methanol in methoxide[6] to form dimethyl 1-methoxy-1-methylcyclopropane-*trans*-2,3-dicarboxylate[1e] (IV, R = CH_3), cleaved by hot dilute methanolic hydrochloric acid to dimethyl acetosuccinate. The supposed[1g,i] anhydride of IV (R = H) is a γ-methyl-γ-methoxyitaconic anhydride, unsaturated to permanganate and decomposed by excess hot water to levulinic acid.

The diethyl ester of the Feist acid is isomerized at 240° to a substance considered[1i] as diethyl 1-butyne-1,4-dicarboxylate. However, *the isomerized ester shows no acetylenic infrared absorption:* the most probable structure is a stereoisomer of ethyl 2-carboethoxycyclopropylideneacetate (V). Further investigations[7] of these remarkable methylenecyclopropane derivatives, including reduction and reaction with diazo compounds (possible syntheses of spiropentanes), are under way.

(6) The stability of the Feist acid and esters in *acid*[1a,b,i] evidences against α,β-unsaturation (contrast V[1j]).

(7) Dr. J. H. Sturdivant and Mr. D. R. Petersen, California Institute of Technology, are analyzing the crystal structure of the Feist acid.

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THE EFFECT OF THE MEDIUM UPON HAMMETT'S SIGMA VALUES OF *p*-ALKYL GROUPS AND HYPERCONJUGATION

Sir:

For a number of *p*- and *m*-substituted anilines we compared the ionization constant in water (expressed as pK_a) with their catalytic constant in *n*-hexane (expressed as log k_c) on a prototropic rearrangement of a certain sulfone.[1] A linear relation exists between pK_a and log k_c, the Brønsted relation[2]; the stronger the base, the higher its catalytic effect. However, it was found that *p*-toluidine deviated; its log k_c (in *n*-hexane) is smaller than is expected from its pK_a (in water).

The effect of substitution in aniline on pK_a and on log k_c can also be expressed by means of Hammett relations.[3] Hammett's substitution constant σ for *p*-CH_3 derived from the pK_a of *p*-toluidine in water (−0.19) is in accordance with the one given by Hammett (−0.170),[3] the latter being derived from the ionization constant of *p*-toluic acid in water. However, a less negative value, *viz.*, −0.08, is derived from log k_c of *p*-toluidine in *n*-hexane.

That the effect of *p*-CH_3 in *p*-toluidine depends upon the medium[4] is, however, not restricted to this compound. With the aid of the values given by Hammett for the basic constants (log k_0 and ρ) of the recorded equilibria and reaction rates,[5] we calculated σ for the *p*-CH_3 group in the following media from the experimental data which Hammett used to compose his list of constants.[6]

Medium	Number of relations	σ
Water	9	−0.17
25–50% alcohol	3	−0.17
87–98% alcohol	5	−0.15
Alcohol	6	−0.14
Methanol	1	−0.11
Ether-alcohol	1	−0.105

Our own value in *n*-hexane (−0.08) fits excellently in this series and we conclude that *the σ-value for p-CH_3 depends upon the medium.*

Many data recorded in the literature since the publication of Hammett's list of σ-values give a better agreement when this dependence is taken into account.

The same effect is found for 3,4-xylidine. From its pK_a in water[7] as well as from the ionization constant of 3,4-xylenol in water a σ-value is found (−0.23) which is considerably more negative than the value derived from the log k_c of 3,4-xylidine in *n*-hexane (−0.10). The effect of the 3,4-dimethyl grouping is about the sum of the effect of the *m*-CH_3 and the medium dependent effect of the *p*-CH_3 group.

The fact that *p*-toluidine but not *m*-toluidine showed the deviation in the Brønsted relation, led us to suspect that the phenomenon known as hyperconjugation (Baker–Nathan effect) was involved.[8] Further evidence for this view was obtained from the observation that in the series *p*-CH_3, *p*-C_2H_5, *p*-*i*-C_3H_7 and *p*-*t*-C_4H_9 aniline the deviation from the Brønsted relation became smaller. In the same sequence hyperconjugation decreases.[8]

This is in accordance with recent data of Herbst and Jacox.[9] These authors derived the σ-values of *p*-alkyl groups from the rate of hydrolysis of *p*-alkyl benzoates in 87.8% alcohol and compared the values thus found with Hammett's values, derived from the ionization constants of *p*-alkylbenzoic acids in water. They found less negative values for *p*-CH_3 and *p*-C_2H_5, but agreeing values for *p*-*i*-C_3H_7 and *p*-*t*-C_4H_9.

(1) For details we refer to the thesis of H. Kloosterziel, Groningen, 1952, and to papers to be published in *Rec. trav. chim.*; *cf.* Abstracts of Papers, XIIth Intern. Congress of Pure and Applied Chemistry, New York, 1951, p. 444.

(2) J. N. Brønsted and K. J. Pedersen, *Z. physik. Chem.*, **108**, 135 (1924).

(3) L. P. Hammett, "Physical Organic Chemistry," New York, N. Y., 1940, Chapt. VII.

(4) There is another indication for this in the work by J. C. James and J. G. Knox, *Trans. Far. Soc.*, **46**, 254 (1950).

(5) Ref. 3, pp. 189–190.

(6) Some data have been disregarded for obvious reasons, *cf.* L. P. Hammett, THIS JOURNAL, **59**, 96 (1937).

(7) F. Kieffer and P. Rumpf, *Compt. rend.*, **230**, 2302 (1950).

(8) For a recent monograph, see J. W. Baker, "Hyperconjugation," Oxford Press, New York, N. Y., 1952.

(9) R. L. Herbst and M. E. Jacox, THIS JOURNAL, **74**, 3004 (1952).

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THE π HELIX—A HYDROGEN BONDED CONFIGURATION OF THE POLYPEPTIDE CHAIN

Sir:

In a recent letter, Dr. M. L. Huggins[1] proposed a new helical polypeptide chain configuration as a possible alternative to the Pauling-Corey α helix.[2] In the Huggins structure, the amide group is not planar and, as Pauling and Corey[3] have observed, the strain energy is great in comparison with the

(1) M. L. Huggins, THIS JOURNAL, **74**, 3963 (1952).

(2) L. Pauling and R. B. Corey, *ibid.*, **72**, 5349 (1950).

(3) L. Pauling and R. B. Corey, *ibid.*, **74**, 3964 (1952).

α helix. There is, however, a helical configuration for the polypeptide chain not hitherto described which satisfies all the major Pauling, Corey and Branson[4] restrictions and which can be formed using the Corey-Donohue[5] polypeptide chain dimensions. The configuration is obtained when the polypeptide chain is coiled into a helical form in such a way that each amide group is hydrogen bonded to the fourth amide group beyond it along the chain. In this sense, it is intermediate between the α and γ helices in which the amide groups are hydrogen bonded to the third and fifth amide groups beyond them respectively. We have named it, therefore, the π helix.[6] There are approximately 4.4 amino acid residues per turn, with a unit residue translation along the helical axis of approximately 1.14 Å., giving a pitch of about 5 Å. The structure involves some slight distortion (less than 5°) in the intra-chain α carbon bond angle. Angular distortions of the "tetrahedral" carbon bond angle of this order are not unknown[7] and changes of less than 5° should introduce only a small amount of strain energy.

There is a cylindrical hole down the center of the helix, and it has been criticized on this basis.[8] The hole is less wide than that down the center of the γ helix, and it is, therefore, not large enough to accommodate a water molecule. Thus, there is no way of bridging the long intra-chain van der Waals distances across the cavity. Since the original Pauling–Corey restrictions were enunciated, a further stereochemical limitation has been postulated by these workers,[9] which is considered adequate to exclude the γ helix completely. The restriction is concerned with the potential function for orientation about a single bond between the α carbon (tetrahedral) and the peptide nitrogen or peptide carbon. The orientations about the α C–N and α C–C bonds for the π helix have not yet been determined. Calculations of the X-ray form factor and Fourier transforms for the helix are now proceeding (with H. J. Grenville-Wells). They will be published together with a more precise formulation of the helix later.

The π helix is certainly under some slight strain and the α helix represents a lower potential energy minimum for the atoms of the bare chain $(HCCONH)_n$. The π helix can probably not be ruled out, however, on this basis since the potential energy function for the protein chain with attached polyfunctional (R) groups $(RCHCONH)_n$ may well be rather different from that of the bare chain.

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(4) L. Pauling, R. B. Corey and H. R. Branson, *Proc. Nat. Acad. Sci.*, **37**, 205 (1951).

(5) R. B. Corey and J. Donohue, THIS JOURNAL, **72**, 2899 (1950).

(6) B. W. Low and R. B. Baybutt, reported at the Royal Society (London) discussion, "The Structure of Proteins," in May, 1952, by J. T. Edsall, *Nature*, **170**, 53 (1952).

(7) See for example the tetrahedral carbon angles of 113° and 104° found in the threonine molecule, D. P. Shoemaker, J. Donohue, V. Schomaker and R. B. Corey, THIS JOURNAL, **72**, 2328 (1950).

(8) L. Pauling, private communication.

(9) L. Pauling and R. B. Corey, *Proc. Nat. Acad. Sci.*, **37**, 729 (1951).

ON THE STABILITY OF SERUM LIPOPROTEINS AND EVIDENCE OF A STABILIZING FACTOR

Sir:

Research into the origin of atherosclerosis has been stimulated by the introduction of ultracentrifugal techniques for the isolation and characterization of serum lipoproteins.[1] Correlations are found[2] between the levels of lipoproteins in the S_f 10–100 classes and the incidence of atherosclerosis in humans [rabbits show a quite analogous behavior[3]]. Perhaps the lipid constituents are deposited in the formation of the atherosclerotic lesions. Other factors are, however, involved since the presence of these lipoproteins is frequently without effect.

Physical chemical studies in this Laboratory on ultracentrifugally isolated lipoprotein fractions from the sera of humans and rabbits have shown that lipoproteins of the S_f 5–30 classes are unstable when dialyzed against buffered saline solutions. Several related changes take place *in vitro* that are due neither to thermal nor biological degradation:

(1) The S_f value (s) gradually decreases. By controlled dialysis progressively lower S_f values are obtained, ultimately even leading to sedimentation. With a homogeneous fraction of given initial S_f value this instability results in a decrease in lipoprotein within the initial S_i range and in an increase in sedimenting material.

(2) The ultracentrifugal pattern spreads, indicating increased heterogeneity.

(3) Lipid material is released from the lipoprotein and in a low centrifugal field forms a layer on the surface of the solution. Also, the turbidity of the dialyzed fraction may increase. With S_f 5–9 lipoproteins this is not readily apparent to the eye, but higher S_f fractions become markedly turbid.

These changes do not occur when the lipoproteins are dialyzed against saline solution to which a concentrate obtained from bovine or rabbit serum has been added. It appears that a stabilizing factor is contained in the isolated material. In Fig. 1 the sedimentation behavior obtained in a typical dialysis experiment is reproduced.

These findings lead us to postulate an equilibrium between a lipoprotein complex and its components (protein, lipid and stabilizing factor), although we have been unable so far to reconstitute the complex in our *in vitro* experiments.

This equilibrium permits one to speculate on a possible mechanism for the deposition of lipid within the arterial wall. If the concentration of the stabilizing factor were insufficient, or were destroyed by metabolic or excretory pathways, lipoprotein in the region of the arterial wall would degradate by a loosening of its lipid components.

(1) J. Gofman, F. Lindgren, H. Elliott, W. Mantz, J. Hewitt, B. Strisower, V. Herring, and T. Lyon, *Science*, **111**, 166 (1950).

(2) A series of contributions by Gofman and co-workers; see, for instance: J. Gofman, H. Jones, T. Lyon, F. Lindgren, B. Strisower, D. Colman and V. Herring, *Circulation*, **5**, 119 (1952).

(3) D. Cook, R. Ray, E. Davisson, L. Feldstein, L. Calvin and D. Green, *J. Exp. Med.*, **96**, 27 (1952).