and observed[4] previously, but this is the first instance in which the difference in rates has been found to be comparable in magnitude to those associated with the normal effect.

A serious consequence of this observation is the introduction of an ambiguity into the interpretation of kinetic studies such as ours. It is entirely conceivable that some reactions which involve breaking bonds to atoms of different masses will not show any considerable isotope effect because of a fortuitous similarity of zero-point energies of the transition and resting states of the reactants.

While the lack of a detailed knowledge of the configuration of the transition state for our reaction does not permit a complete interpretation of the observed results, it seems likely that the abnormal effect should be attributed in large part to the fact that the reaction effectively involves the displacement of a hydride ion. Because of the rather low electron affinity of hydrogen atoms (17 kcal. mole^{-1})[5] we would not expect to observe such a displacement at ordinary temperatures unless the hydrogen is continuously bound to some other atom or atoms throughout the course of the reaction. This means that if the old bond has been largely destroyed in the transition state, the new bond (hydrogen–hydrogen) must have already attained considerable strength. Since the hydrogen–hydrogen bond has a rather large stretching force constant (5.76×10^5 dynes cm.$^{-1}$)[6] the restoring force for vibrational displacement of the hydrogen atom may well be larger in the transition state than in the silane. Reversal of the argument outlined above for the normal isotope effect would then account for the abnormal effect observed here.

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THE *IN VIVO* CONVERSION OF GLUTAMIC ACID INTO PROLINE AND ARGININE[1]

Sir:

Several years ago, by the use of compounds "labeled" with isotopes, Schoenheimer and his associates demonstrated conclusively that certain amino acids are converted into each other in the intact mammalian organism. Thus, deuteroörnithine is transformed by the mouse into deuteroarginine,[2] deuteroproline and deuteroglutamic acid[3]; and proline containing both deuterium and N^{15} is converted by the rat into isotopic hydroxyproline, arginine and glutamic acid.[4] These findings provide convincing proof that proline and ornithine (arginine) are mutually interconvertible *in vivo*. However, the authors appear to have made no attempt to determine whether glutamic acid can be transformed into arginine or proline.

In the meantime, investigations in this laboratory[5] showed that albino rats which are deprived of arginine, proline, hydroxyproline and glutamic acid, but receive an otherwise adequate diet, continue to grow but at greatly diminished rates. The addition to the food of either arginine, proline, or glutamic acid improves the rate of gain, though neither of the latter two is so effective as arginine. Under like circumstances, hydroxyproline is without beneficial action. The findings with glutamic acid were interpreted as furnishing "indirect evidence, for the first time, that this amino acid may be transformed *in vivo* into proline or arginine."

The above reaction possesses more than passing interest. Glutamic acid can be formed in the body by the reductive amination of the corresponding α-keto acid. An abundant supply of the latter (α-ketoglutaric acid) arises in carbohydrate metabolism. Therefore, the conversion of glutamic acid into proline or arginine, each of which can be transformed into the other and serve as a precursor of hydroxyproline, would account for the ability of animals to make moderate gains in weight even when deprived of all four of the compounds in question.

In order to obtain *direct* evidence for this relationship, DL-glutamic acid-5-C^{14} has now been synthesized[6] and administered orally to two rats. At the expiration of approximately 27 hours, each animal was sacrificed. From the hydrolyzed carcasses, which were worked up separately, glutamic acid, proline and arginine were isolated in pure condition. Each compound was then oxidized, and the resulting carbon dioxide was tested for radioactivity. The data show that all three of the amino acids were quite active. The order of activity was: proline > arginine > glutamic acid. Probably, the magnitude of the dilution of the radioactive materials by the non-labeled amino acids of the tissues accounts, at least in part, for the differences in C^{14} content of the isolated compounds.

The above findings demonstrate clearly that the reactions whereby proline and arginine are converted into glutamic acid are reversible. The experimental evidence will be presented in full in the near future.

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(4) M. R. Stetten and R. Schoenheimer, *ibid.*, **153**, 113 (1944).

(5) W. Womack and W. C. Rose, *ibid.*, **171**, 37 (1947).

(6) Unpublished work in this laboratory by R. A. Bauman.