

to how formate may be carried by a functional derivative of folic acid. Accordingly, formylfolic acid was prepared by heating 2 cc. of 98% formic acid and 0.5 cc. of acetic anhydride with 26 mg. of folic acid (pteroylglutamic acid) for one hour at 100°. The volatile reactants were removed *in vacuo*, and the light yellow product was precipitated from an alkaline solution by acetic acid. For analysis, a sample was hydrolyzed, and formic acid determined (Calcd.: 9.8%. Found.: 9.5%). The formylfolic acid was as effective as folic acid in stimulating the growth of *Streptococcus faecalis R* and *Lactobacillus casei*.

However, in an inhibition analysis with 7-methylfolic acid,⁴ formylfolic acid was approximately thirty times as active as folic acid in preventing the toxicity of the inhibitor for *S. faecalis R*; the antibacterial index was 3,000 for formylfolic acid as compared with 100 for folic acid over a range of inhibitor concentrations from 10 to 100 γ per 10 cc. In 10 cc. of medium,² a mixture of 0.3 γ of folic acid with 0.03 γ of formylfolic acid was no more effective than 0.03 γ of formylfolic acid alone in preventing the toxicity of the inhibitor. Synthetic rhizopterin³ was two to three times as effective as folic acid in preventing the toxicity of the inhibitor. The toxicity of methylfolic acid was increased several fold by treating with 98% formic acid at 100° for two hours. For *L. casei* formylfolic acid was only slightly more effective than folic acid in preventing the toxicity of the inhibitor.

These results indicate that formylfolic acid is a functional derivative of folic acid and is competitively inhibited by methylfolic acid. The activity of rhizopterin indicates that it probably is converted directly to formylfolic acid.

These and other unpublished experiments offer additional evidence that the biochemical functions of *p*-aminobenzoic and folic acid derivatives involve the introduction of the single carbon unit into purines, pyrimidines and probably histidine.

The possibility of enhanced activity and decreased toxicity for formylfolic acid as compared with folic acid in treatment of pernicious anemia indicates the desirability for clinical testing.

(4) Crude product from the condensation of α,β -dibromobutyraldehyde, 2,4,5-triamino-6-hydroxypyrimidine and *p*-aminobenzoylglutamic acid obtained from Dr. E. L. R. Stokstad (Franklin, *et al.*, *J. Biol. Chem.*, **169**, 427 (1947)).

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CONCERNING THE STRUCTURE OF PHTHIOIC ACID

Sir:

Polgar and Robinson¹ have recently proposed, partly on the basis of the highly questionable deg-

radative evidence of Wagner-Jauregg,² that phtthioic acid,³ isolated from tubercle bacillus, may be 3,13,19-trimethyltricosanoic acid. This acid was synthesized, but since it contains three asymmetric carbons the *dl*-mixture was of no value for comparison with the natural product. By use of the data which have now been collected concerning the optical rotation of fatty acids containing branching methyl groups, it is possible to estimate with some accuracy the maximum rotation to be expected of an acid such as 3,13,19-trimethyltricosanoic acid. Data of interest to this discussion appear in Table I.

TABLE I

| Acid | $[\alpha]_D$ | $[M]_D$ |
|---|-------------------|---------|
| (+)-2-Methylhexacosanoic ⁴ | 6.8° ^a | 28° |
| (+)-2-Methyldodecanoic ⁴ | 13.2° | 28.3° |
| (+)-4-Methylhexanoic ⁵ | 8.4° | 11.0° |
| (+)-12-Methyltetradecanoic ⁶ | 4.7° | 11.4° |
| (+)-10-Methyloctadecanoic ⁷ | 0.06° | 0.2° |
| (+)-3-Methylhendecanoic ⁷ | 5.0° | 10.1° |

^a Taken in chloroform solution, remaining values obtained homogeneous.

As shown by the above data and elsewhere,⁶ the molecular rotation remains reasonably constant for a given relationship of methyl group to the ends of the chain. Variables such as solvent and temperature have appreciable but not large effects in these compounds. For the case of 3,13,19-trimethyltricosanoic acid, it seems safe to assume that (a) the contribution of each asymmetric carbon to the rotation is unaffected by the presence of the other branching groups, (b) the contribution of carbon-19 is less than the rotation of the third or fourth acids listed in Table I, (c) the contribution of carbon-13 is similar to that of the fifth acid in Table I, (d) the contribution of carbon-3 is the same as the rotation of the sixth acid in Table I. It follows that the maximum molecular rotation for 3,13,19-trimethyltricosanoic acid should be approximately 22°, less than half the value of 49.7° observed for phtthioic acid. Thus, it seems impossible that phtthioic acid could have the structure suggested by Polgar and Robinson.

It is of interest that 2,3,21-trimethyltricosanoic acid has a calculated maximum molecular rotation of approximately 49.5° (ignoring any effect caused by the proximity of the 2- and 3-methyl groups), and all other trimethyltricosanoic acids would have a lower rotation. Thus, if phtthioic acid is a long-chain acid with several branching methyl groups (evidence supporting this proposition seems doubtful), three of these groups are probably in the 2-, 3- and anteiso positions. Additional methyl groups between the 3- and anteiso positions should contribute little to the rotation.

(2) Wagner-Jauregg, *Z. Physiol. Chem.*, **247**, 135 (1937).

(3) Spielman and Anderson, *J. Biol. Chem.*, **112**, 759 (1936).

(4) Ställberg-Stenhagen, *Arkiv Kemi, Mineral. Geol.*, **23**, No. 15 (1946).

(5) Welt, *Compt. rend.*, **119**, 855 (1894).

(6) Weitkamp, *THIS JOURNAL*, **67**, 447 (1945).

(7) Prout, Cason and Ingersoll, *ibid.*, **69**, 1233 (1947).

(1) Polgar and Robinson, *J. Chem. Soc.*, 389 (1945).

It would appear, however, that the absence of rings and quaternary carbons in phthioic acid has hardly been demonstrated.

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THE EXCHANGE REACTION BETWEEN THE TWO OXIDATION STATES OF THALLIUM IN PERCHLORIC ACID SOLUTIONS

Sir:

We have studied the exchange reaction between thallos and thallic ions in aqueous perchloric acid and wish to make a preliminary report of the results. This reaction is of interest in that it involves transfer of two electrons between the reacting species and in that it is found to proceed at a slow and measurable rate, in contrast to the several other electron-transfer exchange reactions which have been reported to be fast.¹ Earlier studies of this reaction^{2,3} were handicapped by the short half-life of the radioactive tracer used (ThC'' , half-life 3.1 min.) and gave results which are difficult to interpret.

Using $\text{Tl}^{204,206}$ (half-life *ca.* 3 years), we have observed the exchange reaction and have investigated the dependence of the rate of exchange on the concentrations of thallos and thallic perchlorates, on the acid concentration, and on the temperature. The thallos perchlorate concentration was varied from 0.003 f. to 0.015 f., that of thallic perchlorate from 0.0006 f. to 0.003 f.

The method employed was to mix stock solutions of active thallic perchlorate and inactive thallos perchlorate in a stoppered flask immersed in a constant temperature bath, to withdraw samples at intervals, and to determine the distribution of activity between the two oxidation states of thallium. Thallos chromate was precipitated from the sample by the addition of a mixture containing chromate, cyanide, ethanol and excess ammonia. This method was found to give a reasonably clean separation, and not to induce a significant amount of exchange during precipitation.

The activity in the thallos fraction was found to vary with time in the simple exponential manner expected for an exchange reaction occurring at chemical equilibrium.^{4,5} The rate of exchange was found to be proportional to the first power of the concentration of each reactant. The specific rate constant is 2.0 moles⁻¹ liter hours⁻¹ at 49.5° (perchloric acid 0.4 f.). The experimental activation energy is 12 kcal./mole. The addition of a neutral salt (LiClO_4 0.6 f.) increased the rate,

suggesting that ions of like sign participate in the exchange.

When the acid concentration was varied, the rate constant showed a maximum at about 1 f. ($k = 2.5$) and decreased to 0.9 at 3.9 f. This behavior doubtless results from the combined effects of ionic strength and hydrolysis of thallic ion.

We have also observed the exchange in 0.2 f. hydrochloric acid and find that the rate is markedly greater than in perchloric acid.

We are continuing these studies.

We are grateful to the Los Alamos Laboratory, in particular to Mr. J. W. Starner and Mr. E. L. Bentzen, for neutron irradiation of the thallium. We also are indebted to Dr. Norman Davidson for his interest and helpful advice.

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EXCHANGE REACTION BETWEEN THALLIUM (I) AND THALLIUM (III) IONS IN PERCHLORIC AND NITRIC ACID SOLUTIONS

Sir:

We have measured the rate of the exchange reaction between thallium(I) and thallium(III) ions in aqueous solutions of perchloric and nitric acid and have found it to be slow and measurable. The data from earlier work^{1,2} on this reaction are difficult to interpret because the short lived tracer, ThC'' (3.1 m.), limited the duration of the experiments.

Part of the $\text{Tl}^{204,206}$ (*ca.* 3.5 y) used as tracer in our experiments was prepared by the $\text{Tl}(d, p)$ reaction in the Washington University cyclotron, the rest by the $\text{Tl}(n, \gamma)$ reaction in the Oak Ridge pile. Our procedure was to mix acid solutions of thallium (I) perchlorate (nitrate) and active thallium (III) perchlorate (nitrate), remove aliquots at definite intervals of time, separate the two oxidation states, and assay and count the two fractions. Two methods of separation were used. (1) Thallium (III) hydroxide was precipitated with ammonium hydroxide; both fractions being subsequently weighed and counted as thallium (I) chromate. (2) Thallium (I) bromide was precipitated with sodium bromide solution, both fractions being weighed and counted as thallium (I) bromide.

A fast, incomplete, but reproducible exchange was induced at the time of separation. The induced exchange (exchange measured at zero time) could be varied from 45 to 70% for the hydroxide separation and from 8 to 13% for the bromide separation by adding the reagents in a different

(1) See for example G. T. Seaborg, *Chem. Rev.*, **27**, 199 (1940).

(2) J. Zirkler, *Z. Physik*, **99**, 669 (1936), *et al.*

(3) V. Majer, *Z. Physik Chem.*, **A179**, 51 (1937).

(4) H. A. C. McKay, *Nature*, **142**, 997 (1938).

(5) R. D. Duffield and M. Calvin, *This Journal*, **68**, 557 (1946).

(1) J. Zirkler, *Z. Physik*, **87**, 410 (1934); **98**, 75 (1935); **99**, 669 (1936); *Z. Physik Chem.*, **A187**, 103 (1940).

(2) V. Majer, *ibid.*, **A179**, 51 (1937).