and approximately 0.001 *M* in chromium(II) chloride were measured. Cr^{+2} is necessary to effect solution of the chromium(III) halides.[4] It has been assumed that the final state of chromium in the solution after dissolution of $CrCl_3$ is the same as that when CrI_3 is dissolved (similarly for the chromium(II) halides), *i.e.*, that the concentration of iodine complexes is negligible in the presence of the comparatively high concentration of chloride ions. Hence the mean values of the heats of solution (Table I) have been combined to determine heats of the reactions.

$$CrCl_2(c) + 2KI(c) = CrI_2(c) + 2KCl(c) \qquad \Delta H = 5.0 \text{ kcal.} \quad (1)$$

$$CrCl_3(c) + 3KI(c) = CrI_3(c) + 3KCl(c) \qquad \Delta H = 9.2 \text{ kcal.} \quad (2)$$

TABLE I

MOLAR HEATS OF SOLUTION

Solute, millimoles	ΔH soln., kcal.	Solute, millimoles	ΔH soln. kcal.
$CrCl_3$		CrI_3	
1.184	−32.3	0.7798	−41.1
1.277	−33.0	0.9215	−41.6
1.502	−32.9	2.563	−41.3
2.065	−32.7		
			−41.3
	−32.7	CrI_2	
$CrCl_2$		2.198	−22.6
0.8525	−18.1	2.221	−22.8
1.426	−17.9	2.389	−22.5
5.216	−17.9	2.907	−22.6
	−18.0		−22.6
KCl		KI	
29.02	4.0	11.00	4.3
36.50	3.9	12.74	4.2
41.61	4.1	14.96	4.4
42.95	4.0	16.12	4.0
	4.0		4.2

HEATS OF SOLUTION OF CHROMIUM IODIDES AND EXCESS IODINE IN 0.02 *N* HCl

		CrI_2–CrI_3 mixtures		
		CrI_2	CrI_3	Contribution of CrI_3
CrI_2				
1.141	−54.8	0.4809	1.149	−44.0
1.700	−54.8	.2272	1.445	−42.3
2.075	−54.8	.4829	1.709	−44.6
2.861	−54.4	.4047	1.990	−44.4
		1.571	3.260	−43.2
	−54.7			
				−43.7

Using standard heats of formation for the chromium chlorides and potassium halides, values are obtained for the chromium iodides. The sensitivity of the calorimeter was not sufficient to detect any variation in the molar heats of solution with the slightly differing quantities dissolved. Somewhat larger samples (than required by reactions 1 and 2) of the potassium halides were used to obtain a sufficiently large thermal effect for accurate measurement. The relatively small difference in the change of heats of solution with concentration for these substances indicates that this does not introduce a significant error.

The combined heats of chromium(II) and halogen ions in the KCl solution is essentially the same as the sum of the standard values for these ions; the observed heat of solution, if assigned to the simple reaction

$$CrI_2(c) = Cr^{+2}(aq) + 2I^-(aq)$$

gives −37.3 kcal. for the heat of formation of CrI_2 (using −33.2 kcal. for Cr^{+2} (aq)[1] and −13.37 kcal. for I^- (aq)[1]). A similar treatment with $CrCl_2$ leads to a heat of formation of −95.2 kcal. (accepted value[1] −94.6).

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[1] F. D. Rossini, *et al.*, "Selected Values of Chemical Thermodynamic Properties," National Bureau of Standards Circular 500, U. S. Government Pr. Office, Washington, D. C., 1952.

[2] M. A. Mosnier, *Ann. chim. phys.*, **12**, 374 (1897).

[3] $I_2(c)$ taken as the standard state for iodine.

[4] The concentration of Cr^{+2} is not critical. In a series of experiments with $CrCl_3$, no dependence of the heat of solution with concentration of Cr^{+2} was observed as the latter was varied between 0.001 and 0.0035 *m*.

From the heats of formation, an enthalpy change of 10 kcal. is predicted for the reaction

$$CrI_3(c) = CrI_2(c) + {}^1/_2I_2(c) \qquad (3)$$

3 kcal. less than previously estimated by extrapolation of thermal dissociation equilibrium data at 570°.[5] The heat of reaction (3) at 25° has been determined by comparison of the heats of solution of CrI_3 and CrI_2 with excess solid iodine in 750 ml. of 0.02 N HCl solution. Known mixtures of CrI_3 and CrI_2 were dissolved and iodine was subsequently introduced. The heat of solution of pure CrI_2 was determined under similar conditions and the contribution of each component in the mixtures calculated. Inasmuch as iodine readily oxidizes chromium(II) to chromium(III), the final state of chromium after dissolving CrI_2 is the same as that with CrI_3. The results for the mixtures are somewhat less consistent than those for the pure substances; however, the difference between the mean values, 11 kcal. (Table I), agrees with the predicted result within experimental uncertainty.

Experimental Procedure

A description of the simple adiabatic calorimeter and its operation[6] and the preparation of CrI_3[7] have been given previously. Heats of solution were measured at 25 ± 1°. CrI_2 was prepared by thermal decomposition of CrI_3 in vacuum (400–500°), followed by sublimation in vacuum at 700°. The chromium chlorides were also purified by sublimation. The composition of these substances was checked by analysis; deviation from theoretical values did not exceed 0.5%. Samples were introduced into the calorimeter in sealed thin glass capsules, previously filled in a dry-box.

It is a pleasure to acknowledge support of this work by the Office of Ordnance Research, United States Army.

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(5) L. L. Handy and N. W. Gregory, THIS JOURNAL, **74**, 2050 (1952).

(6) J. C. M. Li and N. W. Gregory, *ibid.*, **74**, 4670 (1952).

(7) L. L. Handy and N. W. Gregory, *ibid.*, **72**, 5049 (1950).

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The Stability of Hydroxystreptomycin

BY IRVING R. HOOPER AND MURRAY A. KAPLAN

RECEIVED AUGUST 4, 1953

An unknown antibiotic isolated in the antibiotic screening program carried out at these laboratories was found to be identical with hydroxystreptomycin.[1-4] In the course of our degradation studies, it was found remarkably resistant to hydrolytic inactivation, compared to streptomycin.[5]

The stability of hydroxystreptomycin in water and methanol solutions is shown in Table I. Solutions initially contained 10 mg./ml. of hydroxystreptomycin base and were followed by bioassays.

TABLE I

Solvent	pH	Time, days	Temp., °C.	Activity remaining, %
Water	2	8	20	>95
Water	6.5	8	20	>95
Water	12	8	20	>95
Water	2	1	100	56
Water	6.5	1	100	58
Methanol	2	4	65	72
Methanol	6.5	1	65	83

Hydroxystreptomycin is much more stable to acid hydrolysis under mild conditions than is streptomycin. Table II shows the results obtained from stability studies on streptomycin and hydroxystreptomycin in 2 N hydrochloric acid at 20°. Initial concentrations were 4 mg. of antibiotic base/ml. The figures are taken from the best line fitted to the plot of the logarithm of concentration against time.

TABLE II

	Activity remaining, %			
	1 day	2 days	7 days	21 days
Streptomycin	50	19	<1	
Hydroxystreptomycin	93	85	58	20

The hydrogenated derivatives are very similar to the unreduced compounds with respect to stability in hydrochloric acid.

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(1) W. E. Grundy, J. A. Schenk, R. H. Clark, Jr., N. P. Hargie, R. K. Richards and J. C. Sylvester, *Arch. Biochem.*, **28**, 150 (1950).

(2) R. G. Benedict, F. H. Stodola, O. L. Shotwell, A. M. Borud and L. A. Lindenfelser, *Science*, **112**, 77 (1950).

(3) F. H. Stodola, O. L. Shotwell, A. M. Borud, R. G. Benedict and A. C. Riley, Jr., THIS JOURNAL, **73**, 2290 (1951).

(4) W. E. Grundy, A. L. Whitman, M. E. Hanes and J. C. Sylvester, *Antibiotics and Chemotherapy*, 1, 309 (1951).

(5) F. P. Regna, L. A. Wasselle and I. A. Solomons, *J. Biol. Chem.*, **165**, 631 (1946).

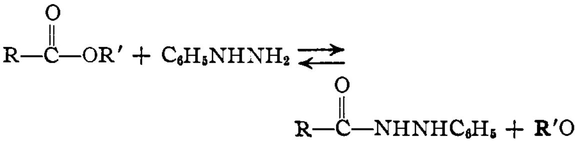
The Reaction of Esters with Phenylhydrazine in the Presence of Phosphoric Acid[1]

BY T. O. JONES, R. E. HALTER AND W. L. MYERS

RECEIVED MAY 9, 1953

The reactions of esters with ammonia, hydroxylamine and hydrazine to produce the corresponding amide, hydroxamic acid or hydrazide are well known. Cohn[2] and Meyer[3] reported a reaction between methyl salicylate and phenylhydrazine to produce the corresponding phenylhydrazide, and Baidakowski, Reformatski and Slepak[4] prepared a few phenylhydrazides by heating the ester and phenylhydrazine in a sealed tube at 210°, but no other examples of this reaction have since been reported.

Various modifications and adaptations of earlier procedures for carrying out similar reactions were tried for the reaction



$$R-\overset{\overset{O}{\|}}{C}-OR' + C_6H_5NHNH_2 \rightleftarrows R-\overset{\overset{O}{\|}}{C}-NHNHC_6H_5 + R'OH$$

using the ester and the free base in various solvents or using the ester and the hydrochloride or sulfate salts, all without results. It was noted that when the phenylhydrazine salts were used, they remained unchanged during the trials so the phenylhydrazine

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(1) Supported in part by a grant from the Research Corporation, 405 Lexington Ave., New York 17, N. Y.

(2) G. Cohn, *J. prakt. Chem.*, [2] **61**, 548 (1900).

(3) H. Meyer, *Monatsh.*, **28**, 1383 (1907).

(4) L. Baidakowski, S. Reformatski and I. Slepak, *J. Russ. Phys.-Chem. Soc.*, **35**, 61 (1902).

salt of a weaker acid, phosphoric acid, was tried and found to be singularly effective for the formation of hydrazides.

Other acids, *e.g.*, sulfuric, hydrochloric, benzenesulfonic, dichloroacetic, potassium bisulfate and sodium dihydrogen phosphate made up to hydrogen ion concentrations comparable to that of the phosphoric acid used, gave no yield of the phenylhydrazide in any case. Sodium benzenesulfonate and other phosphate salts were tried with negative results.

It appears that the reaction proceeds by a base–acid-catalyzed mechanism in which the phosphoric acid is the acid and the $H_2PO_4^-$ is the base in as much as the amount of acid required to catalyze the reaction lies within a minimum and maximum limit. The effect of minimum and or excess amounts of phenylhydrazine on the yield also seems to support this view.

Experimental

In a typical experiment to prepare the β-acetylphenylhydrazine, 8.8 g. (0.1 mole) of ethyl acetate, 43 g. (0.4 mole) of phenylhydrazine, 5.4 g. (0.3 mole) of water and 1.2 g. (0.01 mole) of sirupy phosphoric acid (85%) were placed in a 100-ml. round-bottom flask and refluxed gently for 1 hour. The water, unreacted ester, and excess phenylhydrazine were then removed by distillation at reduced pressure (*ca.* 20 mm.), the distillation being stopped when the temperature rose above 100° to prevent decomposition of the residue. The material remaining in the flask was then extracted with 100 ml. of hot benzene, from which on cooling, about 9 g. (60% yield) of the phenylhydrazide crystallized out. A single recrystallization from hot benzene produced the silvery platelets characteristic of the phenylhydrazides, m.p. 128° (uncor.), reported 129°.[5] The solubility of the phenylhydrazides in benzene is greatly increased by small amounts of ester or phenylhydrazine. Failure to obtain a solid product on extraction of the residue from the vacuum distillation was usually due to incomplete removal of these reactants.

The same general procedure was suitable for preparing other phenylhydrazides except for the length of time of refluxing. For formates, 0.5 hour was sufficient while for the higher aliphatic esters and benzoates, up to 3 hours were required. For esters of the higher dibasic acids such as ethyl adipate and for methyl salicylate, up to 5 hours of reflux time were needed. The reaction has been tried on all the aliphatic esters through the caprylates, giving yields from 60% for the lower members of the series to as low as 20% for the higher members. For esters of the dibasic acids the yields were about 20%.

When moderate amounts of phenylhydrazides of acids were desired as derivatives for identification purposes,[6] it was found that an adequate yield was produced by heating together under reflux for 1 hour a mixture containing 1 g. of an ester, *e.g.*, ethyl propionate, 4 g. of phenylhydrazine, 0.3 g. of water and 1 drop of phosphoric acid. The hot solution after refluxing was poured into about 75 ml. of 1.4 *N* hydrochloric acid at 30° and stirred until the phosphate salt of the unreacted phenylhydrazine and phenylhydrazine dissolved (*ca.* 5 min.). It was found necessary to maintain these conditions closely because an increase in the temperature or the concentration of the acid caused hydrolysis of the product while a decrease in the temperature or acid concentration extended unnecessarily the time required to dissolve the phenylhydrazine and its salts. After filtering, the crystals were washed free of the ester and other adsorbed impurities with cold cyclohexane or ligroin (b.p. 75–110°), and recrystallized from benzene.

The effect of varying the amount of phenylhydrazine used while holding the quantities of the other reactants and conditions constant was tried. The maximum yields were obtained using 4 equivalents of phenylhydrazine. When the amount of phenylhydrazine was reduced to 2.8 equivalents or increased to 5.6 equivalents the yield was about half of the maximum. If the amount of phenylhydrazine was increased to 8 equivalents or reduced to 1 equivalent, the yield dropped to 5–10%.

The effect of varying the amount of phosphoric acid used while holding the amounts of the other reactants and conditions constant was tried with similar results. The maximum yield was produced with 0.1 molar equivalent of phosphoric acid with little or no yield resulting if the amount of the acid was reduced to 0.025 or increased as high as 0.3 molar equivalent. Decreasing the amount of water to 1 molar equivalent or increasing to 8 molar equivalents cut the yield to about 10%. No yield was obtained in trials when no water was present or when the water was increased to 15 molar equivalents or more.

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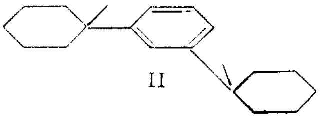
The Structure of Di-(methylcyclohexyl)-benzenes from the Cycloalkylation of 4-Methylcyclohexene with Benzene in the Presence of Hydrogen Fluoride[1]

BY V. N. IPATIEFF,[2] J. E. GERMAIN AND HERMAN PINES

RECEIVED JUNE 30, 1953

It was reported[3] that 4-methylcyclohexene reacts with benzene in the presence of hydrogen fluoride to form 1-methyl-1-phenylcyclohexane in about 75% yield. The remainder of the product consisted of dicycloalkylated benzene from which a solid was separated which melted at 70–71° and to which the structure of *p*-di-(methylcyclohexyl)-benzene (I) was assigned. In order to determine the composition of the dicycloalkylated benzene the higher boiling fractions from several experiments were combined and redistilled on a 30-plate, 26-mm. Oldershaw column.[4] The various cuts were further redistilled using a spinning band Piros–Glover column having an efficiency at a total reflux and at atmospheric pressure of about 60 theoretical plates. Two main fractions were separated: A and B.


I


II

A: b.p. 163.5° at 3.0 mm., $n^{20}\text{D}$ 1.5340, d^{20}_4 0.9688. *Anal.* Calcd. for $C_{20}H_{30}$: C, 88.82; H, 11.18; *Mr*D, 86.56. Found: C, 89.32; H, 11.18; *Mr*D, 86.75.

B: b.p. 181.5° at 3.7 mm., $n^{60}\text{D}$ 1.5238, m.p. 70–71° after crystallization from ethanol. *Anal.* Calcd. for $C_{20}H_{30}$: C, 88.82; H, 11.18. Found: C, 88.74; H, 11.17.

Based on spectrographic analyses and boiling point the polycycloalkylated benzene consisted of 23% compound II, most probably *m*-di-(1-methylcyclohexyl)-benzene, and 64% compound

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[5] Beilstein, "Handbuch der organischen Chemie," Vol. XV, p. 241.

[6] G. H. Stempel, Jr., and G. S. Schaffel, THIS JOURNAL, **64**, 470 (1942).

[1] This work was made possible in part through the financial assistance of the Universal Oil Products Company, Des Plaines, Illinois.

[2] Deceased, November 29, 1952.

[3] V. N. Ipatieff, E. E. Meisinger and H. Pines, THIS JOURNAL, **72**, 2772 (1950).

[4] F. C. Collins and V. Lantz, *Ind. Eng. Chem., Anal. Ed.*, **18**, 673 (1946).

I. The remainder was composed of higher boiling hydrocarbons most probably tri-(methylcyclohexyl)-benzene.

Proof of Structure. Fraction B.—Eighteen grams of B dissolved in 30 ml. of benzene was dehydrogenated by passing it over chromia–alumina catalyst[5] at 450°, according to the procedure described previously.[3] The solution was passed five times over the catalyst at an hourly liquid space velocity of 0.10, and the crystals removed between each pass. The gases, 8.3 liters, produced during the dehydrogenation consisted of 21% methane and 79% hydrogen. The crystalline material, amounting to 6.5 g., melted after crystallization from absolute ethanol at 202–205°.

Anal. Calcd. for $C_{10}H_{14}$: C, 93.87; H, 6.12. Found: C, 93.58; H, 6.56.

The melting point of a known sample of *p*-terphenyl, which was crystallized from ethanol, was 206–207.5°. The mixed melting point of the two samples was 204–205°. The infrared spectra showed that the sample obtained from dehydrogenation contained about 95% of *p*-terphenyl. Minor intensity bands at wave lengths of 12.3 μ which are characteristic of *m*-disubstituted aromatics were present.

Fraction A.—The product, 16.2 g., was dehydrogenated as indicated above. After four passes 12.0 g. of liquid and 7.7 liters of gas were recovered, the latter was composed of 86.6% hydrogen and 11.3% methane. From the liquid hydrocarbons 1.2 g. of solid separated on cooling, which after crystallization from ethanol melted at 83–85°. It did not depress the melting point of an authentic sample of *m*-terphenyl. The infrared spectra of the two compounds were identical.

The liquid product obtained from dehydrogenation distilled at 204–230° at 12 mm., $n^{20}D$ 1.6070. Since the original product appears, according to infrared spectra and physical constants to consist of a pure compound, it is possible that during dehydrogenation a migration of a methyl group occurred.

Spectroscopic Data.—The wave lengths of the absorption bands of I (fraction B), II (fraction A), *p*-terphenyl and *m*-terphenyl are listed below in order of decreasing band intensity, expressed in microns.

I—*p*-di-(1-methylcyclohexyl)-benzene—6.88, 12.04, 6.60, 9.82, 7.27, 9.03, 10.37, 7.40, 7.66, 9.04, 7.14, 10.78 and 11.64.

II—*m*-di-(1-methylcyclohexyl)-benzene(?)—14.10, 12.58, 7.24, 7.02, 6.21, 6.69, 11.12, 10.32, 7.36, 9.00, 7.68, 8.33, 11.56, 11.66, 13.07, 10.75, 9.75, 8.12, 8.65, 9.60 and 12.07.

p-Terphenyl—13.32, 14.39, 11.90, 12.97, 13.81, 9.89, 9.28, 10.95 and 8.96.

m-Terphenyl—13.33, 14.33, 14.29, 13.07, 12.48, 11.16, 9.26, 9.67 and 9.83.

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(5) R. C. Archibald and B. S. Greensfelder, *Ind. Eng. Chem.*, **37**, 356 (1945).

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Spectral Absorption of Solutions of Iodine in Liquid Hydrogen Fluoride

BY L. I. KATZIN AND J. J. KATZ

RECEIVED AUGUST 3, 1953

It is generally accepted that the colors of solutions of iodine reflect specific solvation interactions, the "violet" solutions in solvents like carbon tetrachloride, carbon disulfide or aliphatic hydrocarbons displaying no effect of solvent on the vapor-like absorption of the iodine, and the various red through brown solutions in the benzenoid hydrocarbons and oxygenated solvents showing shifts of the peak of the absorption toward the ultraviolet in relation to the strength of the specific interaction between the iodine and the solvent.[1–7] Mass action constants for formation of monosolvates have been determined for many of these systems, and similar relations have been shown for solutions of bromine in benzenoid hydrocarbons.[8]

Water as a solvent shifts the iodine spectrum in the same sense as do the oxygenated organic compounds. A recent publication[9] on another oxygenated inorganic solvent, 96% sulfuric acid, reports that iodine shows a red color (absorption at 502 mμ instead of the 517 mμ of carbon tetrachloride or 450 mμ of water), while in the oxygenated organic solvent, trifluoroacetic acid, iodine shows an absorption maximum at 515 mμ. We have hereby been stimulated to publish our observations on the absorption of iodine in liquid hydrogen fluoride, for which we find a broad absorption maximum centering at about 514 mμ. The solution is violet colored. Tracing the absorption with a Cary recording spectrophotometer, we can find no second absorption peak down to the limit of the instrument (and the cell system) at 220 mμ. This is therefore apparently not analogous to the case of iodine in *cis*-dichloroethylene, trichloroethylene and tetrachloroethylene, in which optically "violet" solutions show an intense absorption in the ultraviolet, in the vicinity of 270–280 mμ, which gives evidence of complex formation.[10,11]

If the color of the iodine solution in hydrogen fluoride is due to minimal solvent–solute interaction, addition of a strong-base solvent, such as diethyl ether, should affect the absorption. If iodine is dissolved in a mixture of one part by weight diethyl ether to 10 parts hydrogen fluoride, the solution is a red-orange, and the absorption peak is shifted down to about 508 mμ. With 33% ether, the orange color is more marked, and the absorption peak is at about 500 mμ. With a solution composed of 75% ether and only 25% hydrogen fluoride, a yellow-brown solution is found, with a principal absorption at about 360 mμ (it was followed only down to 340 mμ) and a lesser shoulder or peak with its maximum at about 460 mμ. The latter corresponds presumably to the iodine absorption in ether, and the intense 360 mμ peak is undoubtedly the long-wave length peak of the triiodide ion doublet, the second member falling below 300 mμ.

Qualitatively similar color changes could be seen for methanol–hydrogen fluoride mixtures as solvent, but spectral observations were impractical because of apparently accelerated reaction between the iodine and the nickel of the observation cell in this system. All of the colors seemed further

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(1) J. H. Hildebrand and B. L. Glascock, THIS JOURNAL, **31**, 26 (1909).

(2) J. Groh, M. Radvanyi, L. Urbanek and K. Lanyi, *Z. anorg. u. allgem. Chem.*, **162**, 287 (1927).

(3) J. Kleinberg and A. W. Davidson, *Chem. Revs.*, **42**, 601 (1948).

(4) H. A. Benesi and J. H. Hildebrand, THIS JOURNAL, **71**, 2703 (1949).

(5) R. S. Mulliken, *ibid.*, **72**, 600 (1950).

(6) J. A. A. Ketelaar, C. van de Stolpe and H. R. Gersmann, *Rec. trav. chim.*, **70**, 499 (1951).

(7) J. S. Ham, *J. Chem. Phys.*, **20**, 1170 (1952).

(8) R. M. Keefer and L. J. Andrews, THIS JOURNAL, **72**, 4677 (1950).

(9) R. E. Buckles and J. F. Mills, *ibid.*, **75**, 552 (1953).

(10) L. J. Andrews and R. M. Keefer, THIS JOURNAL, **74**, 458 (1952).

(11) J. A. A. Ketelaar and C. van de Stolpe, *Rec. trav. chim.*, **71**, 805 (1952).

shifted to the violet than with the ether system (*i.e.*, iodine in methanol was orange-brown, addition of fractional amounts of hydrogen fluoride gave orange-red solutions, and this color persisted over a large range of HF–methanol mixture compositions; a violet coloration appeared at higher methanol concentrations than in the ether system).

A noticeable characteristic of the system was the difference in solubility of iodine in the oxygenated solvents and in hydrogen fluoride. Starting with even a dilute solution of iodine in methanol, addition of hydrogen fluoride to about 75% by weight precipitated iodine, and precipitation continued with further addition of hydrogen fluoride. Iodine dissolves slowly in pure hydrogen fluoride.

Some question might be raised concerning the relatively small effects of the lower concentrations of the oxygenated electron donors on the iodine spectrum. It should be pointed out that hydrogen fluoride will compete with the iodine for the electrons of the donor, so that the effective concentration of the latter is considerably diminished. From the evidence as a whole it does not seem that hydrogen fluoride interacts significantly with iodine dissolved in it.

Visual observations and solution make-up were performed with test-tubes formed of fluoride-resistant aluminum phosphate glass ("Fluorex"). The experimental procedures for following absorption spectra in liquid hydrogen fluoride will be described elsewhere.[12]

(12) J. J. Katz and H. H. Hyman, *Rev. Sci. Instruments*, to be published.

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Significance of Fungus Growth in Analytical and Radiochemical Work with Strontium-containing Solutions[1]

BY S. Z. LEWIN, PETER J. LUCCHESI AND JOHN E. VANCE

RECEIVED JULY 15, 1953

Dipping-type Geiger–Mueller tubes employed in an investigation of rates of dissolution of radioactively-labeled crystals of strontium sulfate in distilled water were observed, in runs at room temperature, to acquire an activity which increased regularly with time. The activity was in the form of an adherent deposit on the surface of the tube, for when removed from the solution and rinsed repeatedly with water, the tube gave practically the same high count as it had when immersed in the solution. The activity recorded by the tube did not decrease at all when the tube was left immersed in a large volume of a solution containing a high concentration of stable Sr^{++}, showing that the radioactive strontium deposited on the tube does not enter into exchange with strontium ions in solution. Firm wiping of the tube removed a large part of the activity, but vigorous scrubbing with a mild abrasive was necessary to remove the remainder. The same effects were observed with glass, stainless steel, and glyptal-coated dip tubes at room temperature, but they were no longer observed when the experiments were carried out at temperatures near 0°.

These observations suggested that the deposit on the G–M tube might be a fungus capable of ingesting strontium. To test this hypothesis, the solution from one of the runs (consisting of two liters of water approximately saturated with $Sr^{89}SO_4$) was made 0.5% in dextrose, and set aside for one month at room temperature. A luxuriant growth of mold mycelium was present at the end of this period; it was filtered, air-dried and measured for radioactivity. A 0.24-g. sample of the mold mycelium gave 937 ± 10 counts per minute over background; the same weight of the solution gave 5 c.p.m.

The effect of $SrSO_4$ on the rate of growth of the fungus was investigated by preparing a number of 1% dextrose solutions, half of which were saturated with strontium sulfate, and inoculating all with equal amounts of the mold mycelium obtained as described above. After one day, the solutions containing $SrSO_4$ were decidedly more turbid, due to the mold, than the other solutions; after one month, the strontium-containing solutions had large colonies of mycelium which did not adhere to the walls of the flask, whereas the solutions containing the same nutrient, but no $SrSO_4$, showed only a thin growth which adhered firmly to the glass surface.

The fungus, when cultured on bread slices, produced black colonies having the appearance characteristic of *Rhizopus nigricans*. It is concluded that this mold grows in solutions of strontium sulfate (even when the only nutrient available is what falls into the solution from the laboratory air), that its growth is actually accelerated by the presence of the Sr^{++}, and that it ingests strontium and incorporates it into its structure in a form that does not exchange with strontium ions in solution.

Analyses of solutions of $SrCl_2$ and $SrSO_4$ in water by a colorimetric procedure[2] show that the concentration of strontium ions in these solutions may decrease considerably with time; for example, a 0.06% solution of $SrCl_2$ in distilled water in a glass-stoppered flask decreased in concentration by about 60% over a three-month period.

It follows that the possibility of loss of Sr^{++} due to fungus activity must be considered in all analytical and radiochemical work with strontium-containing solutions.

(1) This work was supported in part under Contract No. AT (30-1)-1256 between the Atomic Energy Commission and New York University.

(2) P. J. Lucchesi, S. Z. Lewin and J. E. Vance, *Anal. Chem.*, in press.

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The Preparation of Ethyl 1,1,2,2,3,4-Butene-3-hexacarboxylate

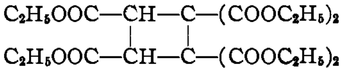
BY C. G. OVERBERGER AND PETER KABASAKALIAN

RECEIVED JULY 1, 1953

In connection with other work, we attempted to synthesize ethyl 1,1,2,2,3,4-cyclobutanehexacarboxylate (I). Reid and Sack[1] have recently re-

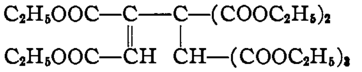
(1) E. B. Reid and M. Sack, THIS JOURNAL, 73, 1985 (1951).

ported an attractive synthesis for this ester. Repetition of this synthesis however has revealed that this reported product is actually its precursor, ethyl 1,1,2,2,3,4-butene-3-hexacarboxylate (II).



$$\begin{array}{l} C_2H_5OOC—CH—C—(COOC_2H_5)_2 \\ \qquad\qquad\quad | \qquad | \\ C_2H_5OOC—CH—C—(COOC_2H_5)_2 \end{array}$$

I



$$\begin{array}{l} C_2H_5OOC—C—C—(COOC_2H_5)_2 \\ \qquad\qquad\quad \| \quad | \\ C_2H_5OOC—CH\ CH—(COOC_2H_5)_2 \end{array}$$

II

Chromatographic analysis of the product resulting from this procedure on a Florisil column indicated that the material was homogeneous. The infrared absorption spectrum was found to be identical to the one obtained by Reid and Sack.[1] A carbon–carbon double bond absorption was present at 1635 cm.$^{-1}$. The ultraviolet absorption spectrum had an approximate maximum at 208 mμ with ϵ of 7,600 indicative of an α,β-unsaturated ester. At 208 mμ, the ϵ of ethyl maleate is 6,800; ethyl fumarate, 17,600, and ethyl ethylenetetracarboxylate, 11,200. The accuracy of these values is not completely satisfactory due to the accuracy of the instrument at 208 mμ; however, the approximate values obtained strongly support structure II.

Polarographic reduction gave a diffusion current which indicated the presence of one conjugated double bond per mole of ester. This was determined by comparing the diffusion current with those obtained for ethyl maleate, ethyl fumarate and ethyl ethylenetetracarboxylate. Ozonolysis gave oxalic acid in 40% yield. Only structure II is consistent with this evidence.

Experimental

Ethyl 1,1,2,2,3,4-Butene-3-hexacarboxylate (II).—Ethyl acetylenedicarboxylate was treated with ethyl 1,1,2,2-ethanetetracarboxylate in the presence of sodium ethoxide according to the procedure of Reid and Sack.[1] Ethyl 1,1,2,2,3,4-butene-3-hexacarboxylate (II) was isolated contaminated with ethyl ethanetetracarboxylate. The separation of starting material from product was only accomplished by successive fractional crystallization from 80% ethanol, the starting material being more insoluble. In a typical experiment a 50% yield of starting material, the ethanetetracarboxylate, m.p. 74–76°, was recovered, along with product. Recrystallization of the crude product gave a 16% yield, m.p. 77–78°. *Anal.* Calcd. for $C_{22}H_{32}O_{12}$: C, 54.10; H, 6.56. Found: C, 54.43; H, 6.66; mol. wt., 455 (cryoscopically in benzene).

Proof that starting material was obtained in 50% yield was afforded by a mixed melting point 74–76° and a comparison of the infrared spectra which were identical.

Ozonolysis of Ethyl 1,1,2,2,3,4-Butene-3-hexacarboxylate (II).—The method of Farmer, Gosal and Kon[2] was followed, who ozonized compounds of a similar type, for example, ethyl-α-carbethoxy-α-methyl aconitite. Ozonolysis was carried out for 13 hours with *ca.* 6% ozone (oxygen flow 1 liter/min.). The oxalic acid was isolated as calcium oxalate monohydrate in 40% yield (by titration). Liberation of the oxalic acid from the calcium salt with sulfuric acid followed by ether extraction gave crystalline oxalic acid, m.p. 189° dec.

Physical Data.—Infrared spectrum of a Nujol mull was determined with a Perkin-Elmer model 21 recording spectrophotometer with a sodium chloride prism.

Ultraviolet absorption measurements were determined on methanolic solutions with a Cary recording spectrophotometer, model 11.

Polarographic measurements on 0.001 *M* solutions in 50% ethanol (0.1 *N* KCl as electrolyte) were made using the Sargent recording polarograph, model XXI.

Acknowledgment.—Dr. E. B. Reid independently has recently obtained other evidence to substantiate structure II, which has been published elsewhere.[3] We are grateful to Dr. Reid for his coöperation and help.

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[2] E. H. Farmer, S. C. Gosal and G. A. R. Kon, *J. Chem. Soc.*, 1804 (1936).

[3] E. B. Reid, *Chem. and Ind.*, **32**, 846 (1953).

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Equilibria in Solutions of +3 and +4 Vanadium

BY LOUIS MEITES

RECEIVED MAY 15, 1953

In the course of some other work it became essential to secure estimates of the hydrolysis constants of vanadium in its +3 and +4 oxidation states. While the data for these calculations have been available for some years,[1] an error in their original interpretation has led to the belief that they cannot be used for this purpose. Since the constants themselves are of some interest and the method used in their derivation, though rather simple, appears not to have been previously described or used, it seems desirable to offer a brief account of our method and conclusions.

Vanadic ion, V^{+++}, hydrolyzes in two steps[2,3]

$$V^{+++} + H_2O = VOH^{++} + H^+; \quad K_1 = [VOH^{++}][H^+]/[V^{+++}] \quad (1)$$

$$VOH^{++} = VO^+ + H^+; \; K_2 = [VO^+][H^+]/[VOH^{++}] \quad (2)$$

Now

$$[V^{+++}] + [VOH^{++}] + [VO^+] = c \quad (3)$$

where c is the total analytical concentration of +3 vanadium, and the stoichiometry of the reactions gives

$$[H^+] = [VOH^{++}] + 2[VO^+] \quad (4)$$

Combining equations 3 and 4 and expressing $[V^{+++}]$ and $[VO^+]$ in terms of $[VOH^{++}]$ gives

$$[VOH^{++}]([H^+]^2 - K_1K_2)/K_1[H^+] = c - [H^+] \quad (5)$$

Equations 2 and 4 give

$$[VOH^{++}] = [H^+]^2/([H^+] + 2K_2) \quad (6)$$

Eliminating $[VOH^{++}]$ from equations 5 and 6 yields, finally

$$(c - [H^+])/[H^+] = ([H^+]^2 - K_1K_2)/(K_1[H^+] + 2K_1K_2) \quad (7)$$

Rearranging and differentiating, we secure

$$[H^+](\Delta[H^+]^2/\Delta(c - [H^+])) = K_1[H^+] + 2K_1K_2 \quad (8)$$

Values of the term $\Delta[H^+]^2/\Delta(c - [H^+])$ are secured from a large-scale plot of $[H^+]^2$ *vs.* $(c - [H^+])$ by measuring the slope of the tangent to the curve at each experimental point. These slopes, when multiplied by the corresponding values of $[H^+]$, give values of the right-hand side of equation 8.

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[1] G. Jones and W. A. Ray, THIS JOURNAL, **66**, 1571 (1944).

[2] J. J. Lingane and L. Meites, *ibid.*, **70**, 2525 (1948).

[3] S. C. Furman and C. S. Garner, *ibid.*, **72**, 1785 (1950).

These, when plotted against the concentration of hydrogen ion, should give a straight line whose slope is equal to K_1 and whose zero intercept is equal to $2K_1K_2$. Such a plot is shown as Fig. 1: from it we conclude that the hydrolysis constants of vanadic ion are

$$K_1 = [VOH^{++}][H^+]/[V^{+++}] = (1.2 \pm 0.3) \times 10^{-3}$$
$$K_2 = [VO^+][H^+]/[VOH^{++}] = (3 \pm 1.5) \times 10^{-4}$$

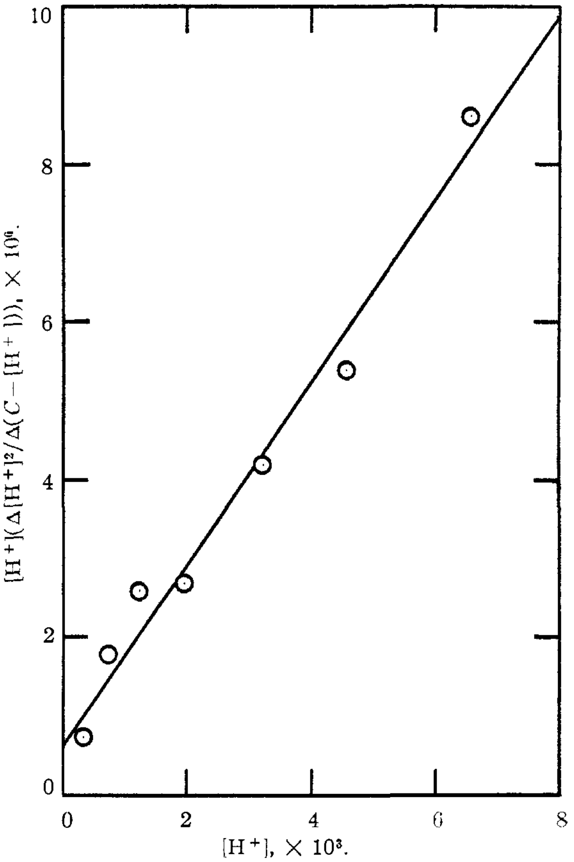

Fig. 1.—Plot of $[H^+](\Delta[H^+]^2/\Delta(c - [H^+]))$ *vs.* $[H^+]$ for the data of Jones and Ray on the *p*H values of vanadic sulfate solutions at concentrations between 0.0004 and 0.040 *M* in +3 vanadium.

The data on which these calculations were based were secured by Jones and Ray,[1] who measured the *p*H values of solutions of carefully purified vanadic sulfate at a number of concentrations from 0.0001 to 1 *M* in +3 vanadium. They assumed that VO^+ was the only hydrolysis product and attempted to compute a hydrolysis constant from their data, but failed because their equations could not correctly describe the relationship between the concentration of hydrogen ion and that of unhydrolyzed vanadic ion.

Two assumptions were made in these calculations: that the measured *p*H is equal to $-\log[H^+]$, and that all activity coefficients may be set equal to unity. In the range of ionic strengths used in constructing Fig. 1, these assumptions probably do not lead to errors much greater than those corresponding to the uncertainties in the data themselves.

In addition to its use in the calculation of consecutive hydrolysis constants, this method is in principle also suitable for the calculation of the dissociation constants of any dibasic acid from data on $[H^+]$ and *c*. In practice, however, it is useful only if K_1 and K_2 are not too widely separated: if this is not the case, the terms representing the contribution of the second dissociation or hydrolysis step become relatively very small and the experimental errors are enormously magnified in the calculation of K_2.

We have also used the data of Jones and Ray[1] on the *p*H values of vanadyl sulfate solutions to calculate the hydrolysis constant of VO^{++}. As the calculations are perfectly straight-forward, we shall record only the final result. For $0.0001 \leqslant c \leqslant 0.050$

$$K = [VOOH^+][H^+]/[VO^{++}] = (4.4 \pm 0.4) \times 10^{-6}$$

Acknowledgment.—It is a pleasure to acknowledge the interest and valuable assistance of Dr. S. C. Furman in the preparation of this manuscript.

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DEPARTMENT OF CHEMISTRY, YALE UNIV.
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Some Observations on High Temperature Gallate (III) Formation

BY THERALD MOELLER AND GLENDALL L. KING

RECEIVED MAY 18, 1953

Physicochemical studies[1] on gallium(III) salt solutions have shown the gallium ion to be comparatively acidic. Further information on the acidic properties of gallium in this oxidation state might be expected from investigations of reactions of the oxide with more basic oxides and hydroxides. Although gallate(III) formation in aqueous solution is well recognized,[1,2] the species present are somewhat difficult to characterize. On the other hand, high temperature reactions yield easily studied products. The preparation and properties of spinel-like gallates of the type $M^{II}Ga_2O_4$, where M^{II} is magnesium,[3,4] zinc[5] or cadmium,[6] have been described. These observations have been checked and extended to materials derived from other basic oxides. All products have been examined by X-ray diffraction techniques.

Experimental

Gallium metal, containing only spectroscopic traces of impurities, was converted to the oxide by dissolution in acid, precipitation with ammonia, and ignition. Weighed samples (0.05–0.10 g.) of gallium(III) oxide were sintered with sufficient quantities of various chemically pure metal oxides or nitrates to give 1:1 mole ratios of the two oxides. Heating was effected in porcelain containers, the conditions being summarized in Table II. The cooled products were stirred thoroughly and sampled carefully for X-ray diffraction studies. Powder patterns were obtained with Hayes powder diffraction cameras of 7 cm. radius, using Machlett,

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[1] T. Moeller and G. L. King, *J. Phys. Colloid Chem.*, **54**, 999 (1950).

[2] B. N. Ivanov-Emin and Ya. I. Rabovik, *J. Gen. Chem.* (*U.S.S.R.*), **14**, 781 (1944).

[3] H. Hauptmann and J. Novák, *Z. physik. Chem.*, **B15**, 365 (1932).

[4] F. Machatschki, *Z. Krist.*, **82**, 348 (1932).

[5] F. Buschendorf, *Z. physik. Chem.*, **B14**, 297 (1931).

[6] W. Rüdorff and B. Reuter, *Z. anorg. Chem.*, **253**, 194 (1947).

Hayes and Picker tubes. In all cases, copper targets with nickel filters were operated at 40 kv. and 15 ma.

Results and Discussion

An analysis of the powder patterns obtained[7] gave the d spacings summarized in Table I as characteristic of the gallates formed, other lines of low intensity in the patterns being those of small quantities of unreacted starting materials. Spinel formation is indicated with copper(II), magnesium, zinc and cadmium, results for the last three agreeing well with those previously reported.[3-6] Data for the lanthanum compound, $LaGaO_3$, indicate a perovskite type of structure, a structure characteristic of the comparable compounds $LaFeO_3$, $LaMnO_3$ and $LaCrO_3$.[8] The perovskite structure appears probable for the strontium compound as well (compare SrV_2O_4[9]), but the data for the barium compound are completely different and do not indicate a cubic structure by the "slide-rule test." An apparently hexagonal structure is tentatively assigned to this material. No evidences of gallate formation were obtained with calcium materials.

TABLE I

SUMMARY OF d VALUES FOR GALLATES

Mg-Ga_2O_4	Cu-Ga_2O_4	Zn-Ga_2O_4	Cd-Ga_2O_4	La-GaO_3	Sr-Ga_2O_4	Ba-Ga_2O_4
4.78	4.81	4.83	4.96	2.73^a	2.86^a	3.15^a
2.93^d	2.94^d	2.96^d	3.05^d	1.93^c	2.02^c	2.68^b
2.50^a	2.51^a	2.52^a	2.59^a	1.58^b	1.65^b	2.17^f
2.07	2.08	2.09	2.15	1.37	1.43	2.04^d
1.69	1.70	1.71	1.77	1.22	1.28	1.97^f
1.60^c	1.60^c	1.60^c	1.66^c	1.12	1.17	1.82^f
1.47^b	1.47^b	1.48^b	1.52^b	1.03	1.08	1.70^e
1.32	1.32	1.33	1.37	0.966	1.01	1.68^e
1.25	1.25	1.26	1.30	0.865	0.952	1.63^c
1.20	1.20	1.21	1.24		.903	1.55^e
1.11	1.11	1.12	1.15		.862	1.50^f
1.08	1.08	1.09	1.12		.824	1.44^f
1.04	1.04	1.04	1.07		.791	1.28^f
						1.24^f

[a] First intensity. [b] Second intensity. [c] Third intensity. [d] Fourth intensity. [e] Weak (W). [f] Very weak (VW).

Unit cell lengths (a_0) for the spinel and perovskite structures are summarized in Table II. Where other data are available for comparison, agreement is excellent. It is apparent that unit cell length varies directly with dipositive cation radius in the spinels. Increase in cation radius beyond a certain value destroys the spinel structure. From the data presented here, it appears that spinel-like gallates can result only when this radius is below 1.00 Å. Increase in cation radius beyond this limit gives first the perovskite (also cubic) and then a non-cubic arrangement. Cation radius is not, of course, the only structure-determining factor, but it appears to be of importance.

TABLE II

HIGH TEMPERATURE GALLATE(III) FORMATION

Material sintered with Ga_2O_3	Sintering conditions, hr.	°C.	Results from powder patterns	a_0, Å.	Cation radius Å.
MgO	5	1250	$MgGa_2O_4$: spinel	8.29 ± 0.05	0.65
CuO	22	900	$CuGa_2O_4$: spinel	8.31 ± .05	.70
ZnO	22	900	$ZnGa_2O_4$: spinel	8.37 ± .05	.74
CdO	20	900	$CdGa_2O_4$: spinel	8.59 ± .05	.97
$Sr(NO_3)_2 \cdot 4H_2O$	12	850	$SrGa_2O_4$: perovskite(?)	*ca.* 4.04	1.13
	20	900			
$Ba(NO_3)_2$	12	850	$BaGa_2O_4$: hexagonal(?)		1.35
	20	900			
La_2O_3	7	1250	$LaGaO_3$: perovskite	3.86 ± 0.05	1.15

Although high basicity in general promotes reaction between a metal oxide and gallium(III) oxide, factors such as surface effects, previous treatment and volatility may nullify this trend. Thus, cadmium oxide reacts readily at 900°, but magnesium oxide reacts scarcely at all even on sintering for 72 hr. at 1000°. This is in agreement with the observations of Hauptmann and Novák[3] and is paralleled by similar observations on the magnesium oxide–indium(III) oxide system.[10]

Acknowledgment.—Support received from the Office of Naval Research is gratefully acknowledged.

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(10) T. Moeller and J. G. Schnizlein, *J. Phys. Chem.*, **51**, 771 (1947).

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The Diffusion Coefficient and Molecular Weight of Alkaline Phosphatase

BY JAMES C. MATHIES AND E. D. GOODMAN

RECEIVED JULY 20, 1953

In 1935, Albers and Albers[1] reported diffusion experiments on alkaline phosphatase from swine kidneys, from which they calculated the molecular weight of the enzyme to be 6,000 to 10,000. This is an exceptionally low value for the molecular weight of an enzyme. Kraemer, *et al.*,[2] observed that serum alkaline phosphatase was associated with serum globulins in the ultracentrifuge. Hence a redetermination of the diffusion coefficient of the enzyme appeared of value.

Experimental

Diffusion coefficient determinations were carried out using the diaphragm cell method of Anson and Northrop,[3] as described by Northrop, *et al.*[4] Two cells were used having capacities of 42.4 and 47.7 ml., respectively. They were fabricated with Corning grade "F" fritted glass discs. The cells were calibrated with 2 *N* NaCl at both 5.0 and 25.0° in the manner described by Northrop.[4] The cell constants of 0.301 and 0.272, respectively, were repeatedly redetermined over the two-year period of use and the values obtained were constant within ±0.3%. Only differential diffusion coefficients were determined. Each determination with enzyme consisted of 4 to 5 consecutive 24-hour diffusion intervals. Constancy in the rate of diffusion was usually observed after 48 hours, indicating adequate equilibration of the membrane after this time.

Enzyme assays and preparations were made as previously

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(1) H. Albers and E. Albers, *Z. physiol. Chem.*, **232**, 165, 189 (1935).

(2) E. O. Kraemer, L. Weil, E. B. Sanigar and M. T. Allen, *J. Franklin Institute*, **232**, 587 (1941).

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TABLE I

DIFFUSION OF ALKALINE PHOSPHATASE AT 5°

Cell no.	pH, 25°	Solvent	Enzyme			Diffusion coefficient, cm.^{2} per day	
			Source	Concentration, P.U./ml.	Specific activity, P.U./mg./P.N.	Protein	Enzyme
3	7.2	0.1 ionic strength phosphate buffer	Albers' horse kidney preparation[a]	584	250 approx.	0.0348	0.0238
3	6.9	0.1 M phosphate buffer also 0.5 M NaCl	Albers' horse kidney preparation	602			.0218
3	7.26	0.1 ionic strength phosphate buffer	Swine kidney[b]	1540	600		.0221
3	9.02	0.2 M veronal also 0.01 M DL-alanine	Swine kidney	1600	600		.0200
4	9.04	0.2 M veronal also 0.01 M DL-alanine	Swine kidney	1180	600		.0190
3	7.2	0.1 ionic strength phosphate buffer	Calf intestinal mucosa (Armour's)	120	111		.0161
3	7.2	0.1 ionic strength phosphate buffer	Albers' sheep kidney preparation[a]	178	77		.0180
3	7.2	0.1 ionic strength phosphate buffer	Swine kidney[b]	2800	2500	.0236	.0170
3	7.2	0.1 ionic strength phosphate buffer	Swine kidney	3230	1050	.0257	.0178
3	7.2	0.1 ionic strength phosphate buffer	Swine kidney	756	1050		.0163

[a] Ref. 1. [b] Ref. 5, 7.

described.[5,6,7] Swine kidney alkaline phosphatase preparations employed in this investigation are among the purest that have been reported. Protein was determined colorimetrically by the procedure of Lowry, *et al.*,[8] or by Kjeldahl.[9] Improved accuracy of the colorimetric determination of protein appeared to be obtained by carrying out the entire procedure at 25°. Twice crystallized ovalbumin was used as a standard protein. The concentrated ovalbumin solution was stored at −18° and contained 50% glycerol. Under these conditions it was adequately stable.

Diffusion coefficients for crystalline ovalbumin and crystalline swine pepsin were determined, giving values in accord with the literature.

Results and Discussion

Values obtained at 5° are compiled in Table I. Five additional experiments were carried out at 25° giving an average value of 0.038 cm.^{2} per day. Molecular weight calculations from this latter figure are in fair agreement with those obtained at 5°. It can be seen that the diffusion coefficient ranges between 0.016 to 0.024 cm.^{2} per day, irrespective of the solvent, pH, enzyme source, purity or concentration. In the last two experiments, in which the diffusion of protein was measured, it is apparent that protein is diffusing at a faster rate than enzyme, indicating the presence of impurities, but even so the values are in the same order of magnitude.

Molecular weight calculations from these data give values of 500,000 and over. Admittedly determinations in this molecular size range must be considered to be only approximations. Yet there is complete disagreement between our findings and those of Albers.[1] With this in mind, several experiments with commercial, graded porosity ultra-filters were carried out, and these, too, were indicative of a large molecular weight.

A point of interest is the similarity in results irrespective of the enzyme source. At least in this respect, it has not been possible to demonstrate significant differences between alkaline phosphatases from various sources.

The differential diffusion coefficient for several types of alkaline phosphatase has been determined using the diaphragm cell method.' An average value of 0.0192 cm.^{2} per day was obtained at 5°. Molecular size estimations from these data, making the usual assumptions as to shape and density, are from 500,000 to 1 million, with the best estimation being 800,000. No significant difference was detected with respect to this property, between intestinal and kidney alkaline phosphatase, the latter enzyme being obtained from three species.

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(5) J. C. Mathies, *Biochim. Biophys. Acta*, **7**, 387 (1951); *Science*, **115**, 144 (1952).

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Restricted Coupling in a Substituted Phenol[1]

BY ROBERT L. MCGEACHIN, STANLEY M. PRICE[2] AND RASHID M. DAJANI

RECEIVED JULY 2, 1953

As part of the preparation of 4-arsonophenylazo derivatives of various phenols as potential carcinolytic agents, the coupling of diazotized p-arsanilic acid with 4-(1,1,3,3-tetramethylbutyl)-phenol (also commonly called octylphenol[3] or diisobutylphenol) (I) was studied. It was found that even though both positions in the phenol ortho to the hydroxyl group were unsubstituted, only one 4-arsonophenylazo group could be introduced even when an excess of the diazonium salt was used. This was somewhat surprising since tyrosine[4] couples with two moles of diazonium salt quite readily. Other 4-substituted phenols[5] also have shown coupling in both ortho positions.

It was necessary to add ethyl alcohol to the medium to keep the octylphenol in solution in alkali for the coupling reaction and it was thought that possibly the alcohol might have caused decomposition of enough of the diazonium salt to prevent coupling in both ortho positions. However, no phenylarsonic acid, the expected product from such decomposition, could be isolated from the reaction mixture. Furthermore, when the mono-substi-

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(1) This work was aided by a grant to the University of Louisville from the Kentucky State Medical Research Commission.

(2) Student Summer Research Scholar, 1952.

(3) Kindly furnished by Rohm and Haas Co.

(4) H. Pauly, *Z. physiol. Chem.*, **94**, 284 (1915).

(5) L. Pauling, *et al.*, THIS JOURNAL, **64**, 2994 (1942).

tuted product was isolated, dissolved in alkali in the absence of alcohol and subjected to further attempts at coupling, apparently little, if any, additional coupling occurred. The arsenic content of the product isolated was only a little greater than that calculated for the mono-substituted product and far below that calculated for the di-substituted product. Chromatograms of an aqueous solution of the sodium salt of the product on an activated alumina column showed only one major band in the column on development with water.

Although neither expected nor, from a study of the structure, explainable to the authors, apparently the configuration of the monosubstituted product, 2-(4-arsonophenylazo)-4-(1,1,3,3-tetramethylbutyl)-phenol, is such that there is steric hindrance to the introduction of a second 4-arsonophenyldiazo group.

Experimental

Coupling of Octylphenol with Diazotized *p*-Arsanilic Acid.—To a solution of 2.37 g. of I (0.0115 mole) in 80 ml. of 5% sodium hydroxide and 50 ml. of 95% ethanol at 5° was slowly (1 hr.) added, with stirring, the solution of diazonium salt prepared from 5 g. of *p*-arsanilic acid (0.023 mole) in the usual manner. The resultant blood-red solution was placed in the refrigerator overnight. The product, a red-orange solid, was precipitated by addition of concd. hydrochloric acid, filtered, redissolved in 5% sodium hydroxide, extracted three times with ether, reprecipitated with concd. hydrochloric acid, washed with water and dried at 110° overnight; yield 2.2 g. (43%).

Anal. Calcd. for $C_{20}H_{27}AsN_2O_4$: As, 17.3. Calcd. for $C_{26}H_{32}As_2N_4O_7$: As, 22.7. Found: As, 17.8, 17.5, 17.0, 17.4.

A portion of the product was dissolved in 5% sodium hydroxide, treated with excess diazotized *p*-arsanilic acid and worked up in the manner described above. The product isolated was a red-orange solid.

Anal. Found: As, 18.0.

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The Actinide–Lanthanide Analogy as Exemplified by Solvent Extraction Behavior

BY D. F. PEPPARD, P. R. GRAY AND M. M. MARKUS

RECEIVED JULY 30, 1953

Interest in the actinide hypothesis has been revived in recent years, and due in large part to the studies of Seaborg and co-workers,[1] who have correlated a large mass of data pertaining to the lanthanides(III) and to the elements(III) of atomic numbers 89–98 and successfully applied the hypothesis in devising separations procedures for the trivalent transuranic elements, the term actinide has had wide acceptance as a generic term for those elements of atomic number ranging from 89 (actinium) to 98 (californium, the element of highest atomic number known). However, the wide variation, even though it is a regular one, within this grouping of elements with respect to the most stable valence state in aqueous solution has led to considerable difference of opinion, and Bouissieres and Haissinsky[2] consider the actinide hypothesis untenable. For the purpose of pointing out the similarities between representatives of this grouping of elements, in the trivalent state, and trivalent lanthanides the following comparison of their solvent extraction behavior is presented. This analogy may be compared with the well-documented analogy with respect to ion-exchange behavior.[3]

Distribution ratio studies were performed in a manner described previously,[4] using β-active 40-h La^{140}, 275-d Ce^{144}(III), 2.6-y Pm^{147}, *ca.* 5.4-y Eu^{152,154}(III) and 6.1-h Ac^{228} and α-active 24,100-y Pu^{239}(III), *ca.* 500-y Am^{241}(III), and 150-d Cm^{242}.[5] So that a comparison of relative behavior should be unambiguous, Pm was present in all solutions involved in obtaining Pu, Am and Cm data, and Am was present in all solutions involved in obtaining lanthanide and Ac data. Consequently, each set of measurements had an internal standard. For example, a set of Pu–Am–Cm data was discarded as internally inconsistent unless the K of Pm throughout the set had a constant value within 2%.

A set of self-consistent Pu–Am–Cm data having been established, data for Ac were obtained depending upon Am as the internal standard, etc. Radiometric assays were performed as described previously,[4] aluminum absorbers being used to eliminate α-interference in β-counting. It should be noted that for purposes of this discussion the distribution ratio, K, is considered to be equal to the ratio of measured radioactivities associated with equal aliquots of the equilibrated organic and aqueous phases, respectively.

The results of these experiments show that log K is a linear function of atomic number (at least in the region studied)[5] for both actinides(III) and lanthanides(III) using tri-*n*-butyl orthophosphate,[6] $(n\text{-}C_4H_9O)_3PO$, as the organic phase and 15.6 M HNO_3, 12.0 M HNO_3 or 12.0 M HCl as the aqueous phase. This relationship has been reported previously[4] for the lanthanides in a tributyl phosphate–nitric acid system.

Likewise, the nitric acid dependency of K for Am is found to parallel closely that of K for Pm. The crossing of the acid-dependency curves for Am and Cm has been demonstrated, the crossing of these curves being reminiscent of the crossing of the corresponding curves for two lanthanides or for Pm and Y.[4]

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(1) Among several pertinent publications may be mentioned: G. T. Seaborg, *Chem. Eng. News*, **23**, 2192 (1945); K. Street, Jr., and G. T. Seaborg, THIS JOURNAL, **72**, 2187 (1949); G. T. Seaborg, R. A. James and L. O. Morgan, Natl. Nuclear Energy Ser., Div. IV, **14B**, Transuranium Elements, Pt. II, 1525 (1949); G. T. Seaborg, R. A. James and A. Ghiorso, *ibid.*, p. 1554; and L. B. Werner and I. Perlman, *ibid.*, p. 1586.

(2) G. Bouissieres and M. Haissinsky, *Bull. soc. chim. France*, [5] **18**, 557 (1951).

(3) K. Street, Jr., and G. T. Seaborg, ref. 1.

(4) D. F. Peppard, J. P. Faris, P. R. Gray and G. W. Mason, *J. Phys. Chem.*, **57**, 294 (1953).

(5) The authors were unable to stabilize the trivalent state of Pu in the nitric acid systems studied, and Np(III) could not be studied in either the nitric acid or hydrochloric acid systems. In other studies, the absence of Ce(IV) was assured by the addition of a small quantity of hydrogen peroxide to the feed make-up at 60°; and Pu(III) was obtained by reduction of Pu in any combination of valence states with ferrous ion. All of the other tracers used were automatically obtained in the trivalent state by evaporation with nitric acid or hydrochloric acid.

(6) Tri-*n*-butyl orthophosphate, obtained from Commercial Solvents Corporation, was washed with several portions of 10% aqueous sodium carbonate prior to acid pre-equilibration to assure the absence of phosphoric acid. $(C_4H_9O)(HO)_2PO$ and $(C_4H_9O)_2(HO)PO$.

The distribution ratio for Am has been shown to have an approximate third-power dependence on the tributyl phosphate concentration, expressed as volume per cent. In this, also, Am behavior parallels that of Pm.

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Coprogen, the Isolation of a New Growth Factor Required by *Pilobolus* Species

BY C. PIDACKS, A. R. WHITEHILL, L. M. PRUESS, C. W. HESSELTINE, B. L. HUTCHINGS, N. BOHONOS AND J. H. WILLIAMS

RECEIVED AUGUST 10, 1953

The complex nutrition of the genus *Pilobolus* has been described by several investigators.[1,2] These workers found it necessary to add dung or dung extracts to their culture medium. In a general survey of the distribution of the factor(s) that was essential for the growth of *Pilobolus kleinii*, it was found that the dung extracts could be replaced by the fermentation liquors of a number of species of bacteria and fungi. The isolation of a crystalline, biologically-active compound from such sources has been announced.[3] This substance has been designated "Coprogen" because of its ability to stimulate the growth of the *Coprophyllic* fungi. The method of assay and the general cultural and nutritional characteristics of the genus *Pilobolus* has also been described.[3,4]

Hesseltine and co-workers[4] listed a number of microörganisms that had been tested for their ability to produce the factor essential for *Pilobolus kleinii*. Culture *Penicillium* sp. appeared to be the most feasible organism for large scale production of the growth substance and was, therefore, used to produce adequate amounts of the compound for isolation.

The purification of the compound was initially done by solvent extraction, adsorption and elution from florisil and partition chromatography. Later procedures eliminated the use of the florisil adsorption step.

Crystallization of the active compound was effected by dissolving the active lyophilized fraction from the partition chromatogram in absolute ethanol. On standing a brick-red, crystalline compound separated. If only a slight trace of moisture was present, the compound tended to hydrate and precipitated in an amorphous form. The crystalline material is practically insoluble in ethanol and, for recrystallization, the compound must be dissolved in water, lyophilized and then again crystallized from ethanol.

Elemental analysis of the compound indicated the presence of carbon, hydrogen, nitrogen, oxygen and iron. The organo-iron nature of the compound and the fact that certain metallo porphyrins are growth factors for microörganisms[5-8] suggested that perhaps Coprogen was related to the porphyrin compounds. The absorption spectra and chemical properties of the isolated compound ruled against this possibility.

Coprogen exhibited a broad absorption maximum at 440 mμ with an $E_{1\,\text{cm.}}^{1\%}$ of 36.6 in 50% ethanol. The Soret band which is characteristic of heme compounds was clearly missing.

When Coprogen was dissolved in dilute alkali, ferric hydroxide precipitated and the ultraviolet absorption spectrum of the compound was destroyed. Concomitantly, the biological activity of the compound also was destroyed.

Experimental

Assay Methods.—Initially, the activity of the various fractions was determined by the plate assay method. In subsequent work, *Pilobolus kleinii* was cultured in liquid media and the weight of the mycelia was used as a measure of growth.[4]

Fermentation.—Culture *Penicillium* sp. was cultured in large scale fermentation apparatus equipped for agitation, aeration and temperature control. The medium contained 1% Bacto peptone, 0.1% ammonium sulfate, 0.1% sodium acetate and 0.1% potassium dihydrogen phosphate. Tap water was used throughout. After inoculation the fermentation was continued for three days at a temperature of 26–28° and with an aeration rate of 1 volume of air per volume of medium per minute. Filter-cel (0.1%) was added and the mycelium and Filter-cel was removed in a filter press.

Solvent Extraction.—To the clear filtrate was added 500 g. of ammonium sulfate per liter. The solution was then extracted twice with one-quarter volumes of butanol. The butanol extracts were combined and then concentrated under reduced pressure with the slow, constant addition of water. The distillation was continued until the butanol was completely removed and only a small volume of water remained.

The solution was filtered to remove any suspended matter and then extracted with approximately four one-quarter volumes of benzyl alcohol. The benzyl alcohol extracts were combined and then extracted with a one-tenth volume of water which removed inorganic salts and other impurities. Two volumes of ether or ethyl acetate were added to the combined benzyl alcohol extracts and the solution was then extracted with several one-quarter volumes of water. The activity and color were almost quantitatively extracted into the aqueous phase. The aqueous extracts were combined, concentrated to remove solvents and then lyophilized. The dried product was orange-brown in color, stable for storage and very convenient to handle.

Partition Chromatography.—"Celite 545"[9] (50 g.) was mixed with 25 ml. of the aqueous phase of a mixture of butanol:ethyl acetate:0.01 *N* hydrochloric acid (2:1:1). The moist "Celite" was packed into a column 2 cm. i.d. × 60 cm. Five hundred mg. of the crude lyophilized material was dissolved in 25 ml. of the solvent phase. This solution was placed in the column and immediately followed by fresh solvent.

If the column was extruded after the solvent front had reached the end of the column, several well-defined zones were evident. The first zone was purple and gave a strong $FeCl_3$ test. The second zone was orange, reacted strongly positive with $FeCl_3$ and contained Coprogen. The third and fourth zones were white and pale purple, respectively, and both zones gave a strong $FeCl_3$ test.

A flowing chromatogram was used and the fraction containing the orange band was collected, neutralized with sodium hydroxide and then concentrated under vacuum.

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(2) E. A. Bessey, *Mich. Acad. Sci.*, **32**, 15 (1948).

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(8) J. D. Liberman and M. J. Pickett, *Bact. Proceedings*, P, 54 (1952).

(9) Johns-Manville Co., Lompoc, California.

The residue was dissolved in water and thence extracted into benzyl alcohol and finally partitioned into water as described above. The aqueous solution was lyophilized to yield a chromatographically pure product. The amorphous compound was readily soluble in water, methanol, ethanol, *n*-propanol, benzyl alcohol and the various cellosolves but was insoluble in ether, ethyl acetate, chloroform, benzene or the cellosolve esters.

For crystallization the amorphous compound was dissolved in absolute ethanol. On standing Coprogen separated as clusters of fine, dark brick-red needles. After drying at 110° under reduced pressure, the following analytical values were obtained.

Anal. Found: C, 50.96; H, 6.83; N, 10.26; Fe, 6.61.

Tests for halogen, phosphorus and sulfur were negative. When the compound was dissolved in dilute sodium hydroxide, ferric hydroxide precipitated. Assay with *P. kleinii* indicated that the alkali-treated solution was devoid of growth-promoting activity.

Ultraviolet Absorption Spectra.—Coprogen was dissolved in 50% ethanol at a concentration of 50 mc. per ml. and the ultraviolet absorption spectra was determined with a Beckman Model DU spectrophotometer.

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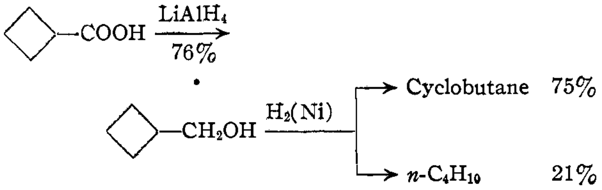
Synthesis of Cyclobutane by the Dehydroxymethylation Method

BY HERMAN PINES, H. G. RODENBERG[1] AND V. N. IPATIEFF[2]

RECEIVED JULY 29, 1953

The synthesis of cyclobutane and its intermediates has been widely studied. One of the procedures used in the preparation of cyclobutane involves the oxidation of methylenecyclobutane with performic acid to 1-(hydroxymethyl)-1-cyclobutanol which on cleavage with lead tetraacetate forms cyclobutanone[3]; the latter is then reduced to cyclobutane. The cyclobutanone also was prepared in 30–36% yield by ozonization of methylenecyclobutane.[4] Another method of synthesizing cyclobutanone in good yields consisted of treating ketene with diazomethane.[5] Other procedures of preparation of cyclobutane utilize cyclobutanecarboxylic acid as a starting material. This acid is converted by a series of known reactions to cyclobutylamine, which, by exhaustive methylation and decomposition, yields cyclobutene.[6] The latter is then hydrogenated to cyclobutane.[7] Cason and Way[8] synthesized cyclobutane by bromination of cyclobutanecarboxylic acid to cyclobutyl bromide and then converted the latter to cyclobutane *via* the Grignard reaction. The over-all yield from cyclobutanecarboxylic acid was about 39%.

It has now been found that the preparation of cyclobutane from cyclobutanecarboxylic acid can be achieved in a 57% yield by a two-step synthesis which involves the reduction of the acid to cyclobutylmethanol and the catalytic dehydroxymethylation of the latter to cyclobutane. This can be presented by the equations



n-Butane is the only by-product of the dehydroxymethylation reaction and the formation of this compound could probably be suppressed by adjusting the experimental conditions. The cyclobutane formed is 99–100% pure.

The dehydroxymethylation method, which has been used previously for the preparation of various hydrocarbons,[9] could very well lend itself to the synthesis of various alkylcyclobutanes.

Experimental Part

Cyclobutylmethanol.—It was prepared by the reduction of cyclobutanecarboxylic acid[10,11] according to the general procedure described in the literature[12] with the modification that a slurry of 9.2 g. (0.24 mole) of lithium aluminum hydride in 350 ml. of ethyl ether was added to a solution of 27 g. (0.27 *M*) of cyclobutanecarboxylic acid. The cyclobutylcarbinol distilled at 142–143.5°, $n^{20}\mathrm{D}$ 1.4450, yield 76%.

Cyclobutane.—The dehydroxymethylation was made in a 450-ml. capacity rotating autoclave. Cyclobutylmethanol, 17.2 g., and 1.8 g. of UOP nickel-kieselguhr catalyst[13] were placed in the autoclave which was then pressured with 100 atmospheres of hydrogen and heated at 154° for 5 hours. The final pressure at room temperature was 87 atmospheres. The non-condensable gases consisted of 89% hydrogen and 10% methane. The remainder of the product which was distilled on a low temperature Podbielniak column[14] consisted of 75% cyclobutane and 21% *n*-butane and the residue consisted of material boiling above 130°.

The cyclobutane was analyzed on a Consolidated Engineering Corporation Mass Spectrograph Type 21-103.[15] The remarkable agreement with the spectrum of 99–100% purity cyclobutane published in the American Petroleum Institute's Research Project 44 catalog of mass spectra, serial 416, indicates that the cyclobutane prepared was of similar purity.

The infrared spectrum of the cyclobutane was identical with that reported in the literature.[3]

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(1) Universal Oil Products Company Fellow, 1951.

(2) Deceased, November 29, 1952.

(3) J. D. Roberts and C. W. Sauer, THIS JOURNAL, **71**, 3925 (1949).

(4) C. P. Krimmel, Ph.D. Thesis, Pennsylvania State College, 1945.

(5) (a) P. Lipp and R. Koster, *Ber.*, **64**, 2823 (1931); (b) Sj. Kaarsemaker and J. Coops, *Rec. trav. chim.*, **70**, 1033 (1951).

(6) R. Willstätter and W. U. Schmaedel, *Ber.*, **38**, 1992 (1905).

(7) R. Willstätter and J. Bruce, *ibid.*, **40**, 3979 (1907).

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(10) G. G. Heisig and F. H. Stodola, *Org. Syntheses*, **23**, 16 (1943).

(11) The yield of diethyl cyclobutanedicarboxylate can be raised to 60% by modifying the experimental conditions: J. Cason and C. F. Allen, *J. Org. Chem.*, **14**, 1036 (1949).

(12) R. F. Nystrom and W. G. Brown, THIS JOURNAL, **69**, 1197 (1947).

(13) V. N. Ipatieff and B. B. Corson, *Ind. Eng. Chem.*, **30**, 1039 (1938).

(14) The distillation was made by M. J. Stross, Universal Oil Products Company.

(15) The mass spectrographic analysis was made by J. B. Grutka, Physics Laboratory, Universal Oil Products Company.

Green Sulfur, A New Allotropic Form

By Francis Owen Rice and Jerome Ditter

Received July 13, 1953

In a previous publication,[1] it was shown that if sulfur vapor in a flowing system at a pressure of about 0.2 mm. and a temperature of about 500°, is suddenly cooled to liquid nitrogen temperatures, a purple solid, probably S_2, condenses out. During the course of this work, a green modification sometimes appeared but the authors[1] did not study this form beyond showing that it was not, as they originally thought, a mixture of yellow and purple sulfur. This hypothesis was disproved by grinding together, under liquid nitrogen, mixtures of purple and ordinary yellow sulfur and showing that there was no formation of green sulfur. In this note we shall give an account of a study of the preparation and properties of green sulfur.

When sulfur, below its melting point, is sublimed in a vacuum onto a liquid nitrogen-cooled surface, only yellow sulfur is obtained. If, however, the sulfur is melted, a green form mixed with yellow condenses on the liquid nitrogen-cooled surface. In order to determine if the green form can be prepared by condensing sulfur vapor in equilibrium with liquid sulfur, we constructed the apparatus shown in Fig. 1. The bulb, A, containing sulfur was evacuated with a separate line which was sealed off before making a run. The temperature of the bath was slowly raised to 200° but at no time did the deposit on the liquid nitrogen-cooled finger have a color other than that of yellow sulfur. Deposition was sufficiently slow to ensure near equilibrium conditions in the vapor in the bulb A since even at 200°, where the vapor pressure of sulfur is 2.12 mm., a visible deposit on the cold finger was obtained only after several minutes.

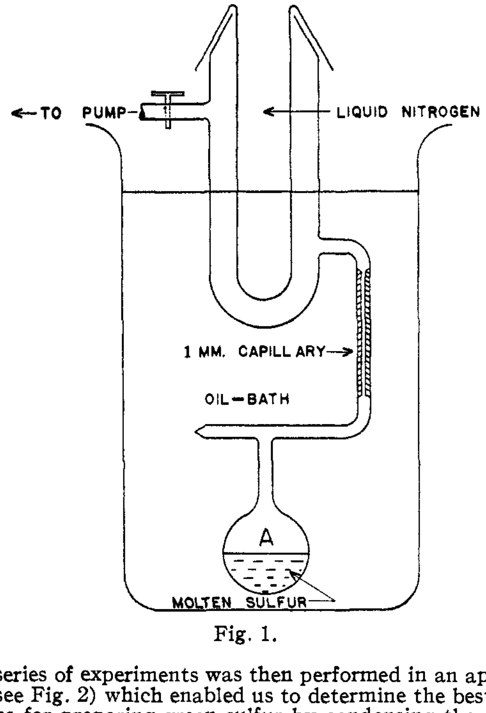

Fig. 1.

A series of experiments was then performed in an apparatus (see Fig. 2) which enabled us to determine the best conditions for preparing green sulfur by condensing the vapor under non-equilibrium conditions. The furnace used in this apparatus was much shorter than that used in the preparation of purple sulfur and therefore, in this experiment, the conditions were not such as to favor the attainment of equilibrium. As might be expected from our preliminary experiment with green sulfur, this form appears even when the furnace is not heated provided the oil-bath is kept above the melting point of sulfur. If the sulfur is maintained below its melting point by keeping the oil-bath in the range 80–110°, only yellow sulfur appears on the cold finger if the furnace is at room temperature but, if its temperature is raised to about 200°, a slightly greenish deposit is obtained which gradually changed to a very deep green as the furnace temperature is raised to about 400°. When the furnace temperature approaches 450°, purple sulfur begins to form as in the experiments previously reported.[1] These results with solid sulfur are obtained both with amorphous and crystalline sulfur.

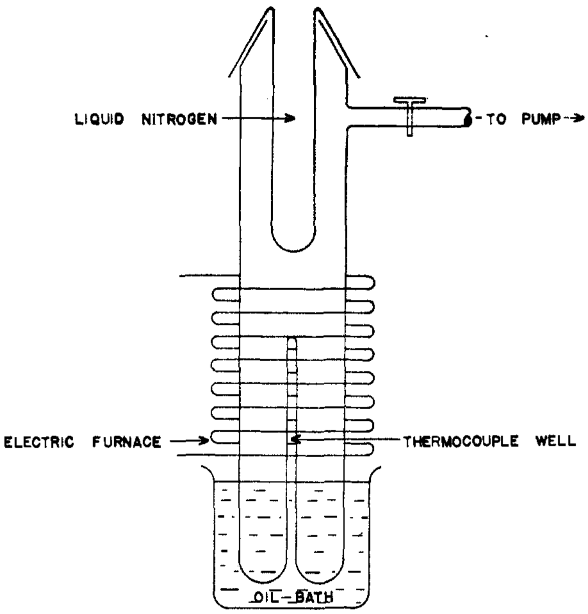

Fig. 2.

We then made a new series of experiments in which the furnace temperature was kept constant at about 200° and the temperature of the sulfur was raised from about 80 to about 170°. As mentioned previously a deposit, colored slightly greenish, was obtained in the lower range of temperature of the oil-bath but as its temperature was raised, the color deepened until in the range of 150–170° an intensely green sublimate formed on the cold finger.

We offer the following tentative hypothesis to account for these phenomena. We think that the molecule of green sulfur is S_8, in which the eight-membered ring of ordinary stable sulfur has opened to form an S_8 chain. This would explain why subliming solid sulfur does not give the green form but subliming liquid sulfur does, since[2] liquid sulfur in the range 30–40° above its melting point appears to be predominantly S_8 chains. The behavior of S_8 rings in the vapor may be understood if we assume that the speed of decomposition of the S_8 chain molecules into smaller molecules is smaller than the speed of the rupture of the S_8 ring molecules into S_8 chain molecules.

We have no conclusive single piece of evidence for this view but it is in agreement with several properties of the green form. This form is stable indefinitely at liquid nitrogen temperatures but changes into yellow sulfur at a measurable rate above −100°. At room temperature the change occurs in a few seconds. When the yellow sulfur formed by transition from the green variety is analyzed by extraction with carbon disulfide in a Soxhlet extractor, the composition is approximately

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[1] F. O. Rice and C. N. Sparrow, This Journal, **75**, 848 (1953).

[2] G. Gee, *Trans. Faraday Soc.*, **48**, 315 (1952).

10% amorphous sulfur and 90% crystalline sulfur, suggesting that the change from green to yellow simply consists of closing the ring.

If green sulfur consists of diradical chains, it would be expected to be paramagnetic in virtue of the unpaired electrons. A qualitative test using a powerful electromagnet showed that green sulfur is very slightly paramagnetic and becomes diamagnetic when it changes to yellow sulfur.

Rate measurements of the transition from green to yellow sulfur were conducted using the method previously described for purple sulfur. We repeated the rate measurements for purple sulfur and confirmed the previous result that there is an initial rapid reaction followed by a slower change at almost constant speed. In the present work we estimated the speed of the initial change for purple sulfur at the four temperatures: −107, −102, −98 and −88° and by plotting the logarithm of the rate against the reciprocal of the time obtained an activation energy of 2.0 kcal. as compared with the previously reported value of 3.1 kcal. for purple sulfur. Using the same method for green sulfur we obtained the value 3.9 kcal. for the activation energy of the change green → yellow sulfur.

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The Isolation of Diosgenin from Solanum Xanthocarpum[1]

BY YOSHIO SATO AND H. GEORGE LATHAM, JR.

RECEIVED JULY 6, 1953

During the course of isolation of solasodine from the dried fruits of *Solanum xanthocarpum* we have encountered a persistent impurity which has now been identified as diosgenin.

Although Gupta and Dutt[2] have reported the isolation of a sterol, carpesterol, $C_{36}H_{54}O_4$, m.p. 248°, and a $\Delta^{\alpha,\beta}$-unsaturated lactone (solanocarpone) $C_{28}H_{42}O_7$, m.p. 78°, the presence of the sapogenin, diosgenin, had been undetected hitherto.

The occurrence of small amounts of diosgenin along with solasodine provokes an interesting speculation as to the possible mode of biogenesis of solasodine. This finding is also of interest in view of the recent report of Briggs and O'Shea[3] who obtained small amounts of diosgenin by treating N-nitrososolasodine with boiling aqueous acetic acid. The main product of this reaction was an isomer of diosgenin.

Experimental[4]

The finely ground dry fruits (2.62 kg.) of *Solanum xanthocarpum* were extracted in a Soxhlet extractor with petroleum ether (4 l., 65–75°) for 44 hours, then with methanol (3.5 l.) for 140 hours. The methanol extract was evaporated to dryness on the water-bath and the semi-solid mass taken up in 10% acetic acid, treated with charcoal at boiling temperature and filtered through Filter-cel. The filtrate was made basic with ammonia and the glycoside collected. After several triturations with petroleum ether the crude, partially solid material was dissolved in hot methanol and hydrochloric acid (2 *N* with respect to methanol), refluxed for 2.5 hours, an additional half-hour with charcoal, and finally filtered through Filter-cel. The precipitated, crude solasodine hydrochloride was collected. Further dilution of the mother liquor with ether yielded more of the same substance. The hydrochloride was dissolved in hot methanol, water added to incipient turbidity, and made alkaline with ammonia gas. The solasodine (24.23 g.) was collected after standing overnight. Eight grams of the above crude, dry solasodine was dissolved in 1200 cc. of dry ether and 140 cc. of 1% ethereal hydrogen chloride was added with agitation. After cooling in ice-water for one-half hour the solasodine hydrochloride was collected and washed with cold dry ether. The ethereal filtrate was washed with Na_2CO_3 solution, water and dried over Na_2SO_4. Evaporation of the solvent yielded 50 mg. of crude diosgenin which after chromatography and recrystallization from acetone afforded 8 mg. of needles, m.p. 194–198°. Its infrared spectrum was identical with that of an authentic specimen of diosgenin.

Anal. Calcd. for $C_{27}H_{42}O_3$: C, 78.21; H, 10.21. Found: C, 77.71; H, 10.00.

In another experiment the crude diosgenin was directly acetylated in the usual manner with acetic anhydride–pyridine and chromatographed over alumina. Crystallization from acetone and recrystallization from methanol yielded flat rods, m.p. 194.5–196°. Its infrared absorption spectrum likewise was identical with that of an authentic specimen of diosgenin acetate.

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[1] The *Solanum xanthocarpum* was obtained from the Institute of Agriculture. Anand. through the generous coöperation of the American Consul General. Bombay. India.

[2] M. P. Gupta and S. Dutt, *J. Ind. Chem. Soc.*, **15**, 95 (1938).

[3] L. H. Briggs and T. O'Shea, *J. Chem. Soc.*, 1654 (1952).

[4] The melting points are uncorrected and taken on the Kofler block.

Some Alkyl Thiocarbamates Prepared from Alkyl Thiocyanates by Riemschneider's Reaction

BY K. SCHMIDT AND P. KOLLEK-BÖS

RECEIVED JUNE 26, 1953

As was shown by Riemschneider and coworkers,[1a] the melting points of the primary aliphatic thiocarbamates differ only slightly from one another. On the basis of this observation the melting points of the hitherto unknown thiocarbamates, *n*-$C_{13}H_{27}$–, *n*-$C_{15}H_{31}$–, *n*-$C_{17}H_{35}$– and *n*-$C_{19}H_{39}$–$SCONH_2$, were predicted.

Since we had in connection with other investigations the thiocyanates *n*-$C_{13}H_{27}$–, *n*-$C_{15}H_{31}$–, *n*-$C_{17}H_{35}$– and *n*-$C_{19}H_{39}$–SCN at our disposal, we converted them by Riemschneider's reaction[1b,c] into the corresponding thiocarbamates and determined the melting points of the latter. The procedure followed was analogous to that given for the preparation of myristyl thiocarbamate.[1c] As is evident from the following table, there is good agreement between the predicted and the observed melting points of the four thiocarbamates.

	M.p., °C.	
	Predicted	Obsd.
n-$C_{13}H_{27}SCONH_2$	110	109.5–110
n-$C_{15}H_{31}SCONH_2$	111–111.5	111.5
n-$C_{17}H_{35}SCONH_2$	111.5–112	111–112
n-$C_{19}H_{39}SCONH_2$	113	113.5

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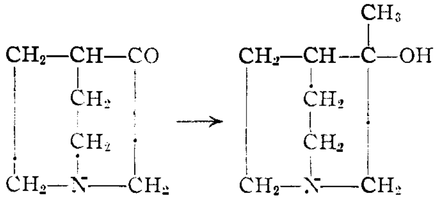
[1] R. Riemschneider and co-workers, (a) *Angew. Chem.*. **64**. 420 (1952): (b) THIS JOURNAL, **73**, 5905 (1951): *Pharmazie*. **4**, 460 (1949); *Chimica e industria* (*Milan*). **34**. 353 (1952): *Z. Naturforsch.*, **7b**, 277 (1952): (c) *Monatsh.*, **84**, 316 (1953).

Antispasmodics. III.[1] Esters of Basic Bicyclic Alcohols and Their Quaternary Salts

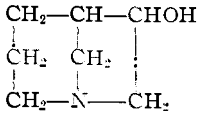
By L. H. Sternbach and S. Kaiser

Received June 29, 1953

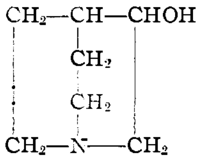
In continuation of our studies of ester type antispasmodics a new amino alcohol, 3-methyl-3-quinuclidinol (II), was prepared by treating 3-quinuclidone (I) with methyllithium. This tertiary alcohol II was esterified with diphenylacetic acid and the ester quaternized with methyl bromide. Since neither this ester nor its methobromide showed high antiacetylcholine activity, no other esters of tertiary alcohols were investigated.



I II



III



IV

However, two new esters were prepared from previously described bicyclic basic secondary alcohols.[2] They were the benzilic acid ester of 1-azabicyclo-[3.2.1]-6-octanol (III), prepared from the corresponding sodium alcoholate and diphenylchloroacetyl chloride, and 3-O-acetylmandelyloxyquinuclidine, prepared from 3-quinuclidinol (IV) and the corresponding acid chloride. The acetylmandelyl derivative was obtained as a mixture of two racemic enantiomorphs. They were not separated, and an analytically pure hydrochloride melting over a range of 9 degrees was used for the pharmacological testing.

The new benzilic acid ester (Ro 2-4569) and some of the formerly described esters were quaternized with methyl bromide. The benzilic[1] and diphenylacetic[1] acid esters of 3-quinuclidinol (IV) were also treated with other alkyl bromides, as well as with allyl bromide and benzyl bromide. One of these quaternary compounds, the methobromide of the benzilic ester of 3-quinuclidinol (Ro 2-3773), was resolved into optical antipodes. Two isomeric *d*-camphorsulfonates were obtained after metathesis of the bromide with silver *d*-camphorsulfonate. They gave a mixed melting point depression, and showed specific optical rotations of $[\alpha]^{30}_{D}$ +30.5 ± 0.5° and $[\alpha]^{30}_{D}$ −13.5 ± 0.5°. This corresponds to a molecular rotation of the N-methylbenziloyloxyquinuclidinium ion of +128.6 ± 2.9° and −125.9 ± 2.4°, respectively. These isomers were prepared in order to study possible differences in their pharmacological properties.

The physical properties, analyses and antiacetylcholine activities of these compounds are listed in Table I.

Pharmacological Activity.[3]—The spasmolytic activities of the various esters (Table I) were determined on the isolated rabbit intestine in a spasm induced by acetylcholine bromide. The potencies were estimated from the doses which produced relaxation equivalent to those caused by known amounts of atropine.

The benzilic acid ester of 1-azabicyclo[3.2.1]-octanol-6 (Ro 2-4569) showed antiacetylcholine activity of the same order as that of atropine. The acetylmandelic acid ester of 3-quinuclidinol (Ro 2-4344) and the diphenylacetic acid ester of 3-methyl-3-quinuclidinol (Ro 2-3631/2) were, however, only about $^1/_{10}$ as active. Quaternization of the diphenylacetic acid esters caused in all cases a considerable decrease in activity. On the other hand, most of the quaternary salts of the benzilic acid esters approximately equaled the non-quaternized compounds in potency.

The two isomeric 1-methyl-3-benziloyloxyquinuclidinium *d*-camphorsulfonates (Ro 2-5044 and Ro 2-5109) showed no significant difference in their antiacetylcholine activity.

Experimental[4]

3-Methyl-3-quinuclidinol (II).—A benzene solution (50 cc.) containing 5 g. of 3-quinuclidone (I) was added to an ether solution (about 50 cc.) of methyllithium, prepared from 1.4 g. of lithium metal and an excess of methyl bromide. The mixture was stirred and refluxed for 2 hours, then decomposed by the addition of 10–20 cc. of water. Sufficient potassium hydroxide and carbonate was added to convert the aqueous layer into a paste. This paste was extracted 3 times with 50 cc. each of benzene. The combined organic solutions were dried, concentrated *in vacuo* and the residue crystallized from a mixture of ether and petroleum ether, forming prisms melting at 109–111°. The yield was 65%.

Anal. Calcd. for $C_8H_{15}ON$: C, 68.04; H, 10.71. Found: C, 68.03; H, 10.28.

The hydrochloride, prepared with the calculated amount of hydrochloric acid and recrystallized from a mixture of ethanol and acetone, forms prisms melting at 291–292°.

Anal. Calcd. for $C_8H_{16}ONCl$: C, 54.07; H, 9.08. Found: C, 53.88; H, 8.76.

Procedures A, B, C and D for the preparation of basic esters and their salts are identical with those described in paper II[1] of this series.

Procedure E. Quaternization of Basic Esters.—To a solution of 0.01 mole of the basic ester[5] in 15 cc. of chloroform was added 0.05 mole of the organic bromide (methyl bromide was used as a 30% solution in acetone). The mixture was left at room temperature for 24 hours and then concentrated *in vacuo*. The residue was recrystallized.

Procedure F. *d*- and *l*-1-Methyl-3-benziloyloxyquinuclidinium *d*-Camphorsulfonate.—A solution of silver *d*-camphorsulfonate was prepared by heating an excess of silver carbonate (6 g.) for a few minutes with an aqueous solution of 4.65 g. (20 mmoles) of *d*-camphorsulfonic acid. The mixture was filtered and the filtrate added to an aqueous solution of 8.65 g. (20 mmoles) of 1-methyl-3-benziloyloxyquinuclidinium bromide. The precipitated silver bromide was filtered off and the solution concentrated *in vacuo*. The

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(1) Paper II. L. H. Sternbach and S. Kaiser, This Journal, **74**, 2219 (1952).

(2) L. H. Sternbach and S. Kaiser, *ibid.*, **74**, 2215 (1952).

(3) The pharmacological studies were carried out by Drs. W. M. Benson, L. O. Randall and their associates in the Pharmacology Department of Hoffmann-La Roche, Inc., Nutley, N. J., to whom the authors are greatly indebted for the data discussed here. Part of the results have been published in detail by L. O. Randall, W. M. Benson and P. L. Stefko, *J. Pharmacol. Exptl. Therap.*, **104**, 284 (1952).

(4) All melting points are corrected.

(5) In the case of Ro 2-3951 the basic ester was liberated from its hydrochloride with aqueous alkali, and extracted with chloroform. The chloroform solution was used for the quaternization without isolation of the free base.

TABLE I

Ro 2-	Esters of Alcohol	Esters of Acid	Salt	Procedure	Recrystallized from	Yield, %	M.p., °C.	Empirical formula	Analyses, % Calcd.	Analyses, % Found	Activity atr. = 1
3631	II	Diphenyl-acetic		B	Pet. ether	65	85–87	$C_{22}H_{25}O_2N$	C. 78.77 H. 7.51	78.68 7.43	
3631/2	II	Diphenyl-acetic	H_2SO_4	D	Acetone[a]	90	205–206	$(C_{22}H_{25}O_2N)_2 \cdot H_2SO_4$	C. 68.72 H. 6.82	68.55 6.51	1/10
4201	II	Diphenyl-acetic	CH_3Br	E	Acetone	80	176–177	$C_{23}H_{28}O_2NBr$	C. 64.18 H. 6.56	64.27 6.61	1/50
3951	III	Diphenyl-acetic	CH_3Br	E	Isopropanol + acetone + ether	80	165–167	$C_{22}H_{26}O_2NBr$	C. 63.46 H. 6.30	63.04 6.33	1/50
4569	III	Benzilic		C	Acetone + ether + pet. ether	15	156–157	$C_{21}H_{23}O_3N$	C. 74.75 H. 6.87	74.39 6.51	1–2[b]
4570	III	Benzilic	CH_3Br	E	Methanol + acetone + ether	85	231–233	$C_{22}H_{26}O_3NBr$	C. 61.11 H. 6.06	61.10 6.14	1–2
3203	IV	Diphenyl-acetic	CH_3Br	E	Ethanol + ether + pet. ether	90	212–213	$C_{22}H_{26}O_2NBr$	C, 63.46 H. 6.30	63.31 6.38	1/5
3528	IV	Diphenyl-acetic	C_2H_5Br	E	Ethanol + ether	90	205–206	$C_{23}H_{28}O_2NBr$	C. 64.18 H. 6.56	63.82 6.43	1/100
5205	IV	Diphenyl-acetic	$CH_2{=}CHCH_2Br$	E	Acetone[a]	80	149–150	$C_{24}H_{28}O_2NBr$	C. 65.15 H. 6.38	65.05 6.12	1/10
4157	IV	Diphenyl-acetic	$C_6H_5CH_2Br$	E	Isopropanol	40	171–173	$C_{28}H_{30}O_2NBr$	C. 68.29 H. 6.14	68.70 6.37	1/100
3773	IV	Benzilic	CH_3Br	E	Methanol + acetone + ether	90	240–241	$C_{22}H_{26}O_3NBr$	C. 61.11 H. 6.06	61.25 6.33	1
	IV	Benzilic	CH_3picr.[c]	G	Ethanol		182–183	$C_{28}H_{28}O_{10}N_4$	C. 57.93 H, 4.86	57.77 4.62	
5044	IV	Benzilic	CH_3CS[d]	F	Methanol + acetone + pet. ether	56	221–223	$C_{32}H_{41}O_7NS$	C, 65.84 H. 7.08	65.48 7.04	1
5109	IV	Benzilic	CH_3CS[d]	F	Methanol + acetone + pet. ether	20	209–210	$C_{32}H_{41}O_7NS$	C, 65.84 H. 7.08	65.93 7.29	1
4174	IV	Benzilic	C_2H_5Br	E	Methanol + acetone	90	229–230	$C_{23}H_{28}O_3NBr$	C. 61.88 H. 6.23	61.86 6.19	1
4665	IV	Benzilic	C_3H_7Br	E	Methanol + acetone + ether	90	251–254	$C_{24}H_{30}O_3NBr$	C. 62.60 H. 6.57	62.92 6.51	1
4550	IV	Benzilic	C_4H_9Br	E	Methanol + acetone + ether	80	246–247	$C_{25}H_{32}O_3NBr$	C. 63.29 H. 6.80	63.14 6.60	1
5084	IV	Benzilic	$CH_2{=}CHCH_2Br$	E	Methanol + acetone + pet. ether	80	181–182	$C_{24}H_{28}O_3NBr$	C. 62.88 H. 6.16	62.48 6.23	1
4148	IV	Benzilic	$C_6H_5CH_2Br$	E	Isopropanol[e]	37	223–224	$C_{28}H_{30}O_3NBr$	C. 66.14 H. 5.95	65.85 5.82	1/25
4344	IV	Acetylman-delic	HCl	A	Ethanol + acetone + ether	65	169–178	$C_{17}H_{21}O_4N \cdot HCl$[f]	C. 60.08 H. 6.53	59.90 6.52	1/25

[a] Dissolved in alcohol; solvent removed *in vacuo*. Residual oil crystallized by trituration with acetone. [b] A solution of the base in the calculated amount of dilute hydrochloric acid was used for the pharmacological studies. [c] Picrate. [d] *d*-Camphorsulfonates of optical antipodes. Ro 2-5044 is the dextrorotatory, Ro 2-5109 the levorotatory isomer. [e] Dissolved in methanol; solvent removed *in vacuo*. Residual oil crystallized by trituration with isopropyl alcohol. [f] A direct oxygen determination (Calcd.: O, 18.82. Found: O, 18.75) showed that the compound was the hydrochloride of the acetylmandelic acid ester and not of the mandelic acid ester. The carbon and hydrogen values of these two ester hydrochlorides are very close.

residual thick sirup was dissolved in methanol. To this solution acetone and ether were added, causing the precipitation of crystals (needles, 2 g.) melting around 200°. Further additions of acetone, ether and petroleum ether caused precipitation of more material melting in the same range. These fractions were combined and recrystallized three times from a mixture of methanol, acetone and petroleum ether, giving finally 3.3 g. (56%) of fine needles (Ro 2-5044), having the constant melting point of 221-223° and a constant specific rotation of $[\alpha]^{30}D$ +30.5 ± 0.5° (*c* 5, in water). This corresponds to a molecular rotation of the *d*-1-methyl-3-benziloyloxyquinuclidinium ion of +128.6 ± 2.9°.

Anal. Calcd. for $C_{32}H_{41}O_7NS$: C, 65.84; H, 7.08. Found: C, 65.48; H, 7.04.

The mother liquors were concentrated and the residues crystallized from a mixture of methanol, acetone and petroleum ether. The lower melting fractions (180–185°) thus obtained were repeatedly recrystallized from the above solvents to yield finally 1.2 g. (20%) of needles having a constant melting point of 209–210° (Ro 2-5109) and giving a distinct mixed melting point depression with the other isomer. The specific optical rotation of this isomer was $[\alpha]^{30}D$ −13.2 ± 0.5° (*c* 5, in water). The molecular rotation of the *l*-1-methyl-3-benziloyloxyquinuclidinium ion calculated from this value is −125.9 ± 2.4°.

Anal. Calcd. for $C_{32}H_{41}O_7NS$: C, 65.84; H, 7.08. Found: C, 65.93; H, 7.29.

Procedure G. 1-Methyl-3-benziloyloxyquinuclidinium Picrate.—A solution of 0.4 g. of 1-methyl-3-benziloyloxyquinuclidinium bromide (Ro 2-3773) in 10 cc. of water was added to a hot aqueous solution (50 cc.) of 0.4 g. of picric acid. The mixture was cooled and the precipitated oil crystallized.

Acknowledgment.—The authors wish to thank Dr. Al Steyermark and his staff for the microanalyses.

NUTLEY, NEW JERSEY

Crystal Structures of Rare Earth Oxychlorides

BY D. H. TEMPLETON AND CAROL H. DAUBEN

RECEIVED JULY 13, 1953

Compounds of the rare earth elements show the effects of ionic size on crystal structure with minimum interference from other factors. The ionic radii decrease in a regular way as the atomic number increases, while the configuration of the outer electrons is changed relatively little. Among the compounds which we have studied are the oxychlorides of composition MOCl, where M is a rare earth element. Of these, structures have been reported only for LaOCl,[1] PrOCl[2] and NdOCl[2] which have the PbFCl type[3] structure. Our work was stimulated by a correlation now being made by Koch and Cunningham of the thermodynamic properties of these substances[4,5] with crystal geometry.

Experimental

The oxychlorides of yttrium and all of the rare earth elements except promethium were prepared by Dr. Charles W. Koch and Mr. Richard J. Borg from very pure oxide stocks (similar to those described by Zalkin and Templeton[6]) by reaction with appropriate mixtures of water and hydrogen chloride vapors at elevated temperatures. Powder patterns were taken in cameras of radius 4.5 cm. with CuKα (λ 1.5418 Å.) and CrKα (λ 2.2909 Å.) radiations.

Results

The oxychlorides of the elements lanthanum to holmium have the tetragonal PbFCl type structure. The oxychlorides of thulium, ytterbium and lutetium have another structure which has not been determined. Erbium oxychloride is dimorphic, having been prepared with each of these two structures. The lattice dimensions and unit cell volumes of the tetragonal oxychlorides are listed in Table I, together with previous results. A plot of the unit cell volume as a function of atomic number is a smooth curve except for the usual cusp at gadolinium.

TABLE I

TETRAGONAL LATTICE PARAMETERS

	a, Å.	c, Å.	Vol. unit cell, Å.^{3}
LaOCl	4.119 ± 0.002	6.883 ± 0.004	116.78
	(4.117)[a]	(6.879)[a]	
	(4.121 ± .003)[b]	(6.885 ± .009)[b]	
CeOCl	4.080 ± .004	6.831 ± .007	113.71
PrOCl	4.051 ± .002	6.810 ± .006	111.76
	(4.053 ± .003)[c]	(6.800 ± .009)[c]	
NdOCl	4.018 ± .002	6.782 ± .004	109.49
	(4.04 ± .03)[c]	(6.77 ± .04)[c]	
SmOCl	3.982 ± .001	6.721 ± .002	106.57
EuOCl	3.965 ± .004	6.695 ± .007	105.25
GdOCl	3.950 ± .002	6.672 ± .004	104.10
TbOCl	3.927 ± .004	6.645 ± .007	102.47
DyOCl	3.911 ± .003	6.620 ± .006	101.26
HoOCl	3.893 ± .003	6.602 ± .004	100.06
ErOCl	3.88 ± .02	6.58 ± .06	99.1
YOCl	3.903 ± .002	6.597 ± .004	100.49
	(3.900 ± .002)[c]	(6.604 ± .004)[c]	

[a] Reference 1. [b] S. Fried, W. Hagemann and W. H. Zachariasen, THIS JOURNAL, **72**, 771 (1950). [c] Reference 2.

The PbFCl structure has atoms in the following positions of space group D_{4h}^7 ($P4/nmm$)

2 M in 2 (c): $0,\frac{1}{2},u;\ \frac{1}{2},0,\bar{u}$
2 O in 2 (a): $0,0,0;\ \frac{1}{2},\frac{1}{2},0$
2 Cl in 2 (c): $0,\frac{1}{2},v;\ \frac{1}{2},0,\bar{v}$

Sillén and Nylander[1] have given the parameters as $u = 0.178$ and $v = 0.635$ for LaOCl, while Zachariasen[2] has given them as 0.18 and 0.64, respectively, for NdOCl, PrOCl, PuOCl and YOCl.

Diffraction intensities were calculated for many combinations of values of u and v for both SmOCl and HoOCl. For both compounds the best agreement was found with $u = 0.17$ and $v = 0.63$. The limits of error are estimated as 0.005 and 0.01 for the two parameters. The reflections considered include l values up to 8. The interatomic distances are listed in Table II. The most interesting feature of these distances is that the two types of metal–chlorine distance remain equal (within experimental error) in spite of the very short chlorine–chlorine distance which results. That is, the anion repulsion is much less than one would expect for conventional ionic radii.

TABLE II

INTERATOMIC DISTANCES IN SmOCl AND HoOCl

Atoms	Distance, Å. SmOCl	HoOCl
M–O	2.30	2.25
M–Cl	3.09,[a] 3.11[b]	3.04,[a] 3.05[b]
Cl–O	3.19	3.12
Cl–Cl	3.31	3.24
O–O	2.81	2.75

[a] One neighbor. [b] Four neighbors.

The explanation may lie in a deviation from spherical symmetry of the chloride ion. This equality of metal–chlorine distances also occurs to within experimental error for LaOCl,[1] PrOCl,[2] NdOCl,[2] YOCl[2] and PuOCl,[2] but in these cases the anion–anion distances are not as small because of the greater cation size.

Acknowledgment.—We thank Dr. Koch and Mr. Borg for preparing the compounds and Professor Cunningham for his interest in the work. The diffraction patterns were obtained by Mrs. Helena W. Ruben. This research was supported by the U. S. Atomic Energy Commission.

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[1] L. G. Sillén and A. L. Nylander, *Svensk. Kem. Tidskr.*, **53**, 367 (1941).

[2] W. H. Zachariasen, *Acta Cryst.*, **2**, 388 (1949).

[3] W. Nieuwenkamp and J. M. Bijvoet, *Z. Krist.*, **81**, 469 (1931).

[4] C. W. Koch, A. Broido and B. B. Cunningham, THIS JOURNAL, **74**, 2349 (1952).

[5] C. W. Koch and B. B. Cunningham, *ibid.*, **75**, 796 (1953).

[6] A. Zalkin and D. H. Templeton, *ibid.*, **75**, 2453 (1953).

An Empirical Quantitative Relationship between Structure and Molecular Rotatory Power

BY TOM R. THOMSON

RECEIVED AUGUST 5, 1953

The relationship between optical rotation and structure has been worked out in part by such well-known methods as Hudson's rules of isorotation. However, a generalized treatment either theoretical or empirical, capable of predicting the magnitude of the rotation from the constitution of the active molecule is as yet lacking. The following describes an empirical relationship that enables the rotation of at least the simpler types of optically active molecules to be calculated with a fair degree of accuracy.

The method makes use of the *asymmetry product* of Guye and Brown[1,2] who, in 1890, related the molecular rotation, (M), to a function of four terms, in turn related to four groups attached to an asymmetric carbon atom

$$(M) = [(a - b)(a - c)(a - d)(b - c)(b - d)(c - d)] \quad (1)$$

Instead of using the masses of the groups for the four terms a, b, c and d, as did Guye and Brown, however, a different method of calculating these contributions is used, wherein the value is derived from the structure of the group, adding a contribution for each atom vectorially.

For example, a methyl group is considered as a carbon atom plus three hydrogen atoms located at tetrahedral angles with respect to the methyl carbon atom. The total effect, then, of this group would be the effect of one carbon atom plus the vector components of each of the three hydrogen atoms along the line joining the methyl carbon atom to the asymmetric carbon atom. Each hydrogen atom can be broken down into two vectors, one along this line and one normal to it. These latter vectors can be neglected if free rotation is possible, since all positions around 360° are equally probable, thus cancelling out any effect.

Bond distances need not be included in at least these simple compounds, since they are included in the values assigned to each element. This assumes, for example, hydrogen always joined to carbon; in cases where hydrogen is joined to oxygen, a slightly different value must be used.

It is also possible to assume tetrahedral bond angles for all carbons; discrepancies will appear when bond angles are strained. When compounds of other multivalent elements are encountered, then their bond angles must be considered.

From studies of homologous series it has been known that the contribution of a given atom or group to the optical rotation drops off with distance from the asymmetric carbon atom. The following comparison of the contribution of a bromine atom in the homologous series $-CH_2Br$, $-CH_2CH_2Br$, etc., as calculated according to the above method, illustrates this point in a quantitative manner.

Assuming the normal bond angle of carbon to be 109° 28′, the structure of a bromomethyl group is shown in Fig. 1.

Considering only the bromine atom, for the moment, the component of its effect along the line ss′ would be given by

$$a = \text{Br}(\cos \beta) = \text{Br}(\cos 70°32') = 0.333\text{Br} = (^1/_3)\text{Br} \quad (2)$$

Similarly, in a bromoethyl group, as shown in Fig. 2, the desired component along tt′ will be $(^1/_3)$-Br, as before, and the component of this along ss′ will be (1/3)(1/3) Br or (1/9)Br.

The contribution of bromine in any normal ω-bromoalkyl group, $C_nH_{2n}Br$, will be found to be $(1/3)^n$ Br. This one-third relationship resulting from the tetrahedral carbon atom might be called a one-third law, since the effect of a group is given by $(1/3)^n X$, where X is the basic rotational value of the group, and n is the number of carbon atoms between the group and the center of asymmetry. The validity of this relationship is evident below from the successful calculation of rotations of various molecules from their structure using this law.

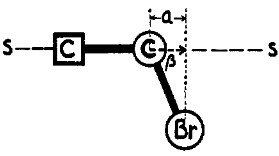

Fig. 1.

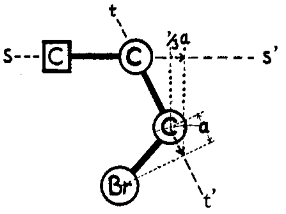

Fig. 2.

Calculation of Vectorial Contributions of Various Alkyl Groups.—On the basis of this relationship, the rotational contributions of various alkyl groups can be assigned as in Table I.

TABLE I

TABLE OF ROTATIONAL CONTRIBUTIONS FOR VARIOUS ALKYL GROUPS FOR USE IN THE MODIFIED GUYE EQUATION

Group	Expression for rotational contribution[a]
Methyl, CH_3	C + 3(1/3)H = C + H
Ethyl, C_2H_5	C + 2(1/3)H + (1/3)(C + H) = (4/3)-C + H
n-Propyl, C_3H_7	(13/9)C + H
Isopropyl, C_3H_7	(15/9)C + H
n-Butyl, C_4H_9	(40/27)C + H
Isobutyl, C_4H_9	(14/9)C + H
n-C_nH_{2n+1}	$[^1/_2(3^n - 1)/3^{n-1}]$C + H

[a] The Rotational Contributions are worked out for the first two members, as examples.

Calculation of the Atomic Rotational Contribution of Carbon.—The atomic rotational constant of carbon can be found by use of equation 1, the group values from Table I, and the observed rotation values for compounds of known structure. It will be noted that if the contributions of the various alkyl groups are substituted into equation 1 since each term contains an identical hydrogen term, the subtraction of one term from the other in the equation eliminates the value for hydrogen, leaving a sixth degree equation with one unknown, which can be solved for the rotational constant for carbon.

Consider, for example, the compound methylethyl-*n*-butylmethane. Equation 1 yields the expression

$$(M) = [(1 - 4/3)(1 - 40/27)(1 - 0)(4/3 - 40/27)(4/3 - 0)(40/27 - 0)]C^6 \quad (3)$$

Substituting in the known rotation, −11.4°, for (M), and solving for C, we obtain the value of 2.50 for the atomic rotational constant for carbon.

Similar calculations on other optically active hydrocarbons of known rotation, chosen from data given by Gilman[3] and Marker,[4] yield consistent values for carbon, as shown in Table II. Only

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(1) P. A. Guye and A. C. Brown, *Compt. rend.*, **110**, 714 (1890).

(2) P. A. Guye and A. C. Brown, *Proc. Roy. Soc. Edin.*, **17**, 181 (1890).

(3) H. Gilman, "Organic Chemistry, An Advanced Treatise," Vol. 2, John Wiley and Sons, Inc., New York, N. Y., 1938, p. 1808.

(4) R. E. Marker, THIS JOURNAL, **58**, 976 (1936).

compounds with rotations of the order of ten degrees or more were used, because the nature of the function makes too great a percentage error in the answer if the percentage uncertainty in the rotation is too large.

TABLE II

ATOMIC ROTATION CONSTANTS FOR CARBON CALCULATED FROM ACCEPTED ROTATIONS AND A COMPARISON OF THE LATTER WITH ROTATIONS CALCULATED USING AN AVERAGE VALUE OF 2.50 FOR CARBON

Compound, methane	Accepted, (*M*)	*C*	Calcd., (*M*)
Methylethyl-*n*-butyl-	−11.4	2.50	−11.5
Methylethyl-*n*-pentyl-	−12.0	2.47	−12.8
Methylethylisobutyl-	−21.3	2.51	−20.8
Methyl-*n*-propylisobutyl-	−14.9	2.50	−15.0
Methyl-*n*-butylisobutyl-	−11.9	2.53	−10.8
Methyl-*n*-pentylisobutyl-	− 9.3	2.49	− 9.6

Table II also includes a column of rotations calculated by use of Table I and equation 1, employing the average value of 2.50 for carbon. As might be expected from the constancy of the values for carbon, good agreement is found with the accepted rotations. This latter column is not intended as any proof of the method; the consistent values for carbon establish its validity. Rather, it is inserted merely to illustrate the proportional change in the calculated rotation when there is a variation in the value for carbon.

Calculation of Molar Rotation of Alkyl Halides.—The method is also applicable to alkyl halides. Using the same general method and a value of 2.50 for carbon, the contribution of the halogen atom can be found, and once known, the rotations of alkyl halides can then be predicted. Actually, like hydrogen the value for the halogen atom alone need not be found, but rather, the value (X–H), the difference in the values for the halogen and hydrogen, is more easily solved for and is sufficient for the calculations.

The following example will illustrate the calculation of the value (Br–H). Consider the compound bromoethylethylmethylmethane. Using the following values for the four groups in the order named: $(4/3)C + (8/9)\mathrm{H} + (1/9)\mathrm{Br}$, $(4/3)\mathrm{C} + \mathrm{H}$, $\mathrm{C} + \mathrm{H}$, H, and substituting into equation 1 and simplifying gives

$$(M) = (4C^3/6561)[36C^2(\mathrm{Br{-}H}) + 15C(\mathrm{Br{-}H})^2 + (\mathrm{Br{-}H})^3] \qquad (4)$$

Using a value of 2.50 for *C*, the equation becomes

$$(M) = 0.009465\ [225(\mathrm{Br{-}H}) + 37.5(\mathrm{Br{-}H})^2 + (\mathrm{Br{-}H})^3] \qquad (5)$$

For this particular compound (*M*) has the value −38.8°. Thus, the quantity (Br–H) can be found by solving the cubic equation. A graphical solution yields the value 7.40 for (Br–H).

TABLE III

A COMPARISON OF CALCULATED AND ACCEPTED ROTATIONS FOR ALKYL BROMIDES

Compound	Accepted, (*M*)	Calcd., (*M*)
1-Bromo-3-methyloctane	14.7	15.2
1-Bromo-5-methylheptane	14.9	15.5
1-Bromo-4-methylhexane	21.9	22.0

Use of this value to calculate rotations for various alkyl bromides yields good agreement with accepted values from the literature as shown in Table III.

Discussion

Though good agreement was obtained between calculated and accepted rotations in the examples presented here and in others not mentioned, notable exceptions were found. Among the alkanes and alkyl halides, these, in all cases, were compounds which, when constructed from Fisher–Hirschfelder–Taylor models, exhibited unavoidable steric hindrance. Compounds which have possible steric hindrance between groups, but which also have configurations which could avoid hindrance, showed good agreement. This seems to indicate that the criterion for applicability of this method is whether or not steric hindrance is *unavoidable*, rather than *possible*. Lack of agreement might thereby indicate unavoidable steric hindrance.

The rotations of compounds with isopropyl groups attached to the asymmetric carbon atom have for some time been known to fall out of line with the rotations of homologous series. Erroneous answers are obtained with this method in such cases. A value other than that given in Table I must be used for the isopropyl group to make the method work. Furthermore, a different value for each case is obtained, showing that the hindrance causing the error depends on the other three groups attached to the asymmetric carbon atom.

It might also be noted that reversing the assignment of groups to the four terms in the equation will result in a change of sign but not of magnitude. The method is thus applicable to predicting the rotation of either isomer and a standardization of method of choosing the order of terms is all that is needed to make the answers conform with absolute configuration.

The particular types of compounds chosen here were those purposely avoiding the many factors complicating the rotation phenomenon, such as association, solvation, hydrogen bonding, chelation, Cotton effect, etc. It is hoped that the method can be extended to include other groups, ring compounds, compounds with more than one asymmetric carbon atom, and even perhaps those with asymmetric atoms other than carbon.

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The Hydrolysis of Some Alkyl Lactates I. Alkaline Hydrolysis[1]

BY KENNETH H. VOGEL AND J. C. WARNER

RECEIVED MARCH 12, 1953

The kinetics of the alkaline hydrolysis of certain normal and branched-chain alkyl acetates[2] and benzoates[3] have been studied, and the effects of lengthening and of branching the alkyl carbon

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[1] Abstracted from a thesis submitted by K. H. Vogel to the Committee on Graduate Degrees, Carnegie Institute of Technology, in partial fulfillment of the requirements for the D.Sc. degree.

[2] H. Olsson, *Z. physik. Chem.*, **118**, 107 (1925).

[3] E. Tommila, *Ann. Acad. Sci. Fennicae*, **A59**, No. 3, 3 (1942).

chain on both the activation energy and the frequency factor have been determined. An investigation of the kinetics of the alkaline hydrolysis of some alkyl and substituted alkyl lactates, initiated several years ago,[4] has now been completed, and the results are given in this paper.

Experiment Method

The hydrolyses of the *n*-alkyl and of the branched-chain and substituted alkyl lactates were carried out in thermostats which held the temperature constant to within ±0.02 and ±0.01°, respectively. Temperatures were measured by calibrated Beckmann thermometers.

Each reaction flask for the hydrolyses of the *n*-alkyl lactates consisted of a 500-ml. and a 300-ml. distilling flask with bulbs joined together so that one side of the vessel could hold 200 ml. of solution and the other side 100 ml. Each reaction flask for the other hydrolyses consisted of two 500-ml. wide-mouth Pyrex erlenmeyer flasks with mouths sealed together and with the ends blown out at an angle of 120°. A length of 25-mm. Pyrex tubing was sealed into each 500-ml. erlenmeyer section, in order to provide means for introducing the solution and for tilting the flask while the solutions were mixed.

To start the hydrolyses of the *n*-alkyl lactates, 100 ml. of standard base was introduced into one side of the reaction flask and 100 ml. of standard aqueous ester into the other, the solutions were allowed to reach the temperature of the thermostat, and were then mixed for about three seconds. The electric stop-watch was started when the combined solution reached the larger side of the reaction flask after mixing. The other lactates were charged into dried, weighed Victor Meyer bulbs blown from 8-mm. Pyrex tubing. A bulb was placed in one side of the reaction flask and a measured amount of standard base in the other. Measured amounts of water to give the desired concentrations of aqueous ester and of base (0.005 *M* for both in most cases) were added to each side of the flask. The bulb was broken, the solutions were allowed to come to the temperature of the thermostat and were then mixed for 45 seconds. The electric stop-watch was started at the moment of mixing.

Samples from all hydrolyses were withdrawn at intervals, discharged into stop-solutions containing a measured excess of standard hydrochloric acid, then back-titrated with standard sodium hydroxide solution. Cresol red indicator was used for the *n*-alkyl lactates and brom phenol blue for most of the others. In the *s*- and *t*-butyl lactate runs, fading of the end-point on back-titration could be avoided only by carrying out the reactions in solutions 0.01 *M* in both ester and base and by using phenolphthalein indicator.

Carbon dioxide-free water and base were used in all experiments, and the reaction mixtures were protected from atmospheric carbon dioxide.

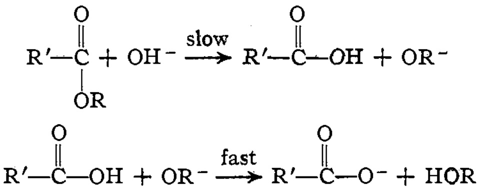
The *n*-alkyl lactates (Eastman Kodak Co.) were dried over "Drierite" for several days, then fractionally distilled. The remaining lactic esters were obtained from the Eastern Regional Laboratory of the United States Department of Agriculture.[5] They were vacuum distilled in an all glass system and stored over anhydrous calcium chloride in a desiccator. The boiling points, refractive indices and saponification equivalents of all esters agreed well with literature values.

Second-order velocity constants (liters mole^{-1} min.$^{-1}$) were determined from the slopes of the best straight-line plots of reciprocal concentration *vs.* time.

Results and Discussion

Second-order velocity constants were determined at 0 and 15° for the alkaline hydrolyses of the *n*-alkyl lactates, at 10 and 30° for the *t*-butyl ester, and at 3 and 10° for the remaining lactates. The rate of hydrolysis of *n*-alkyl lactates in pure water was investigated and shown to be negligible compared to the velocity of the alkaline hydrolysis of these esters[6]; therefore the average rate constants shown in Table I cannot contain appreciable contributions from rates of neutral hydrolyses. The activation energies (E_a) and the "frequency factors" (*PZ*) for the alkaline hydrolysis of the lactic esters were calculated and tabulated (Table I). General agreement with the activation energies and frequency factors calculated from some rate constants determined by Krige and Hollow,[7] Dean[8] and Salmi and Leino[9] was observed.

The results of this work are consistent with the mechanism proposed by Hammett[10] and by Day and Ingold,[11] termed by the latter investigators "bimolecular basic hydrolysis with acyl-oxygen fission" and labeled B′2:



$$R'{-}\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle OR}{|}}{C}} + OH^- \xrightarrow{\text{slow}} R'{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}OH + OR^-$$

$$R'{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}OH + OR^- \xrightarrow{\text{fast}} R'{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}O^- + HOR$$

This process involves a slow attack of hydroxyl ion on the carbonyl carbon, followed by the expulsion of alkoxyl ion, which is converted rapidly and irreversibly to the alcohol by transfer of a proton from the carboxylic acid formed. The nature of the intermediate in the first step has been investigated recently by Bender,[12] but the results of his investigation have no bearing on the work described here or in the two following communications.

TABLE I

Lactic ester	$k_{0°}$	$k_{3°}$	$k_{10°}$	$k_{15°}$	*Ea*, cal.	*PZ* $\times 10^{-8}$
Methyl[4]	21.32			259.2	10,600	67.35
Ethyl[4]	8.98			24.1	10,300	16.74
n-Propyl[4]	7.06			19.4	10,500	19.13
Isopropyl					9,400[a]	0.956[a]
n-Butyl[4]	6.79			19.0	10,700	26.10
Isobutyl		9.07	14.67		10,650	24.8
s-Butyl		1.78	2.65		8,750	0.156
t-Butyl[b]			0.251		12,100	5.62
2-Methoxyethyl		27.44	44.30		10,650	71,7
2-Chloroethyl		58.2	96.6		10,900	258.2

[a] Calculated from rate constants determined by Salmi and Leino.[9] [b] $k_{30°}$ = 1.037.

The energy of activation for the alkaline hydrolysis of *s*-butyl lactate is about 2 kcal./mole lower, and that of the *t*-butyl ester roughly 2 kcal./mole higher, than the essentially constant values observed for the remaining esters (Table I). Except for the case of *s*-butyl lactate, these observations parallel those of Olsson[2] on the aqueous alkaline hydrolysis of acetone. Neither of the latter investigations revealed a significant deviation of activation energy in the case of the *s*-butyl esters.

Values of *PZ* derived from this work and from studies of the alkaline hydrolysis of alkyl acetates[1] and benzoates[2] show a consistent variation; those for isopropyl esters are smaller than those for *n*-

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[4] A. A. Colon and J. C. Warner, *Bol. oficial. asoc. quím. Puerto Rico*, **2**, No. 2, 15 (1943).

[5] Courtesy of Drs. C. H. Fisher and E. M. Filachione.

[6] K. H. Vogel and J. C. Warner, THIS JOURNAL, **75**, 6074 (1953).

[7] G. J. R. Krige and K. Hollow, *Trans. Faraday Soc.*, **30**, 644 (1934).

[8] E. W. Dean, *Am. J. Sci.*, **35**, 605 (1913).

[9] E. J. Salmi and E. Leino, *Suomen Kemistilehti*, **17B**, 19 (1944).

[10] L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., New York, N. Y., 1940, pp. 355–357.

[11] J. N. E. Day and C. K. Ingold, *Trans. Faraday Soc.*, **37**, 686 (1941).

[12] M. L. Bender, THIS JOURNAL, **73**, 1626 (1951).

propyl esters, and those for the branched butyl esters are generally lower than those for primary butyl esters. The variations among the isomeric butyl lactates are much greater, however, than are the differences between members of the corresponding butyl acetates and benzoates. Nevertheless, in all cases a pronounced minimum in the *PZ* factor among the butyl esters is encountered with the *s*-butyl compound. Examination of Fisher–Hirschfelder models reveals the possibility that more mechanical interference with the approach of the attacking hydroxyl group to the carbonyl carbon may be offered by a *s*-butyl ester than by other butyl esters and that the low *PZ* factors may be subject to interpretation on this basis.

A comparison of the data for ethyl, *n*-propyl, β-methoxyethyl and β-chloroethyl lactates demonstrates that substitution of a β-hydrogen atom of the ethyl group of ethyl lactate produces no significant effect of E_a. The rate increases resulting from β-methoxy and β-chloro substitution are caused by increased *PZ* factors.

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The Hydrolysis of Some Alkyl Lactates. II. "Neutral" and Acid Hydrolyses[1]

BY A. ALBERTO COLON, KENNETH H. VOGEL AND J. C. WARNER

RECEIVED MARCH 12, 1953

An investigation of the kinetics of the acid hydrolyses of certain alkyl and substituted alkyl lactates, initiated several years ago,[2] has now been completed, and the effects of lengthening, of branching and of substituting the alkyl carbon chain upon the activation energies and frequency factors are reported in this paper. Studies on the "neutral" hydrolyses of some *n*-alkyl lactates are also reported.

Experimental Method

The sources and methods of purification of the lactic esters, the preparation and care of reagents and solutions and the precision of thermostatic controls were described in the preceding paper.[3] To start a hydrolysis a Victor Meyer bulb containing a known amount of ester was placed in a flask together with the amount of standard hydrochloric acid (acid hydrolysis) or water ("neutral" hydrolysis) necessary to give the desired ester concentration. In the case of the *n*-alkyl lactates, each solution was allowed to reach the temperature of the thermostat before the bulb was broken, but with most of the other lactates the bulb was broken in the catalyzing acid before the flask was placed in the thermostat. Aliquot portions of solutions of the *n*-alkyl esters were discharged into sufficient standard sodium hydroxide solution to neutralize just the catalyzing hydrochloric acid. Aliquot portions of solutions of the other lactates were discharged onto washed cracked ice. Excess acid (acid hydrolysis) or total acid ("neutral" hydrolysis) was titrated with standard sodium hydroxide solution using cresol red indicator. Time was measured with an electric stop-watch.

Second-order rate constants for the acid hydrolyses were evaluated from the slopes of plots of log $1/(a - x)$ *vs.* time in accordance with the pseudo first-order rate equation

$$k = \frac{2.303}{ct} \log \frac{1}{a - x} + \text{constant}$$

in which a represents the initial concentration of ester, x the concentration of lactic acid at time t, and c the essentially constant total acid concentration. Second-order rate constants for the "neutral" hydrolyses were evaluated from the slopes of the plots of log $(a^{1/2} + x^{1/2})/(a^{1/2} - x^{1/2})$ *vs.* time in accordance with the rate equation

$$k = \frac{2.303}{(ab)^{1/2}t} \log \frac{a^{1/2} + x^{1/2}}{a^{1/2} - x^{1/2}} + \text{constant}$$

in which a is the initial concentration of ester and x the concentration of acid formed at time t; the value of b, the ionization constant of lactic acid, was taken from the work of Martin and Tartar.[4] This rate equation is obtained by integrating: $dx/dt = k(a - x)(bx)^{1/2}$. The units of all rate constants are liters/mole^{-1} min.$^{-1}$.

Results and Discussion

In Table I, the second-order rate constants (k), activation energies (E_a), and *PZ* factors for the acid hydrolyses of nine lactic esters are given. Table II shows similar data for the "neutral" hydrolyses of four *n*-alkyl lactates.

TABLE I

ACID HYDROLYSES

Lactate	$10^3k_{30°}$	$10^3k_{40°}$	$10^3k_{50°}$	E_a, cal.	$PZ \times 10^{-8}$ (using $k_{30°}$)
Methyl	9.48	20.11		14150	1.55
Ethyl	10.01	20.69		13700	0.77
n-Propyl[a]	9.73	20.35		13700	0.72
n-Butyl	8.70	18.27		14000	1.04
Isobutyl	10.61	23.97	51.13	15300	11.47
s-Butyl	5.41	11.95	26.07	15300	5.66
t-Butyl	6.75	22.46	81.18	24200	1.77×10^7
2-Methoxy-ethyl	8.39	17.69		14050	1.15
2-Chloroethyl	5.63	12.15		14500	1.61

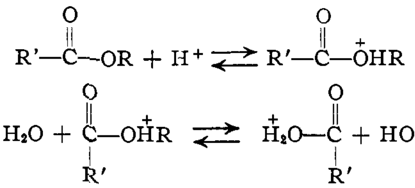
[a] $k_{60°} = 7.899 \times 10^{-2}$.

TABLE II

"NEUTRAL" HYDROLYSES

Lactate	$10^3k_{40°}$	$10^3k_{60°}$	E_a, cal.	$PZ \times 10^{-8}$ (using $k_{40°}$)
Methyl	25.90	118.08	15700	23.10
Ethyl	23.77	113.30	16200	47.49
n-Propyl	22.66	111.50	16500	73.42
n-Butyl	38.28	186.70	16400	105.5

With the exception of the case of *t*-butyl lactate, the pseudo first-order kinetics and the similarity among activation energies and *PZ* factors for the acid hydrolyses of the lactic esters listed in Table I are consistent with the mechanism proposed by Day and Ingold[5] (termed "bimolecular acid hydrolysis with acyl–oxygen fission" and labeled A'2) and by Roberts[6] (labeled II).



$$R'-\overset{\overset{\displaystyle O}{\|}}{C}-OR + H^+ \rightleftharpoons R'-\overset{\overset{\displaystyle O}{\|}}{C}-\overset{+}{O}HR$$

$$H_2O + \underset{\underset{\displaystyle R'}{|}}{\overset{\overset{\displaystyle O}{\|}}{C}}-\overset{+}{O}HR \rightleftharpoons H_2\overset{+}{O}-\underset{\underset{\displaystyle R'}{|}}{\overset{\overset{\displaystyle O}{\|}}{C}} + HOR$$

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[1] Abstracted from theses submitted by A. A. Colon and K. H. Vogel to the Committee on Graduate Degrees, Carnegie Institute of Technology, in partial fulfillment of the requirements for the D.Sc. degree.

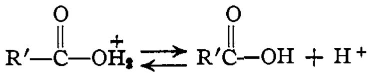
[2] A. A. Colon and J. C. Warner, *Bol. oficial asoc. quim. Puerto Rico*, **2**, No. 2, 15 (1943).

[3] K. H. Vogel and J. C. Warner, THIS JOURNAL, **75**, 6072 (1953).

[4] A. W. Martin and H. V. Tartar, *ibid.*, **59**, 2672 (1937).

[5] J. N. E. Day and C. K. Ingold, *Trans. Faraday Soc.*, **37**, 686 (1941).

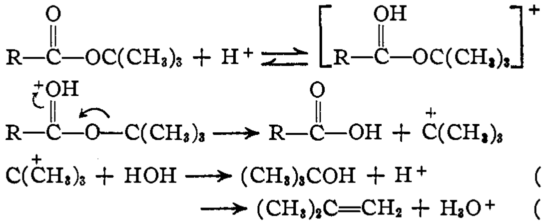
[6] I. Roberts, *Ann. N. Y. Acad. Sci.*, **39**, 375 (1940).



$$R'-\overset{O}{\overset{\|}{C}}-\overset{+}{O}H_2 \rightleftharpoons R'\overset{O}{\overset{\|}{C}}-OH + H^+$$

This series of reversible processes involves first a fast attachment of hydrogen ion to the alkyl oxygen atom of the ester, forming an oxonium ion. In a slow step, the electrophilic carbonyl atom of the oxonium ion is then attacked by a water molecule and a molecule of alcohol is expelled. The resulting oxonium ion rapidly loses a proton to form a carboxylic acid.

The *PZ* factor for the acid hydrolysis of *t*-butyl lactate is about 10^7 times larger than those for the other lactates, and the energy of activation is about 9 kcal./mole greater than the values for the remaining esters. Palomaa, *et al.*,[7] and Drushel and Dean[8] have measured rate constants for the acid hydrolyses of some alkyl acetates. Activation energies and *PZ* factors calculated from their data disclose that these values for the reaction involving *t*-butyl acetate exceed the values for the other acetic esters by about the same margin as that observed in our work on the lactic esters. It is therefore reasonable to assume that the mechanism for the acid hydrolysis of *t*-butyl esters is different from that which characterizes the acid hydrolysis of primary and secondary alkyl esters. Cohen and Schneider[9] have shown that *t*-butyl 2,4,6-trimethylbenzoate undergoes acid-catalyzed methanolysis by alkyl–oxygen fission and have reported evidence suggesting *t*-butyl esters suffer alkyl–oxygen fission on acid hydrolysis. Their mechanism for the alcoholysis is readily adapted to the hydrolysis of *t*-butyl esters.



$$R-\overset{O}{\overset{\|}{C}}-OC(CH_3)_3 + H^+ \rightleftharpoons \left[R-\overset{OH}{\overset{\|}{C}}-OC(CH_3)_3\right]^+ \tag{1}$$

$$R-\overset{\overset{+}{O}H}{\overset{\|}{C}}-O-C(CH_3)_3 \longrightarrow R-\overset{O}{\overset{\|}{C}}-OH + \overset{+}{C}(CH_3)_3 \tag{2}$$

$$\overset{+}{C}(CH_3)_3 + HOH \longrightarrow (CH_3)_3COH + H^+ \tag{3a}$$

$$\longrightarrow (CH_3)_2C{=}CH_2 + H_3O^+ \tag{3b}$$

This process involves the rapid reversible addition of a proton to the acyl oxygen atom of the ester, forming an oxonium ion which yields the carboxylic acid by the slow irreversible loss of the *t*-butylcarbonium ion. The latter may then be converted by water to *t*-butyl alcohol or through the loss of a proton to isobutylene; recent evidence[10] suggests that alcohol formation 3a should predominate over olefin formation 3b under the chosen conditions. It seems probable that steps 2 and 3 are not actually separate and distinct but are the components of a concerted process.

Comparison of the data for the acid hydrolyses of the *n*-alkyl lactates (Table I) and the data reported by Palomaa[7,11] and by Salmi[12] for the corresponding acetates demonstrates that increasing the length of the primary alkyl chain has little effect on the activation energy or the *PZ* factor for this reaction. However, sensible effects of chain branching may be observed. Branching by methyl at the β-position (isobutyl lactate) brings about an approximately tenfold increase in *PZ*, which is sufficient to cause a slight increase in the rate constants despite a simultaneous increase in E_a. Branching by methyl at the α-position (*s*-butyl lactate) likewise effects increases in both E_a and *PZ;* but in this case the former predominates, and the rate constants decrease. Substitution of a β-hydrogen atom in the ethyl group of ethyl lactate by a methyl, an ethyl, or a methoxy group brings about only very small progressive decreases in the velocity constants. Substitution by a β-chlorine atom brings about a somewhat larger decrease in rate, the result of an increased E_a.

The kinetic behavior of the four *n*-alkyl lactates on "neutral" hydrolysis (Table II) is in harmony with the assumption that the major reaction is really an acid hydrolysis in which the catalyzing acid is hydronium ion produced by the dissociation of the lactic acid formed during the reaction. However, the failure of the individual rate constants, E_a, and *PZ* values to agree with the values determined for the same compounds on acid hydrolysis suggests that the "neutral" hydrolysis is in fact a composite reaction of which the major component is acid hydrolysis but of which a hydrolysis reaction or reactions of some other type, possibly an internal displacement, also form a part. The anomalous behavior of *n*-butyl lactate in this series also suggests the operation of a competing hydrolysis reaction different from either acid or alkaline hydrolysis. Table II shows little change in velocity constants from methyl through *n*-propyl lactates on "neutral" hydrolysis. There is a progressive increase in both E_a and *PZ* through this series of compounds. However, the rate constants increase substantially in passing to *n*-butyl lactate, an effect caused largely by an increased *PZ* factor, as E_a is held constant. No such rate maximum for *n*-butyl lactate is found in either the acid or the alkaline hydrolysis.

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[7] M. H. Palomaa, E. J. Salmi, J. I. Jansson and T. Salo, *Ber.*, **68B**, 303 (1935).

[8] W. A. Drushel and E. W. Dean, *Am. J. Sci.*, **35**, 486 (1913).

[9] S. G. Cohen and A. Schneider, THIS JOURNAL, **63**, 3382 (1941).

[10] J. B. Levy, R. W. Taft, Jr., and L. P. Hammett, *ibid.*, **75**, 1253 (1953); H. C. Brown and H. L. Berneis, *ibid.*, **75**, 10 (1953).

[11] M. H. Palomaa, *Ann. Acad. Sci. Fennicae*, **A4**, No. 2, 1 (1913).

[12] E. J. Salmi, *Ber.*, **72B**, 1767 (1939).

The Hydrolysis of Some Alkyl Lactates. III. Ethyl O-Acetyllactate and O-Acetyllactic Acid[1]

BY A. ALBERTO COLON, KENNETH H. VOGEL, ROBERT B. CARLIN AND J. C. WARNER

RECEIVED MARCH 12, 1953

A number of investigations have been reported[2,3] on the kinetics of the hydrolysis of diesters in which the ester linkages are equivalent, but few studies have been made on diesters in which the linkages are not structurally equivalent. For this reason an investigation of the kinetics of the alkaline, acid and "neutral" hydrolyses of the diester, ethyl O-

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[1] Abstracted from theses by A. A. Colon and K. H. Vogel presented to the Committee on Graduate Degrees, Carnegie Institute of Technology, in partial fulfillment of the requirements for the D.Sc. degree.

[2] C. K. Ingold, *J. Chem. Soc.*, **133**, 1375 (1930).

[3] J. Meyer, *Z. physik. Chem.*, **67**, 257 (1909).

acetyllactate, was undertaken. To help clarify the mechanism the rate of hydrolysis of O-acetyllactic acid also was studied. The results of these investigations are reported in this paper.

Materials and Method

Ethyl O-acetyllactate and O-acetyllactic acid, obtained from the Eastern Regional Laboratory of the United States Department of Agriculture,[4] were distilled under reduced pressure and stored in a desiccator over calcium chloride.

For ethyl O-acetyllactate: b.p. 175-177° (745.3 mm.), $n^{28}\text{D}$ 1.4051, sapn. equiv., 79.97; reported b.p. 177° (733 mm.),[5] $n^{17}\text{D}$ 1.4085,[5] calcd. sapn. equiv., 80.08.

For O-acetyllactic acid: b.p. 101° (1.5 mm.), $n^{20}\text{D}$ 1.4222, sapn. equiv., 131.45; reported b.p. 101° (1.8 mm.),[6] calcd. sapn. equiv., 132.06.

1,4-Dioxane (Paragon Purified Grade) was refluxed over sodium for 12 hours and distilled through a Hempel column.

The apparatus and experimental procedures for the alkaline, acid and "neutral" hydrolyses were identical with those described in the preceding papers of this series.[7,8]

For each alkaline hydrolysis of O-acetyllactate ion in dioxane-water solution, dioxane was weighed into the reaction flask by means of a torsion balance, accurate to ±0.05 g. A Victor Meyer bulb charged with a known amount of O-acetyllactic acid was placed in the flask, and sufficient water and standard sodium hydroxide solution were added to give the desired concentrations of O-acetyllactate ion and catalyzing base and to produce a solution of predetermined dielectric strength. Dielectric constants were taken from the data of Akerlof and Short.[9]

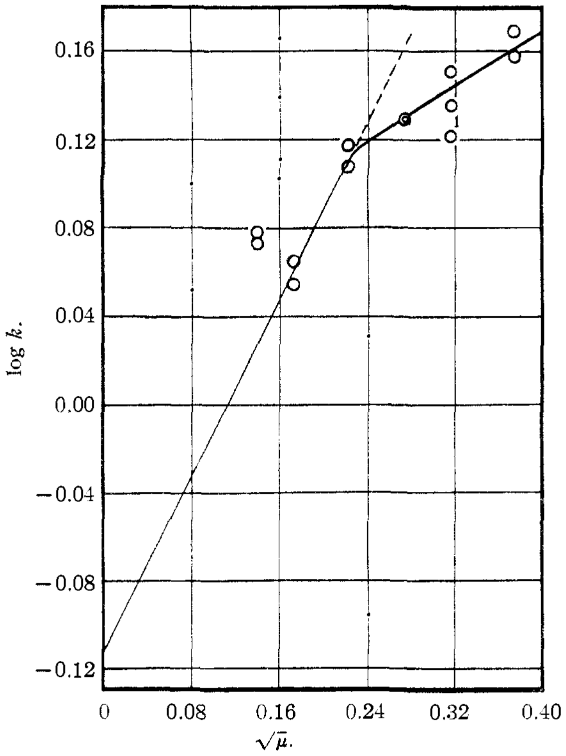


Fig. 1.—Rate constant as a function of ionic strength for alkaline hydrolysis of O-acetyllactic acid.

Alkaline Hydrolyses

Experimental Results.—Rate constants (all in liters mole^{-1} minute^{-1}) were calculated from the slopes of the best straight line plots of the data substituted into standard second order rate equations. Second order rate constants and activation energies for the alkaline hydrolysis of O-acetyllactate ion and for the two distinct steps of the alkaline hydrolysis of ethyl O-acetyllactate are summarized in Table I. The effect of changing ionic strength on the rate of the second step of the hydrolysis of ethyl O-acetyllactate is shown by a comparison of two rate constants determined in water solution at 40°. In solutions of ionic strengths 0.050 and 0.075, the respective average velocity constants were 1.862 and 2.549. A more detailed quantitative study of this effect was carried out in a series of alkaline hydrolyses of O-acetyllactate ion in water solution at 30°. The relationship between log k and $\mu^{1/2}$ is shown in Fig. 1. Table II summarizes the variation in the rate constant for the alkaline hydrolysis of O-acetyllactate ion with dielectric constant of dioxane-water solutions.

TABLE I

ALKALINE HYDROLYSES

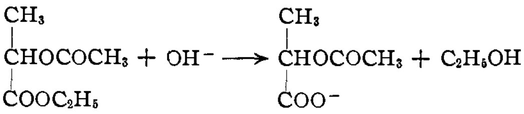
Ester	$k_{0°}$	$k_{10°}$	$k_{15°}$	$k_{40°}$	Ea. calcd.
Ethyl O-acetyllactate (1st step)	19.6	32.4			7,700
Ethyl O-acetyllactate (2nd step)	0.1018		0.3151	2.198	11,700
O-Acetyllactate ion	.1175		.3872	2.184	11,300

TABLE II

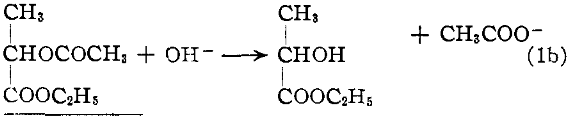
EFFECT OF DIELECTRIC CONSTANT ON THE RATE OF ALKALINE HYDROLYSIS IN SOLUTIONS OF CONSTANT IONIC STRENGTH (μ = 0.030)

Dioxane, %	Dielectric constant	$k_{30°}$
7.64	70	1.105
19.10	60	1.090
30.64	50	1.005

Discussion of Results.—The rates of the two steps which make up the complete alkaline hydrolysis of ethyl O-acetyllactate differ so markedly that each can be measured readily. The kinetic data support the belief that the mechanism for the alkaline hydrolysis of ethyl O-acetyllactate and of O-acetyllactate ion, like that of other alkyl esters, involves the nucleophilic attack of hydroxyl ion on the carbonyl carbon atom followed by acyl oxygen fission.[7,10] Since the attack might occur at either of the two ester groups in the ethyl O-acetyllactate, both the reaction sequence 1a, 2a and the sequence 1b, 2b must be considered.



$$\begin{array}{l}CH_3\\ |\\ CHOCOCH_3\\ |\\ COOC_2H_5\end{array} + OH^- \longrightarrow \begin{array}{l}CH_3\\ |\\ CHOCOCH_3\\ |\\ COO^-\end{array} + C_2H_5OH \quad (1a)$$



$$\begin{array}{l}CH_3\\ |\\ CHOCOCH_3\\ |\\ COOC_2H_5\end{array} + OH^- \longrightarrow \begin{array}{l}CH_3\\ |\\ CHOH\\ |\\ COOC_2H_5\end{array} + CH_3COO^- \quad (1b)$$

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[4] Courtesy of Drs. Lee T. Smith, C. H. Fisher and E. M. Filachione.

[5] L. T. Smith and H. V. Claborn, *Ind. Eng. Chem.*, **32**, 692 (1940).

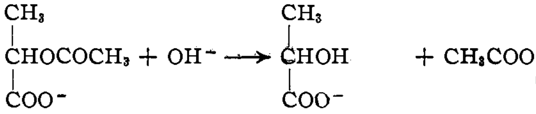
[6] Drs. C. H. Fisher and E. M. Filachione, private communication.

[7] K. H. Vogel and J. C. Warner, THIS JOURNAL, **75**, 6072 (1953).

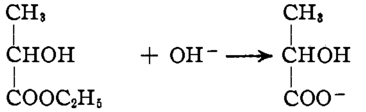
[8] A. A. Colon, K. H. Vogel and J. C. Warner, *ibid.*, **75**, 6072 (1953).

[9] G. Akerlof and O. A. Short, *ibid.*, **58**, 1241 (1936).

[10] J. N. E Day and C. K. Ingold, *Trans. Faraday Soc.*, **37**, 686 (1941).



$$\mathrm{CH_3CH(OCOCH_3)COO^-} + \mathrm{OH^-} \longrightarrow \mathrm{CH_3CH(OH)COO^-} + \mathrm{CH_3COO^-} \quad (2a)$$



$$\mathrm{CH_3CH(OH)COOC_2H_5} + \mathrm{OH^-} \longrightarrow \mathrm{CH_3CH(OH)COO^-} + \mathrm{C_2H_5OH} \quad (2b)$$

Information previously available on the rates of alkaline hydrolysis of alkyl lactates and acetates pointed to reactions 1a and 2a as the more probable of the two sequences. One would expect the rate constant for reaction 1a to be approximately of the same order of magnitude as the known rate constant for reaction 2b (24.1 l. mole^{-1} min.$^{-1}$ at 15°)[8]; similarly, the rate constant for reaction 1b should not differ greatly from that for *s*-butyl acetate (0.816 l. mole^{-1} min.$^{-1}$ at 20°).[11] A comparison of these values with the rate constant for the first step in the alkaline hydrolysis of ethyl O-acetyllactate (Table I) strongly favors reaction 1a over 1b. Furthermore the small rate constants for the second step (Table I) eliminates 2b from consideration. Confirmatory evidence for reaction 2a was obtained by determining the rates and activation energies for the alkaline hydrolysis of O-acetyllactate ion (Table I) and comparing these quantities with analogous values for the second step.

The effect of changing ionic strength of the medium provides further evidence in support of the reaction sequence 1a and 2a. Strong positive salt effects both on the rate of the second step of the alkaline hydrolysis of ethyl O-acetyllactate and of that on the alkaline hydrolysis of O-acetyllactate ion were observed. The Brønsted–Bjerrum rate equation and the Debye-Hückel theory may be combined to yield the following equation[12] for water solutions at 25°

$$\log k = \log k_0 + 1.02 Z_A Z_B \mu^{1/2} \qquad (3)$$

where the Z terms are integers representing the charges on the ions A and B undergoing reaction, k and k_0 are the rate constants for a reaction measured in solutions of finite and infinite dilutions, respectively, and μ is the ionic strength of the former. This equation predicts a positive salt effect on the rate of a reaction such as 2a, which involves the interaction of two ions of like charge sign. The degree to which experimental data from the alkaline hydrolysis of O-acetyllactate ion approaches the limiting equation 3 is shown by Fig. 1. The straight line extrapolation to zero ionic strength in Fig. 1 has the theoretical slope 1.02, and the data appear to conform to a curve which approaches this straight line at lower ionic strengths.

Table II indicates a decrease in the rate of alkaline hydrolysis of O-acetyllactate ion with decreasing dielectric strength of the medium. This effect is to be expected of a reaction between two ions of like charge sign, in view of Scatchard's equation[13]

$$\frac{\log k_0}{(1/D)} = -\frac{Z_A Z_B \epsilon^2}{2.303 r \mathbf{k} T} \qquad (4)$$

where the Z terms and k_0 have the meanings assigned them in equation 3, D is the dielectric constant, ϵ is the unit electric charge, $\mathbf{k}$ is Boltzmann's constant, T is the absolute temperature and r is the radius of the activated complex. The rate constants (k) of Table II had to be transformed in some way to the corresponding rate constants at infinite dilution (k_0) before an effort could be made to apply equation 4. If the assumption is made that equations analogous to 3 hold for solutions having ionic strengths less than 0.030, then log k_0 values can be calculated from the k values of Table II, which were measured in solutions of ionic strength 0.030. In view of the comparatively small ionic strength of these solutions, the assumption is not likely to lead to gross errors. Figure 2 shows that a plot of log k_0 values, calculated in this way, against $1/D$ closely approximates the linear relationship predicted by equation 4. Since this equation indicates that the slope of the best straight line (Fig. 2) should be equal to $-Z_A Z_B \epsilon^2/2.303 r\mathbf{k}T$, r, the radius of the transition state of reaction 2a, may be calculated as 8.1 Å. Compared with the distance of critical ionic separation for similar reactions,[14] this value seems too high even when one takes into account the uncertainty in extrapolating rate constants. Nevertheless, the observed effect of dielectric constant on rate qualitatively supports the proposed mechanism.

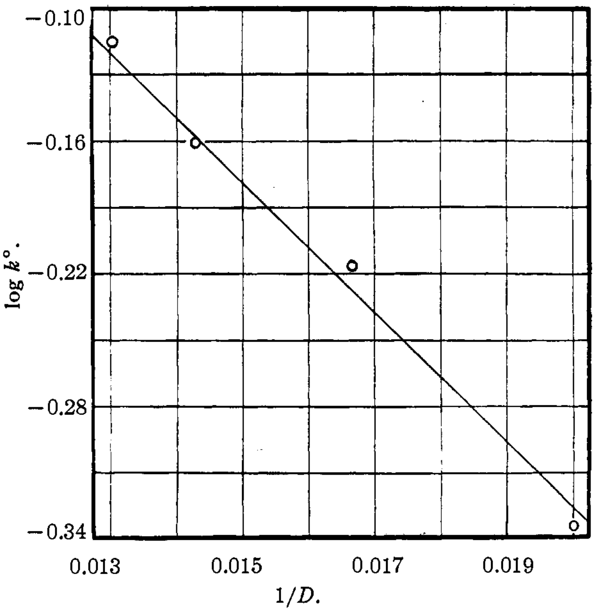


Fig. 2.—Rate constant extrapolated to zero ionic strength as a function of dielectric constant for alkaline hydrolysis of O-acetyllactic acid.

Acid Hydrolyses

Experimental Results.—Second-order rate constants (all in liters mole^{-1} minute^{-1}) for the acid hydrolyses of ethyl O-acetyllactate were evaluated from the slopes of the plots of log ($2a$ − x) *vs.*

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[11] H. Olsson, *Z. physik. Chem.* **118**, 107 (1925).

[12] See S. Glasstone, K. J. Laidler and H. Eyring, "The Theory of Rate Processes," McGraw-Hill Book Co., Inc., New York, N. Y., 1941, p. 428.

[13] G. Scatchard, *Chem. Revs.*, **10**, 229 (1932).

[14] See E. A. Moelwyn-Hughes, "The Kinetics of Reaction in Solutions," 2nd edition, Oxford, Univ. Press, New York, N. Y., 1947, p. 106.

time in accordance with the pseudo first-order rate equation

$$k = \frac{-2.303}{ct} \log (2a - x) + \text{constant} \qquad (5)$$

in which a represents the initial concentration of ester, x the concentration of the resulting acid at time t, and c the essentially constant total acid concentration. The plots were linear up to conversions of about 70%, whereas log $(a - x)$ *vs.* time plots, according to the equation

$$k = \frac{-2.303}{ct} \log (a - x) + \text{constant} \qquad (6)$$

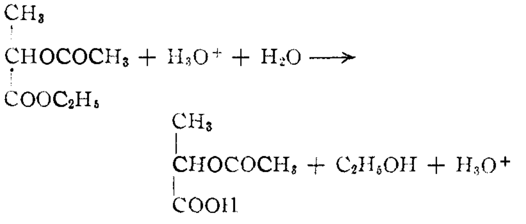
were linear up to only 25–30% conversions. However, log $(a - x)$ *vs.* time plots were linear for the acid hydrolysis of O-acetyllactic acid to a high degree of conversion; accordingly the rate constants for this reaction were evaluated by means of equation 6. "Initial" rate constants for the acid hydrolysis of ethyl O-acetyllactate were computed from the slopes of the linear portions of plots of log $(a - x)$ *vs.* time, obtained at low conversions, and equation 6. Table III shows the rate constants and activation energies for the acid hydrolysis of ethyl O-acetyllactate and for the acid hydrolysis of O-acetyllactic acid.

TABLE III

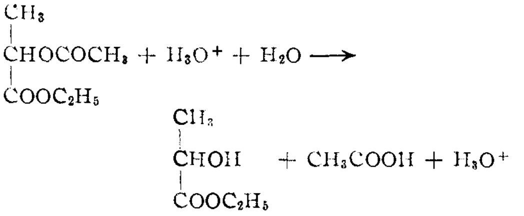
ACID HYDROLYSES

Ester	$k_{0°}$ × 10^3	$k_{40°}$ × 10^3	$k_{60°}$ × 10^3	E_a Cal.
O-Acetyllactic acid		6.24	30.86	16,600
Ethyl O-acetyllactate	2.57	6.17	30.85	16,500
"Initial" rate ethyl O-acetyllactate	5.41	13.82		17,700

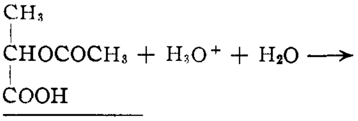
Discussion of Results.—The kinetics of and the activation energies for the acid hydrolysis of ethyl O-acetyllactate and of O-acetyllactic acid indicate that the mechanism is the same as that which controls the acid hydrolysis of esters of primary alcohols.[8,10,15] Hydrolysis of ethyl O-acetyllactate might proceed by either of the routes 7a, 8a or 7b, 8b or by both simultaneously.

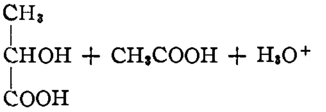


$$\begin{array}{l}CH_3\\ |\\ CHOCOCH_3\\ |\\ COOC_2H_5\end{array} + H_3O^+ + H_2O \longrightarrow \begin{array}{l}CH_3\\ |\\ CHOCOCH_3\\ |\\ COOH\end{array} + C_2H_5OH + H_3O^+ \qquad (7a)$$

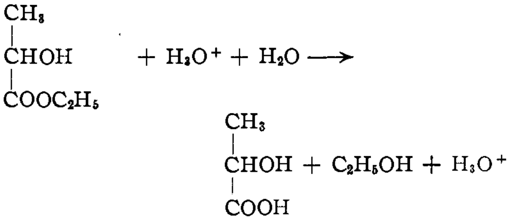


$$\begin{array}{l}CH_3\\ |\\ CHOCOCH_3\\ |\\ COOC_2H_5\end{array} + H_3O^+ + H_2O \longrightarrow \begin{array}{l}CH_3\\ |\\ CHOH\\ |\\ COOC_2H_5\end{array} + CH_3COOH + H_3O^+ \qquad (7b)$$





$$\begin{array}{l}CH_3\\ |\\ CHOCOCH_3\\ |\\ COOH\end{array} + H_3O^+ + H_2O \longrightarrow \begin{array}{l}CH_3\\ |\\ CHOH\\ |\\ COOH\end{array} + CH_3COOH + H_3O^+ \qquad (8a)$$



$$\begin{array}{l}CH_3\\ |\\ CHOH\\ |\\ COOC_2H_5\end{array} + H_3O^+ + H_2O \longrightarrow \begin{array}{l}CH_3\\ |\\ CHOH\\ |\\ COOH\end{array} + C_2H_5OH + H_3O^+ \qquad (8b)$$

The results of the kinetic studies support the belief that reactions 7a, 7b and 8a all proceed at essentially identical rates and have identical activation energies; reaction 8b has been studied previously[8] and is known to proceed at a rate about five times greater and to have an activation energy of about 3 kcal./mole less than the other three reactions. The function $(2a - x)$ measures the *concentration of all ester linkages* in solution; the function $(a - x)$ approximates the concentration of unchanged ethyl O-acetyllactate only during the early part of the reaction when nearly all of the ester linkages are present as unchanged ethyl O-acetyllactate. Therefore, the fact that log $(2a - x)$ is linear with time for a substantial portion of the reaction whereas log $(a - x)$ is linear with time only at low conversions indicates that the rate of acid hydrolysis of ester linkages of all types is being measured and all types of ester linkages being hydrolyzed are undergoing reaction at nearly identical rates, until high conversions are reached. The rate constants (Table III) for ethyl O-acetyllactate, derived from the log $(2a - x)$ plot, are in liters min.$^{-1}$ (*ester equivalent*)$^{-1}$; the initial rate constants, derived from the linear portions of the log $(a - x)$ *vs.* time plots, are in liters min.$^{-1}$ (*mole* of ethyl O-acetyllactate)$^{-1}$. Since the initial rates per mole are about twice those per ester equivalent, it is then reasonable to conclude that the two ester linkages of ethyl O-acetyllactate undergo acid hydrolyses (reactions 7a and 7b) at about the same rate and that the two reactions have about the same activation energy. It is also striking to observe (Table III) that the ester linkage of O-acetyllactic acid undergoes acid hydrolysis (reaction 8a) at the same rate and with the same activation energy as reactions 7a and 7b. If the foregoing deductions concerning the rates of reactions 7 and 8 are correct, then it follows that acetylation of the hydroxyl group of ethyl lactate causes about a fivefold decrease in rate of acid hydrolysis of the carbethoxyl group at room temperature and an increase of about 3 kcal./mole in activation energy (compare 8b and 7a). On the other hand esterification of O-acetyllactic acid with ethanol has no perceptible effect on the rate of acid hydrolysis of the acetoxyl group or on its activation energy. The activation energy is also virtually identical with the value 16,550 cal./mole calculated from the rate data of Palomaa, *et al.*,[16] on the acid hydrolysis of an analogous ester, *s*-butyl acetate.

The "neutral" hydrolysis of ethyl O-acetyllactate

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[15] I. Roberts, *Ann. N. Y. Acad. Sci.*, **39**, 375 (1940).

[16] M. H. Palomaa, E. J. Salmi, J. I. Jansson and T. Salo, *Ber.*, **68B**, 303 (1935).

has been studied briefly and found to behave kinetically like the *n*-alkyl lactates. Therefore, the major reactions are again probably the hydronium ion-catalyzed hydrolyses of ester linkages, the hydronium ions being provided by the organic acids formed during the hydrolysis. Thus reactions 7 and 8 are doubtless concerned in the "neutral" hydrolysis in the same way that they are in the acid hydrolysis.

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Infrared Spectra and Structure of Crystalline Ammonia Hydrates

BY R. D. WALDRON AND D. F. HORNIG

RECEIVED AUGUST 20, 1953

Recent very careful studies of the heat capacity and thermodynamic properties of $NH_3 \cdot H_2O$ and $2NH_3 \cdot H_2O$,[1] as well as earlier studies of the solid phases of the ammonia–water system,[2] have demonstrated that the two ammonia hydrates are well-defined compounds of exact composition.

The structure of these compounds is of some interest since they might exist either as simple hydrates or as ionic crystals. Although considerable experimental evidence exists to indicate that aqueous solutions of ammonia are only slightly ionized,[3] Hildenbrand and Giauque regard the crystalline hydrates as ammonium salts, *i.e.*, $(NH_4)OH$ and $(NH_4)_2O$.

No previous spectroscopic studies of the solid phases of the NH_3–H_2O system were uncovered in a survey of the literature although the infrared and Raman spectra of aqueous ammonia[4,5] have been obtained.

In the present study mixtures of NH_3 and H_2O vapor were admitted to a low temperature infrared cell[6] and condensed on NaCl or KBr plates cooled with liquid nitrogen. The spectra obtained were consistent with an ammonia hydrate structure and definitely exclude an ionic structure.

Results

Figure 1 shows the spectra obtained for mixtures of NH_3 and H_2O at −195°, together with those of pure NH_3, H_2O and NH_4X for comparison. It is immediately clear that the spectra bear little resemblance to that of the NH_4^+ ion, and the absence of the NH_4^+ ion bending vibration at about 1400 cm.$^{-1}$ is conclusive. On the other hand, they closely parallel the spectra of crystalline NH_3 and H_2O, although there are some clear differences.

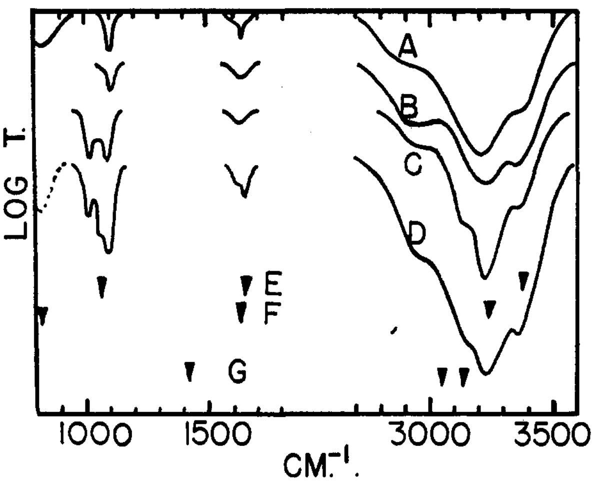

Fig. 1.—Infrared spectra of crystals of the NH_3–H_2O system at −195° together with comparison spectra: A, $NH_3 \cdot H_2O + H_2O$; B, $NH_3 \cdot H_2O$; C, $2NH_3 \cdot H_2O$; D, $NH_3 + 2NH_3 \cdot H_2O$ (some frost formation entailed by a small vacuum leak); E, crystalline NH_3; F, Ice; G, ammonium ion.

The interpretation of the low frequency region of the spectrum is most obvious. The strong ice band at 812 cm.$^{-1}$[7] appears in the spectrum with excess H_2O (A) but not in (B) or (C), so that the H_2O in the compounds is included in a lattice different from ice. If the 812 cm.$^{-1}$ band is a lattice vibration connected with the torsional oscillations of the H_2O molecules, the H_2O molecules cannot be as tightly bound in the hydrates as in ice; *i.e.*, one of the O–H · · · O bonds must have been replaced by an O–H · · · N bond. The symmetrical bending vibration of ammonia, which occurs at 1060 cm.$^{-1}$ in the pure crystal,[8] appears at 1102 cm.$^{-1}$ in $NH_3 \cdot H_2O$ (B) and as a doublet, 1020 and 1091 cm.$^{-1}$, in $2NH_3 \cdot H_2O$ (C). The doubling probably indicates that the environment of the two NH_3 molecules is not identical. Excess NH_3 (D) produces an additional shoulder at 1069 cm.$^{-1}$ which may be identified as free NH_3.

Both the bending vibration of H_2O and the doubly degenerate bending vibration of NH_3 may contribute to the absorption near 1625 cm.$^{-1}$. However, since the symmetric bending vibration is far more intense than the degenerate one in both gaseous and crystalline NH_3, it does not seem likely that very much of the observed absorption in this region is caused by NH_3.

The stretching region cannot be analyzed so straightforwardly. The peak at 2950 cm.$^{-1}$ occurs in the spectrum of both hydrates but is relatively more intense in that of $NH_3 \cdot H_2O$ (B). It is probably too low in frequency to be ascribed to OH, since only acidic OH in very strong H-bonds absorbs at so low a frequency, and then only rarely. Similarly, NH · · · N bonds would probably not lead to such a low frequency, leaving an NH · · · O bond as the most likely explanation for this band. If this is correct, it seems likely that in $2NH_3 \cdot H_2O$ only one of the ammonia molecules is involved. The peak at 3140 cm.$^{-1}$ (C) belongs to $2NH_3 \cdot H_2O$ and may represent a weaker NH · · · O bond from the second NH_3 molecule.

The remaining peaks at 3220 and 3365 cm.$^{-1}$ are characteristic of hydrogen bonded O–H and N–H vibrations and cannot be assigned in detail. Although some of the 3220 cm.$^{-1}$ absorption in A is

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[1] D. L. Hildenbrand and W. F. Giauque, THIS JOURNAL, **75**, 2811 (1953).

[2] I. L. Clifford and E. Hunter, *J. Phys. Chem.*, **37**, 101 (1933).

[3] P. F. van Velden and J. A. A. Ketelaar, *Chem. Weekblad*, **43**, 401 (1947).

[4] G. Costeanu, R. Freymann and A. Naherniac, *Compt. rend.*, **200**, 819 (1935).

[5] B. P. Rao, *Proc. Indian Acad. Sci.*, **20A**, 292 (1944).

[6] E. L. Wagner and D. F. Hornig, *J. Chem. Phys.*, **18**, 296 (1950).

[7] F. P. Reding, Thesis, Brown University, 1951.

[8] F. P. Reding and D. F. Hornig, *J. Chem. Phys.*, **19**, 594 (1951).

undoubtedly caused by ice and some of the 3365 cm.$^{-1}$ absorption in D by ammonia, it should be noted that the addition of NH_3 in passing from B to C increases the relative intensity of the 3220 cm.$^{-1}$ peak. It follows therefore that NH_3 also absorbs in this region.

Structural Conclusions

It seems clear that neither hydrate of ammonia contains ammonium ions. In addition to the reasons previously outlined, the presence of NH_4^+ ion would imply OH^- or O^{--} ions. In the former case a frequency higher than any observed would be expected (OH^- absorption occurs at 3638 cm.$^{-1}$ in NaOH[9]); in the latter there is no explanation for the two highest frequencies.

$NH_3 \cdot H_2O$ is a bimolecular crystal. There are five H atoms and only three unshared electron pairs per mole, so at least two H atoms must be either nonbonded or very weakly bonded. If, as in crystalline NH_3, three weak hydrogen bonds are formed to the single electron pair of NH_3, only two strong bonds can be formed. From the spectrum it can be concluded that a strong $NH \cdots O$ bond is formed (2.8 Å. or less from the magnitude of the frequency shift observed) and that both hydrogens from H_2O are involved in at least weak hydrogen bonds (since free H_2O absorbs near 3700 cm.$^{-1}$). This implies at least one $O\text{–}H \cdots N$ bond.

$2NH_3 \cdot H_2O$ is a trimolecular crystal. The two NH_3 molecules appear to be non-equivalent. The structure includes at least one strong $NH \cdots O$ bond and all of the hydrogens from H_2O are hydrogen bonded.

(9) W. Busing. Symposium on Molecular Structure and Spectroscopy. The Ohio State University. June. 1953.

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A New Reaction of Organogermanium Compounds

BY ROBERT WEST

RECEIVED JULY 27, 1953

Among organometallic compounds, those of arsenic have long been considered to be unique in that primary and secondary derivatives can be reduced to mono- or dialkylarsines, $RAsH_2$ or R_2AsH, by zinc and hydrochloric acid.[1] We have found that organogermanium compounds can be reduced to the corresponding hydrides under similar conditions. This reaction is interesting since all attempts to reduce organotin or organosilicon compounds to the hydrides in the same way have been unsuccessful. Thus a solution of triphenylgermanium bromide, when treated with amalgamated zinc and aqueous HCl, is readily reduced to triphenylgermane. The product can be identified easily by the strong Ge–H fundamental stretching vibration at 2400 cm.$^{-1}$ in the infrared spectrum.[2] However, under similar conditions triphenyltin chloride or iodide gave no material showing Sn–H absorption (at 1870 cm.$^{-1}$)[3]; and diphenyldichlorosilane and triphenylchlorosilane gave no products showing Si–H absorption (at 2100 cm.$^{-1}$).[4]

The reduction of organogermanium compounds to hydrides in this way parallels the known reaction of inorganic germanium compounds with alkali and aluminum, in which small amounts of GeH_4 are formed.[5] The reason for the anomalous easy formation of Ge–H bonds in reductions of this type is not known, but it is interesting to note that such reduction is consistent with Sanderson's recent conclusion that germanium is actually more electronegative than either silicon or tin.[6] The evidence found by Johnson and Harris for the metalation of triphenylgermane by phenyllithium[7] is another possible indication of abnormally high electronegativity for germanium.

Experimental

Triphenylgermane.—To 15 g. of amalgamated zinc dust was added 2 g. of triphenylgermanium bromide[8] dissolved in 100 ml. of 1:1 ethanol–ethyl ether. Over two hours, 50 ml. of 12 *N* aqueous HCl was added, with occasional stirring. The solution was then decanted and partitioned between water and ether; the organic layer was washed with water, dried and evaporated to give 0.6 to 1.0 g. of oily material, principally triphenylgermane. This crude product contained about 15% of tetraphenylgermane, m.p. 230°, which could be obtained by washing with methanol.

Crude triphenylgermane from two such runs was passed through an alumina chromatographic column in cyclohexane solution; the cyclohexane was then evaporated and the residual oil was crystallized from methanol to give 0.5 g. of triphenylgermane as transparent hexagonal plates of the β-form, m.p. 27°.[7,8] The infrared absorption spectrum in chloroform solution showed bands at 4200, 3030, 2040, 1950, 1880, 1818, 1726, 1610, 1490, 1433, 1382, 1338, 1308, 1260, 1098, 1068, 1027 and 1002 cm.$^{-1}$.

Further elution of the chromatogram with 1:1 benzene–chloroform gave 0.3 g. of solid material, m.p. 130°, probably triphenylgermanol.[8]

Dimethylgermane.—To 20 g. of amalgamated zinc dust was added 4.0 g. of dimethylgermanium sulfide[9] dissolved in 50 ml. of ethanol. Over 1 hour, 50 ml. of 12 *N* HCl was added. The gaseous products were condensed in a trap held at −78°. The contents of the trap (dimethylgermane, ethanol and hydrogen sulfide) were separated by bulb-to-bulb distillation on a vacuum chain to give 0.2 g. of dimethylgermane; mol. wt. calcd. 105, found 97, 99 (vapor density). The gas had strong infrared absorption bands at 2985 (C–H), 2060 (Ge–H) and 844 cm.$^{-1}$ (Ge–C), as well as weaker bands at 898 and 882 cm.$^{-1}$.

A similar reaction was carried out using methylgermanium trichloride instead of dimethylgermanium sulfide. No methylgermane was found in the trap, which was held at −120° during the reaction.

Attempted Reduction of Tin and Silicon Compounds.—These reactions were carried out similarly to the reduction of triphenylgermanium bromide, except that the crude products were not chromatographed. Diphenyldichlorosilane and triphenylchlorosilane were treated with amalgamated zinc and gaseous HCl in absolute ethanol to prevent irreversible hydrolysis. The only compounds found in the products from these reactions were diphenylsilanediol and triphenylsilanol, respectively.

Triphenyltin chloride and iodide were treated in the same way as triphenylgermanium bromide, except that the reactions were carried out under nitrogen to prevent any oxida-

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(1) A. W. Palmer and W. M. Dehn, *Ber.*, **34**, 3594 (1901); W. M. Dehn, *Am. Chem. J.*, **33**, 101 (1905); **40**, 88 (1908); W. M. Dehn and B. B. Wilcox, *ibid.*, **35**, 1 (1906).

(2) W. B. Steward and H. H. Nielsen, *Phys. Rev.*, **48**, 861 (1935); J. W. Straley, C. H. Tindal and H. H. Nielsen, *ibid.*, **62**, 161 (1942).

(3) D. R. Lide, Jr., *J. Chem. Phys.*, **19**, 1605 (1951).

(4) J. A. Hawkins and M. K. Wilson, *ibid.*, **21**, 360 (1953); R. West and E. G. Rochow, *J. Org. Chem.*, **18**, 303 (1953).

(5) J. H. Müller and N. H. Smith, THIS JOURNAL, **44**, 1909 (1922).

(6) R. T. Sanderson, *ibid.*, **74**, 4792 (1952).

(7) O. H. Johnson and D. M. Harris, *ibid.*, **72**, 5566 (1950).

(8) C. A. Kraus and L. S. Foster, *ibid.*, **49**, 457 (1927)

(9) E. G. Rochow, *ibid.*, **70**, 1801 (1948).

tion of Sn-H bonds. The reaction products were apparently mixtures, containing no detectable amount of triphenylstannane.

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COMMUNICATIONS TO THE EDITOR

THE SYNTHESIS OF AN ARGINYL PEPTIDE

Sir:

The synthesis of peptides containing arginine has presented unusual difficulties, and only a few dipeptides have been reported. No peptide in which the carboxyl group of arginine is linked to another amino acid has been synthesized.[1] It has now been found that the pyrophosphite method[2] can be used for this purpose.

Carbobenzoxy-L-arginine hydrobromide[3] (0.010 mole) and methyl L-leucinate (0.010 mole) were added to 7 cc. of diethyl phosphite, then tetraethyl pyrophosphite (0.020 mole) was added. After 30 minutes heating on a steam-bath, methyl carbobenzoxy-L-arginyl-L-leucinate hydrobromide hydrate was precipitated as a gum by 100 cc. of anhydrous ether. This was crystallized by dissolving in 5 cc. of methanol, bubbling in hydrogen bromide a moment, then adding 40 cc. of anhydrous ether; yield 3.06 g. (57%). A further 0.47 g. was obtained from the original filtrate on dilution with ether, giving 3.53 g. in all (66%). Solution in 10 cc. of methanol and dilution with 40 cc. of water yielded 2.79 g. (52%), m.p. 90–92°,[4] $[\alpha]^{23}\text{D}$ −20.3° (*c* 2, methanol).

Anal. Calcd. for $C_{21}H_{36}N_5O_6Br$: C, 47.2; H, 6.79; N, 13.1; Br, 15.0. Found: C, 47.4; H, 6.99; N, 13.3; Br, 15.2.

Carbobenzoxy-L-arginyl-L-leucine was obtained by heating 2.83 g. of the methyl ester hydrobromide hydrate on a steam-bath in 28 cc. of *N* hydrobromic acid for an hour, making slightly alkaline with ammonium hydroxide and chilling. The crystalline product was recrystallized from 30 cc. of *N*/6 hydrobromic acid by the addition of ammonium hydroxide; yield 1.20 g. (54%), m.p. 223–224° dec., $[\alpha]^{24}\text{D}$ −26° (*c* 2, 0.4 *N* HBr). *Anal.* Calcd. for $C_{20}H_{31}N_5O_5$: C, 57.0; H, 7.41; N, 16.6. Found: C, 57.2; H, 7.64; N, 16.6.

L-Arginyl-L-leucine hydrobromide hydrate was obtained by hydrogenation with a palladium catalyst of 1.06 g. of the carbobenzoxy derivative in 40 cc. of water plus 2.5 cc. of 1.04 *N* HBr. A crystalline product obtained by evaporation of the filtered solution under vacuum was washed out with acetone, then recrystallized by dissolving in 4 cc. of water and slowly adding 40 cc. of acetone; yield 0.78 g. (80%), m.p. 162–163° dec., $[\alpha]^{24}\text{D}$ +8.6° (*c* 2, water).

Anal. Calcd. for $C_{12}H_{28}N_5O_4Br$: C, 37.3; H, 7.3; N, 18.1; Br, 20.7. Found: C, 37.1; H, 7.2; N, 18.2; Br, 20.7.

Paper chromatography gave an R_f value of 0.58 in a butanol–water–acetic acid (5:4:1) system, and showed the presence of arginine and leucine in an acid hydrolysate.

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STAMFORD, CONNECTICUT

RECEIVED SEPTEMBER 2, 1953

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[1] J. S. Fruton, "Advances in Protein Chemistry," Vol. V, Academic Press, Inc., New York, N. Y., 1949, p. 64.

[2] G. W. Anderson, J. Blodinger and A. D. Welcher, THIS JOURNAL, **74**, 5309 (1952).

[3] Prepared by R. Janice Joyce, of these laboratories: m.p. 177–179.5°, $[\alpha]^{24}\text{D}$ −6.9° (*c* 2, water); calcd. for $C_{14}H_{21}N_4O_4Br$: 20.8% Br. Found: 20.6% Br.

[4] Melting points were taken on a calibrated Fisher–Johns block.

TWO DIMENSIONAL PHASE TRANSITION OF ETHANE ON SODIUM CHLORIDE

Sir:

The chief evidence for first-order phase transitions of films adsorbed on solid surfaces has been the adsorption isotherms measured by Jura, *et al.*, for *n*-heptane on graphite,[1] ferric oxide[2] and reduced silver powder.[3] Adsorption isotherms for *n*-heptane on the same solids (but not the same samples) have subsequently been repeated by Smith[4] and by Young, Beebe and Bienes,[5] who report that their work provides no evidence of first-order phase transitions in those systems. Their papers support the trend to interpret all experimentally observed discontinuities in adsorption isotherms as caused by slow rates or diffusion inside the sample or errors in the apparatus.

The chief remaining evidence for a first-order phase transition of an adsorbed film on a solid surface now devolves on the adsorption isotherms of ethane on sodium chloride and on potassium chloride crystals at 90°K., reported by Ross and Boyd,[6] and since verified in this laboratory on a different sample of sodium chloride at 90°K. by Mr. W.

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[1] G. Jura, W. D. Harkins and E. H. Loeser, *J. Chem. Phys.*, **14**, 344 (1946).

[2] G. Jura, E. H. Loeser, P. R. Basford and W. D. Harkins, *ibid.*, **14**, 117 (1946).

[3] Jura, *et al.*, *ibid.*, **13**, 535 (1945).

[4] R. N. Smith, THIS JOURNAL, **74**, 3477 (1952).

[5] D. M. Young, R. A. Beebe and H. Bienes, *Trans. Faraday Soc.*, **49**, 1086 (1953).

[6] S. Ross and G. E. Boyd, "New Observations on Two-Dimensional Condensation Phenomena," MDDC Report 864, 1947.