# COMMUNICATIONS TO THE EDITOR

## PAULING'S THEORY OF METALS IN CATALYSIS

*Sir:*

Beeck's systematic investigation of ethylene hydrogenation on various metal films[1] emphasizes the influence of the frequency factor on catalytic activity. Since, in this case, the lattice parameter bears no relation to a constant activation energy, it has been related to the entropy term. Indeed, in a plot log specific activity *vs.* lattice distance, all the data can be fitted on a curve presenting a maximum for rhodium. Chromium, however, falls off the curve. As a conclusion, Beeck gives arguments in favor of the "geometric" interpretation of active centers.

More recent work on the other hand[2,3] tries to correlate catalytic activity with the electronic structure of metals. The band theory has been exclusively used so far in such comparisons, with the accent on the filling-up of *d*-bands or Brillouin zones. Insofar as Pauling's theory of metals[4,5] has a more chemical background and is now generally accepted,[6] it seems opportune to use some of its results in connection with chemical problems such as catalysis.

In particular, Pauling[7] succeeded in correlating metallic radii with the percentage of *d* character of the metallic bond. Since Beeck has found a relationship between lattice distance and activity, we should expect a connection between activity and per cent. *d* character of the bond. This is actually verified: using Beeck's data, we find the logarithm of the activity to be a steadily increasing function of the per cent. *d*-character. All the data fit the curve, including chromium but with the exception of tungsten. It is to be hoped that Beeck's important results will soon be published with all the detail they deserve. The anomaly of tungsten could then be elucidated and further light thrown on the meaning of the relationship found. To be sure, the activation entropy term must be related to the geometry of the catalyst surface, but in assessing the relative importance of geometry in the definition of active centers, it should be kept in mind that the lattice parameter is not to be considered solely as a cause but as an effect. The primary cause has to be sought in the electronic structure of the metal and a deeper insight into the latter may be obtained by means of Pauling's theory. It is suggested that active centers are better defined in terms of metallic bond properties than in terms of geometry. It is to be noted however that in the case studied by Beeck, both interpretations, far from being mutually exclusive, lead to the same prediction concerning the activity of the metals involved.

(1) O. Beeck, *Rev. Mod. Phys.*, **17**, 61 (1945).
(2) G. M. Schwab, *Trans. Faraday Soc.*, **42**, 689 (1946).
(3) Cooper and Eley, *Nature*, **164**, 578 (1949).
(4) L. Pauling, THIS JOURNAL, **69**, 542 (1947).
(5) L. Pauling and F. J. Ewing, *Rev. Mod. Phys.*, **20**, 112 (1948).
(6) L. Pauling, *J. chim. phys.*, **46**, 276 (1949).
(7) L. Pauling, *Proc. Roy. Soc.* (*London*), **A196**, 343 (1949).

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## THE ACTIVITY OF A HYDROLYSATE OF ADRENOCORTICOTROPIC HORMONE IN RHEUMATOID ARTHRITIS

*Sir:*

Dialysates of pepsin digests of adrenocorticotropic hormone (ACTH) have been found active in rheumatoid arthritis.

ACTH was previously isolated from the pituitary glands of sheep[1] and hogs.[2] Its physiological functions included stimulation of the adrenal cortex[1,2] in animals. It was reported by Li[3] that the hormone, a protein of molecular weight about 20,000,[1,2] retained its adrenocorticotropic activity in hypophysectomized female rats after partial hydrolysis into peptide fragments with an average chain length of eight amino acid units.

In human subjects, the stimulation of the adrenal cortex upon administration of ACTH caused increased excretion of glycogenic corticoids, 11-oxysteroids and 17-ketosteroids.[4,5] Thus, even before the announcement[6] that ACTH was active in rheumatoid arthritis, it was of interest to determine whether the biologically active peptide fragments were also active clinically. Demonstration of such activity might lead to synthesis of a clinically useful product.

Pig pituitary glands were extracted and the ACTH isolated[7] as a potent concentrate according to Fishman.[8] Analyses showed N, 15.14%; amino-N (Van Slyke), 0.7%. In an adrenal ascorbic acid depletion assay[9] using intact rats in which the pituitary was blocked by adrenal cortical extract,[10] this ACTH concentrate showed

(1) Li, Evans and Simpson, *J. Biol. Chem.*, **149**, 413 (1943).
(2) Sayers, White and Long, *ibid.*, **149**, 425 (1943).
(3) Li, Josiah Macy, Jr., Foundation, Transactions of the Seventeenth Meeting, Conference on Metabolic Aspects of Convalescence, New York, N. Y., 1948, p. 114.
(4) Venning, *ibid.*, p. 159.
(5) Mason, Power, Rynearson, Ciaramelli, Li and Evans, *J. Clin. Endocrinol.*, **8**, 1 (1948).
(6) Hench, Kendall, Slocumb and Polley, *Proc. Staff Meet., Mayo Clin.*, **24**, 181 (1949).
(7) We are indebted to Dr. E. E. Howe and his co-workers of this laboratory, who kindly furnished us with the ACTH used in this work.
(8) Fishman, *J. Biol. Chem.*, **167**, 425 (1947).
(9) *Cf.* Sayers, Sayers and Woodbury, *Endocrin.*, **42**, 378–393 (1948).
(10) This modified assay was developed and the assays carried out by Drs. H. C. Stoerk, C. C. Porter and R. H. Silber of the Merck Institute for Therapeutic Research.

an activity arbitrarily designated as 100%. A 1.233-g. portion was digested in 250 ml. of 0.05 *N* hydrochloric acid with 132 mg. of pepsin.[8] After dilution, the solution was dialyzed for five days against distilled water. The dialysates were collected daily, concentrated *in vacuo*, and lyphilized.

The combined product, a yellow solid, weighed 0.605 g. *Anal.* Found: N, 13.69; amino-N, 1.7. It showed an average assay value of 140%. The material was administered to a patient with rheumatoid arthritis, and found to be fully active[11] at a dosage of 18 mg., four times daily, in maintaining a remission obtained by previous treatment with ACTH.

In another experiment, the dialysate was collected after one day, and yielded a product having 12.63% nitrogen and 1.89% amino-nitrogen. It was fully active clinically in maintaining remission at a level of 10 mg., four times daily. In a third clinical trial, material obtained during the third day of dialysis was found fully active when given in four 12.5-mg. doses daily. We gratefully acknowledge the coöperation of Dr. Charles Ragan,[12] who carried out the clinical tests.

The chemical nature of the clinically active component(s) is being investigated.

Complete acid hydrolysis of ACTH and of the combined dialysates of the pepsin digest, followed by paper strip chromatography,[13] revealed in each the presence of at least seven or eight common amino acids. Paper chromatograms of the dialysate of the pepsin digest showed no substances which reacted with ninhydrin to give colored spots under the usual conditions for detecting amino acids.[13]

It is our understanding[14] that Dr. Li also prepared a pepsin digest of ACTH which was active in a case of rheumatoid arthritis.

(11) The effect was equivalent to the clinical response obtained with Armour Standard ACTH (L. A. 1050).

(12) Columbia University, College of Physicians and Surgeons, New York, N. Y., private communication.

(13) Consden, Gordon and Martin, *Biochem. J.*, **38**, 224 (1944); **41**, 590 (1947).

(14) Private communication.

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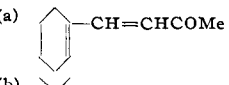
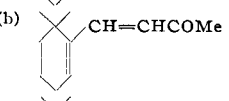
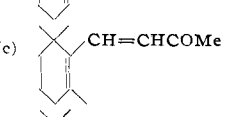
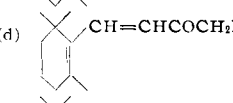
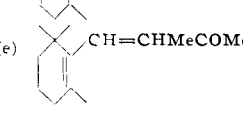
## STRUCTURE AND LIGHT ABSORPTION OF METHYLIONONES

*Sir:*

In a recent communication, Lusskin and Winston[1] have recorded the ultraviolet light absorption properties of "*β-i*-methylionone" and conclude that the somewhat anomalous spectrum of this compound (see table) is incompatible with the structure (e) proposed by Köster.[2] Lusskin and Winston suggest that in view of its high-intensity band in the 2300 Å. region, *β-i*-methylionone is probably an enone rather than a dienone. This suggestion does not, however, account for the lower-intensity band near 2800 Å.; yet there is no reason to doubt that *β-i*-methylionone, regenerated from its pure semicarbazone, is a homogeneous compound.

We have recently reported and discussed[3] the spectral properties of a comprehensive series of natural and synthetic homologs of *β*-ionone and have shown that the anomalous absorption exhibited by *β*-ionone itself and by some of its homologs can be explained in terms of steric interference between the side-chain and methyl substituents in the ring. As a result of this interference, the unsaturated side-chain is displaced out of the plane of the cyclohexene ring and resonance interaction between the two parts of the molecule is decreased. As the inhibition of resonance increases, the intensity of the long wave length band near 2800 Å. characteristic of the dienone chromophore decreases, while the intensity of the short wave length band near 2300 Å. characteristic of the partial enone chromophore increases.

TABLE I

| | | "Enone" band | | Dienone band | | Steric inhibition |
|---|---|---|---|---|---|---|
| | | Å. $\lambda_{max}$ | $\epsilon_{max}$ | Å. $\lambda_{max}$ | $\epsilon_{max}$ | |
| (a) |  | .. | ... | 2810 | 20800[3] | |
| (b) |  | 2280 | 4100 | 2810 | 13000[3] | |
| (c) |  | 2230 | 6500 | 2960 | 10700[3] | |
| (d) |  | 2200 | 6500 | 2950 | 9400[1] | |
| (e) |  | 2280 | 11600 | 2780 | 4500[1] | |

Increase

An approximate scale projection of formula (e) in the *s*-transconfiguration, using covalent radii which represent a measure of minimum interfering properties,[3] shows that the extra methyl group considerably increases steric interference in *β-i*-methyl ionone as compared with *β*-ionone. On the other hand, no additional interference is caused byt he extra methyl group in *β-n*-methylionone (d), the absorption of which is very similar to that of *β*-ionone (c). The spectral data for *β-i*-methylionone are thus fully in agreement with formula (e) and with the generalizations of Braude, Jones, Koch, Richardson, Sondheimer and Toogood.

(1) Lusskin and Winston, THIS JOURNAL, **71**, 2412 (1949).

(2) Köster, *Ber.*, **80**, 248 (1947).

(3) Braude, Jones, Koch, Richardson, Sondheimer and Toogood, *J. Chem. Soc.*, 1890 (1949).