In addition to the families of reactions exemplified by eq. i, ii and iii, pathways II and III of the *o*-carboxyphthalimide hydrolysis are but special cases of two more families of reactions not previously recognized as leading to bell-shaped rate profiles.[37]

These can be written schematically

$$BH^+ \overset{\text{fast}}{\rightleftharpoons} B + H^+ \qquad B + H_2O \underset{k_2}{\overset{k_1}{\rightleftharpoons}} I$$

$$I + H^+ \overset{\text{fast}}{\rightleftharpoons} IH^+ \qquad IH^+ \xrightarrow{k_3} \text{products} \qquad \text{(iv)}$$

and

$$B + H^+ \overset{\text{fast}}{\rightleftharpoons} BH^+ \qquad BH^+ + H_2O \underset{k_2}{\overset{k_1}{\rightleftharpoons}} IH^+$$

$$IH^+ \overset{\text{fast}}{\rightleftharpoons} I + H^+ \qquad I \xrightarrow{k_3} \text{products} \qquad \text{(v)}$$

Again, it should be noted that the schemes iv and v are "conjugates" of each other.

The prevalent bell-shaped curves in the *p*H–rate profiles of enzymatic processes have often been interpreted in terms of eq. i. It is a consequence of the above discussion that such curves can be interpreted in terms of any of the eq. i through v. It should be particularly noted that as yet no enzymatic process has been treated according to eq. iv or v. Of course, in the identification of such *p*H–rate profiles with specific groups on the enzyme, the admonitions previously given for the application of *apparent* *p*K*a*'s should be kept in mind.[39]

Acknowledgments.—The authors wish to acknowledge very valuable discussion with Dr. G. A. Hamilton and Dr. K. A. Connors.

(37) In reported work[38] on the hydrolysis of 2-methyl-Δ^2-thiazoline (*q.v.*), no account was taken of the second protonic equilibrium of scheme v, so that the rate constants k_3, k_5 (in the authors' terminology) contain this equilibrium constant. This interpretation invalidates some of the conclusions drawn. With this exception, however, the mechanism postulated is that of scheme v.

(38) R. B. Martin, S. Lowey, E. L. Elson and J. T. Edsall, *J. Am. Chem. Soc.*, **81**, 5089 (1959).

(39) T. C. Bruice and G. L. Schmir, *ibid.*, **81**, 4552 (1959).

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF KANSAS, LAWRENCE, KANS.]

Acid-catalyzed Decomposition of Ferrocenylphenylcarbinyl Azide

BY ABE BERGER, WILLIAM E. MCEWEN AND JACOB KLEINBERG

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The decomposition of ferrocenylphenylcarbinyl azide has been studied in various acidic media. In concentrated sulfuric acid–chloroform solution the products obtained are nitrogen, ferrocenecarboxaldehyde, aniline, the two diastereoisomeric forms of 1,2-diferrocenyl-1,2-diphenylethane, benzoylferrocene, ferrocenylphenylcarbinol, resinous material, and an unidentified iron salt in solution. When the decomposition is carried out in a less strongly acidic medium, namely, sulfuric acid–acetic acid, the amount of ferrocenecarboxaldehyde produced is lowered significantly, and an appreciable quantity of benzylferrocene is formed in addition to the other products cited above. On the basis of the products obtained, it is thought that the Schmidt rearrangement reaction takes place only with a doubly protonated conjugate acid of ferrocenylphenylcarbinyl azide. Decomposition of the azide in sulfuric acid–chloroform solution containing a variety of additives gives rise to products which appear to be formed by radical reactions. For example, decomposition of the azide in the presence of benzaldehyde gives N-benzoylferrocenylphenylcarbinylamine and benzylferrocene in addition to the other products noted previously. Also, decomposition of ferrocenylphenylcarbinyl azide in the presence of benzaldehyde and benzhydryl azide affords 1,1,2,2-tetraphenylethane and diphenylmethane in addition to the usual products.

Benzhydryl azide is known to undergo sulfuric acid-catalyzed decomposition to give nitrogen and the conjugate acid of benzalaniline. A substituted benzhydryl azide gives nitrogen and a mixture of the conjugate acids of two isomeric Schiff bases, the predominant isomer being the one predicted on the basis of analogy with other similar rearrangement reactions.[1] Inasmuch as ferrocene is more reactive than benzene in electrophilic substitution reactions,[2] and since the ferrocenyl group has been reported to undergo exclusive migration in the pinacol–pinacolone rearrangement of 1,2-diferrocenyl-1,2-diphenylethylene glycol, catalyzed by a trace of hydrogen chloride,[3] it was anticipated that the ferrocenyl group would undergo preferential migration in the sulfuric acid-catalyzed rearrangement of ferrocenylphenylcarbinyl azide. Actually, we have found that a complex reaction occurs and that, insofar as the Schmidt rearrangement takes place, there is an apparently exclusive migration of the phenyl group.

Ferrocenylphenylcarbinyl azide (I) was prepared by treatment of ferrocenylphenylcarbinol with hydrogen azide in benzene solution in the presence of trichloroacetic acid as catalyst. After isolation by chromatography on alumina and crystallization from Skelly B solvent, the azide had a melting point of 49–50°. Reaction of the azide with concentrated sulfuric acid in chloroform solution afforded nitrogen and a complex mixture of organic products. After hydrolysis of the mixture there was obtained a deep yellow chloroform phase and a deep blue aqueous phase. The following products were isolated from the organic layer by chromatography on an alumina column: the two diastereoisomeric forms of 1,2-diferrocenyl-1,2-diphenylethane (II)[4] and ferrocenecarboxaldehyde. The material in the blue aqueous phase was reduced by treatment with zinc dust and,

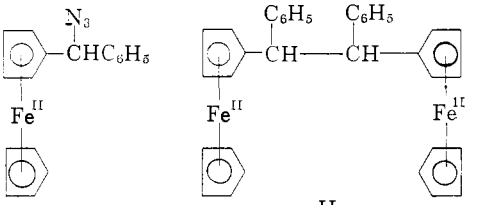
(1) R. F. Tietz and W. E. McEwen, *J. Am. Chem. Soc.*, **77**, 4007 (1955).

(2) G. D. Broadhead, J. M. Osgerby and P. L. Pauson, *J. Chem. Soc.*, 650 (1958).

(3) N. Weliky and E. S. Gould, *J. Am. Chem. Soc.*, **79**, 2742 (1957). It is still an open question whether the proof of structure of the pinacolone offered by these authors is conclusive.

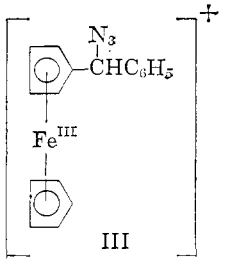
(4) K. L. Rinehart, Jr., C. J. Michejda and P. A. Kittle, *Angew. Chem.*, **72**, 38 (1960).

after extraction with benzene, the following compounds were isolated from the benzene layer by chromatography on alumina: the two diastereoisomers noted above, benzoylferrocene and ferrocenylphenylcarbinol. The aqueous phase remaining after extraction with benzene was made basic, and aniline was obtained by extraction of this solution with ether.



I II

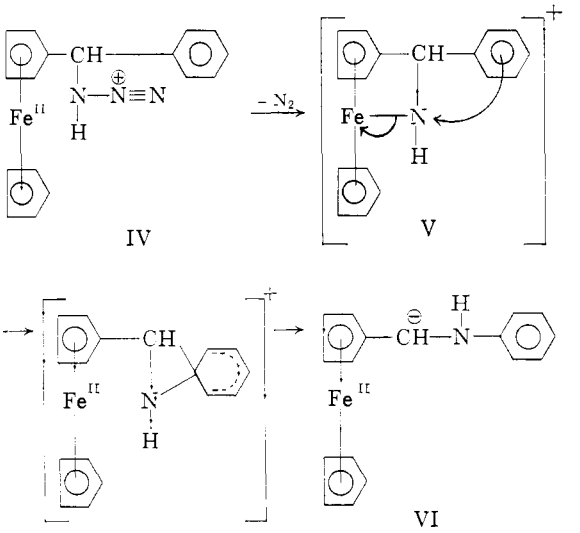
It is striking that no benzaldehyde and aminoferrocene were isolated. At least three alternative explanations can be offered for the course of the rearrangement process. One attractive possibility is based on recent observations[5,6] that the iron atom in ferrocene can be protonated by strong acids. Specifically, as applied to this system, it is envisioned that there are three conjugate acids of I present in solution: one in which just the azido group is protonated; one in which the iron atom alone is protonated; and, finally, one in which both azido group and iron atom are protonated. Furthermore, it is believed that only the diprotonated species undergoes the Schmidt rearrangement. As will be shown below, the conjugate acid in which only the azido group is protonated undergoes loss of hydrogen azide, with anchimeric assistance by the ferrocene nucleus. In the migration step of the Schmidt reaction the phenyl group would be better able to migrate from carbon to cationoid nitrogen than the protonated ferrocenyl group. This interpretation was the one offered in a previous communication.[7] However, a second possibility for the mechanism of rearrangement arises from the observations that, during the course of reaction, a deep blue color characteristic of ferricinium ions develops and that, as mentioned above, ferrocene derivatives are obtained after reduction of the blue aqueous phase of the hydrolysate with zinc dust. Thus, if ferrocenylphenylcarbinyl azide (I) were to be oxidized prior to the rearrangement step to the cation III (the oxidizing agent being the dipositive cations of II formed as described later), then it would be anticipated that the phenyl group would migrate to the cationoid nitrogen at a faster rate than the positively charged ferrocenyl group.



III

An argument against this second possibility lies in the behavior of phenylruthenocenylcarbinyl azide toward sulfuric acid in chloroform solution.[8] In this system, where there is no evidence for the occurrence of readily reversible oxidation-reduction reactions, it is also the phenyl group rather than the metallocenyl group which migrates more readily. However, the first explanation would be as valid for the ruthenocenyl compound as for the ferrocenyl derivative inasmuch as ruthenocene is also protonated in strongly acidic media.[6]

The third possible mechanism of rearrangement involves displacement of nitrogen from the conjugate acid IV derived from I, the pair of electrons from the metallocene ha_g molecular orbital[9] offering anchimeric assistance in the displacement of the nitrogen. This gives rise to intermediate V, in which, for steric reasons, the phenyl group is better able than the ferrocenyl group to migrate to the cationoid nitrogen to form VI (see curved arrows symbolizing *trans* migration of the phenyl group). The actual products, ferrocenecarboxaldehyde and the anilinium ion, are products of the hydrolysis of VI.



IV V VI

A possible argument against this interpretation can be developed from a consideration of the behavior of osmocenylphenylcarbinyl azide in sulfuric acid-chloroform solution.[10] *Here, there is no evidence whatsoever for a Schmidt rearrangement involving migration of either the phenyl or the osmocenyl group.* Yet, on the basis of the observations of Richards and Hill[11] regarding rates of solvolysis of metallocenylmethylcarbinyl acetates, osmium is better able than iron or ruthenium to offer anchi-

(5) M. Rosenblum and J. O. Santer, *J. Am. Chem. Soc.*, **81**, 5517 (1959).

(6) T. J. Curphey, J. O. Santer, M. Rosenblum and J. H. Richards, *ibid.*, **82**, 5249 (1960).

(7) A. Berger, J. Kleinberg and W. E. McEwen, *Chemistry & Industry*, 204 (1960).

(8) D. Bublitz, J. Kleinberg and W. E. McEwen, *ibid.*, 936 (1960).

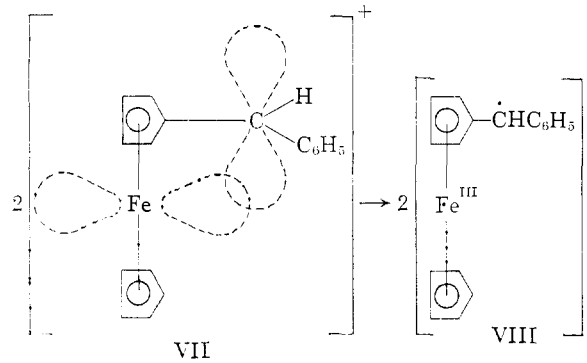
(9) W. Moffitt, *J. Am. Chem. Soc.*, **76**, 3386 (1954).

(10) D. E. Bublitz, W. E. McEwen and J. Kleinberg, unpublished observations.

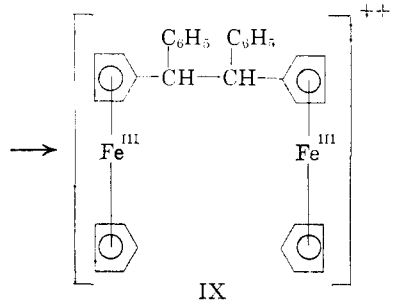
(11) J. H. Richards and E. A. Hill, *J. Am. Chem. Soc.*, **81**, 3484 (1959).

meric assistance in an intramolecular displacement.[12]

The formation of the diastereoisomeric 1,2-diferrocenyl-1,2-diphenylethanes (II) in the acid-catalyzed decomposition of I is another manifestation of the unusual stability and therefore ease of formation of carbonium ions of the α-ferrocenyl type.[11,13] It is visualized that the conjugate acid IV of ferrocenylphenylcarbinyl azide undergoes anchimerically assisted displacement of hydrogen azide to give the ferrocenylphenylmethyl cation VII. The latter then undergoes intramolecular oxidation-reduction to form the radical-ion VIII. This undergoes subsequent coupling to form the diastereoisomeric bipositive cations IX. In part, these cations are reduced to the diastereoisomeric forms of II by intermolecular oxidation-reduction reactions with other ferrocene derivatives present in the reaction mixture. This sequence of reactions is analogous to a similar sequence proposed by Rinehart, Michejda and Kittle.[14]



VII VIII



IX

The decomposition of ferrocenylphenylcarbinyl azide was next studied in sulfuric acid-acetic acid mixtures, media which are less acidic[15] than chloroform-sulfuric acid. The results obtained from the sulfuric acid-acetic acid media were to some extent significantly different from those found in the sulfuric acid-chloroform reaction mixture. First of all, the yields of ferrocenecarboxaldehyde and aniline, the products of rearrangement, dropped when the acidity of the reaction medium was lowered. This fact is entirely consistent with the suggestion offered earlier that rearrangement is preceded by protonation of the ferrocene nucleus (as well as the azido group); double protonation would certainly be expected to occur less extensively the less acidic the medium. Thus, since rearrangement is believed to occur only in the diprotonated conjugate acid of I, a decrease in the amount of rearrangement products would be anticipated in sulfuric acid-acetic acid media as compared with chloroform-sulfuric acid. Furthermore, it would be expected that yields of rearrangement products would decrease in sulfuric acid-acetic acid media as the concentration of sulfuric acid was lowered, and this indeed proved to be the case.

In addition to ferrocenecarboxaldehyde and aniline, the two diastereoisomeric dimers of structure II, ferrocenylphenylcarbinol, benzoylferrocene and benzylferrocene were isolated from decompositions of I effected in sulfuric acid-acetic acid solution. It is not clear why the last-named compound arises in the decompositions carried out in the sulfuric acid-acetic acid but not in those performed in sulfuric acid-chloroform.

In what was to have been a routine control experiment, the ferrocenylphenylcarbinyl azide rearrangement in sulfuric acid-chloroform was effected in the presence of benzaldehyde as additive. (If the quantity of benzaldehyde recovered on completion of the reaction corresponded approximately to that added it could be concluded that this product, had it been formed in the Schmidt rearrangement, would have been isolated.) It was observed that about 81% of the benzaldehyde added apparently was consumed, and, moreover, the rate of evolution of nitrogen substantially exceeded that observed in the reaction when no benzaldehyde was present. Convincing proof that benzaldehyde participated in the reaction was obtained when N-benzoylferrocenylphenylcarbinylamine and benzylferrocene were isolated, both products having been absent from the benzaldehyde-free azide decomposition mixture. Although Boyer and Hamer[16] have proposed a reasonable ionic mechanism to explain the formation of N-benzoylalkylamines in sulfuric acid-catalyzed reactions of certain alkyl azides with benzaldehyde, the concomitant formation of benzylferrocene and N-benzoylferrocenylphenylcarbinylamine in our reaction cannot be explained by the Boyer and Hamer mechanism. Furthermore, certain by-products which ordinarily result when the Boyer and Hamer mechanism is operative are absent from our reaction mixture. It is clear that additional work will have to be performed before a detailed mechanism can be offered for the reaction cited above.

To explore further the scope of the unusual benzoylation reaction noted above, a mixture of ferrocenylphenylcarbinyl azide (I), benzhydryl azide and benzaldehyde was treated with concentrated

(12) In the work of Richards and Hill[11] the pair of electrons of the ha_g molecular orbital is apparently effecting a displacement on an atom directly joined to the metallocenyl ring. On the other hand, the examples being discussed here involve displacement on an atom once removed from the metallocenyl ring. Nevertheless, it seems reasonable to assume that attack at either site would be faster in the osmocene case than in the ferrocene or ruthenocene case. It should be pointed out that benzoylosmocene is the major product in the acid-catalyzed decomposition of osmocenylphenylcarbinyl azide.[10] It is probable that the ketone arises from hydrolysis of the corresponding imine, and it is conceivable that the latter is formed from a transition ion analogous to V by elimination of a proton.

(13) G. R. Buell, W. E. McEwen and J. Kleinberg, *Tetrahedron Letters*, No. 5, 16 (1959).

(14) K. L. Rinehart, Jr., C. J. Michejda and P. A. Kittle, *J. Am. Chem. Soc.*, **81**, 3162 (2959).

(15) C. H. Gudmundsen and W. E. McEwen, *ibid.*, **79**, 329 (1957).

(16) J. H. Boyer and J. Hamer, *ibid.*, **77**, 951 (1955).

sulfuric acid in chloroform solution. Although, as mentioned earlier, benzhydryl azide alone undergoes sulfuric acid-catalyzed rearrangement to give benzalaniline and nitrogen, the mixture noted above yielded substantial amounts of 1,1,2,2-tetraphenylethane and the diastereoisomeric forms of 1,2-diferrocenyl-1,2-diphenylethane (II), together with a number of other products. As suggested in a previous communication,[17] this reaction too appears to be of a free radical nature, and further work is being carried out in an attempt to elucidate the mechanism.

Experimental

Preparation of Ferrocenylphenylcarbinyl Azide (I).—A modification of the procedure of Ege and Sherk[18] was used to prepare the azide I. To 300 ml. of anhydrous benzene was added 15 g. (0.051 mole) of ferrocenylphenylcarbinol[3,19] and 22 g. (0.134 mole) of trichloroacetic acid. The solution was stirred rapidly for 45 min. with cooling in an ice-bath; 300 ml. of a 1.38 *M* solution of hydrogen azide (0.414 mole) in benzene then was added all at once. The resulting dull green solution was stirred at room temperature for 8 hr. The benzene solution next was washed repeatedly with water until the washings (blue-red in color) no longer gave an acidic reaction toward litmus paper. The benzene solution, now deep yellow in color, was dried over anhydrous magnesium sulfate, filtered, the filtrate concentrated to a small volume, and chromatographed on "grade III" alumina.[20] Elution with Skelly B solvent afforded 13.1–15.8 g. (81–98%) of ferrocenylphenylcarbinyl azide. The azide had a m.p. of 49–50° after crystallization from Skelly B solvent. The infrared spectrum of this compound taken in chloroform solution showed the azide absorption peak at 2100 cm.$^{-1}$

Anal. Calcd. for $C_{17}H_{15}N_3Fe$: C, 64.37; H, 4.77; N, 13.25; Fe, 17.61. Found: C, 64.27, 64.47; H, 4.99 4.74; N, 13.13, 12.96; Fe, 17.35.

The chromatographic column was next eluted with benzene and evaporation of the solvent gave benzoylferrocene[19] (1.4 g. in one experiment).

The blue-red aqueous washings (see above) were treated with a large excess of zinc dust with mechanical stirring for 1 hr. at room temperature. The mixture was then extracted with benzene and a concentrate of the yellow benzene solution was chromatographed on "grade III" alumina. Two yellow bands containing the two diastereoisomeric forms of 1,2-diferrocenyl-1,2-diphenylethane were eluted, respectively, with Skelly B solvent and a mixture of Skelly B solvent and benzene (1:1 ratio). The isomer first eluted had a m.p. of 218–220° (cor.), reported[4] m.p. 218°.

Anal. Calcd. for $C_{34}H_{30}Fe_2$: C, 74.21; H, 5.50; Fe, 20.30. Found: C, 74.13; H, 5.67; Fe, 20.38.

The second isomer was found to melt at 276–278° (cor.), reported[4] m.p. 280°.

Anal. Found: C, 74.27; H, 5.36; Fe, 20.50.

Benzoylferrocene[19] was obtained next by elution of the column with benzene. Finally, by elution with benzene–ether (1:3) a compound of melting point 69–71° was isolated. This was shown to be **ferrocenylphenylcarbinylamine** by comparison with a sample prepared as shown later.

Anal. Calcd. for $C_{17}H_{17}NFe$: C, 70.12; H, 5.89; N, 4.81; Fe, 19.18; mol. wt., 291.2. Found: C, 70.49; H, 5.83; N, 4.88; Fe, 19.06; mol. wt., 307.

It is very likely that ferrocenylphenylcarbinylamine arose by the reduction of III by means of the zinc dust and sulfuric acid.

After a typical reaction carried out as described above, there was obtained from the original benzene phase 14.5 g. (90%) of ferrocenylphenylcarbinyl azide (I) and 0.7 g. (4.7%) of benzoylferrocene. From the reduced aqueous phase there were obtained 0.50 g. (1.8%) of 1,2-diferrocenyl-1,2-diphenylethane isomer of m.p. 218–220°, 0.06 g. of the isomer of m.p. 276–278°, 0.05 g. of benzoylferrocene and 0.37 g. (2.5%) of ferrocenylphenylcarbinylamine.

Ferrocenylphenylcarbinylamine.—To an ice-cold, well-stirred slurry of 3 g. of lithium aluminum hydride in 150 ml. of anhydrous ether was added dropwise a solution of 2.4 g. (0.0076 mole) of ferrocenylphenylcarbinyl azide (I) in 100 ml. of anhydrous ether. When the addition of the azide solution had been completed, the reaction was allowed to proceed for an additional 3.5 hr. at room temperature, stirring being maintained. Excess lithium aluminum hydride was decomposed by addition of a solution of water in ether, and the resulting yellow ethereal solution was decanted from solid material. The ether was dried over potassium hydroxide pellets, filtered, the solution evaporated to dryness and the residue taken up in a minimum amount of anhydrous benzene. The mixture was subsequently chromatographed on "grade III" alumina. When the column was eluted with Skelly B solvent, there was obtained 0.22 g. of benzylferrocene, m.p. 74–76° after purification by sublimation; reported[19] m.p. 73–74°. The identity of this compound was established by a mixed m.p. test with authentic benzylferrocene and a comparison of the infrared spectra of the two samples in chloroform solution. Ferrocenylphenylcarbinylamine (1.3 g., 59%), m.p. 69–71°, was obtained by elution with ether. The infrared spectrum of the amine, taken in chloroform solution, was identical with that of the amine isolated from the reduced aqueous phase in the preparation of I (see above).

Decomposition of Ferrocenylphenylcarbinyl Azide (I) in Chloroform–Sulfuric Acid.—A solution of 10 g. (0.032 mole) of I in 90 ml. of chloroform was added within 5 min. with mechanical stirring to a cooled mixture of 25 ml. of concentrated sulfuric acid and 25 ml. of chloroform. The reaction was allowed to proceed for 30 min. at ice-bath temperature and then for an additional 16 hr. at room temperature. At the end of this time, all nitrogen evolution had ceased. The mixture again was cooled in an ice-bath and hydrolyzed by addition of 200 ml. of water. The material was filtered to remove 2.5 g. of resinous solid. The deep blue aqueous layer was separated from the yellow chloroform phase, and the aqueous layer was extracted with fresh chloroform. The combined chloroform extract was dried over anhydrous magnesium sulfate, filtered, and the filtrate evaporated. The residue was dissolved in a minimum amount of benzene and chromatographed on "grade III" alumina. Two yellow bands containing the two diastereoisomeric forms of 1,2-diferrocenyl-1,2-diphenylethane (1.33 g. of the isomer of m.p. 218–220° and 0.13 g. of the isomer of m.p. 276–278°) were eluted, respectively, with Skelly B solvent and Skelly B–benzene (1:1).

Anal. Calcd. for $C_{34}H_{30}Fe_2$: C, 74.21; H, 5.50; Fe, 20.30; mol. wt., 550. Found for the isomer of m.p. 218–220°: C, 74.07; H, 5.24; Fe, 20.09; mol. wt., 555. Found for the isomer of m.p. 276–278°: C, 74.05; H, 5.57; Fe, 20.39.

With benzene as eluent, a red compound was removed from the column. Purification of this compound by sublimation afforded 0.70 g. of ferrocenecarboxaldehyde, m.p. 115–117° (cor.), reported[21] m.p. 124.5°. The infrared spectrum of this compound in chloroform solution was identical with that of an authentic sample of ferrocenecarboxaldehyde prepared by the reaction of ferrocene with N-methylformanilide in the presence of phosphorus oxytrichloride.[21]

Anal. Calcd. for $C_{11}H_{10}OFe$: C, 61.70; H, 4.71; O, 7.49; Fe, 26.10; mol. wt., 214. Found: C, 61.89; H, 4.74; O, 7.40; Fe, 26.08; mol. wt., 225.

To the deep blue aqueous layer (formed on hydrolysis of the original reaction mixture), was added 25 g. of zinc dust with mechanical stirring. When the solution had turned yellow (about 2 hr.), the reduction products were extracted into benzene, and the benzene solution was dried over anhydrous magnesium sulfate. The benzene solution was then concentrated to a small volume and chromatographed on "grade III" alumina. The following compounds were obtained in the order listed.

(17) A. Berger, J. Kleinberg and W. E. McEwen, *Chemistry & Industry*, 1245 (1960).

(18) S. N. Ege and K. W. Sherk, *J. Am. Chem. Soc.*, **75**, 355 (1953).

(19) M. D. Rausch, M. Vogel and H. Rosenberg, *J. Org. Chem.*, **22**, 903 (1957).

(20) H. Brockmann and H. Schodder, *Ber.*, **74**, 73 (1941).

(21) P. J. Graham, R. V. Lindsey, G. W. Parshall, M. L. Peterson and G. M. Whitman, *J. Am. Chem. Soc.*, **79**, 3416 (1957).

Compound	Wt., g.	Eluent
II, m.p. 218–220°	0.95	Skelly B solvent
II, m.p. 276–278°	.40	Skelly B–benzene (1:1)
Benzoylferrocene	.01	Benzene
Ferrocenylphenylcarbinol	.03	Benzene

Excess zinc dust was removed from the aqueous phase which had been extracted with benzene. After the solution had been made alkaline, it was extracted with ether, the ether solution dried over anhydrous potassium carbonate, and the ether evaporated. There remained 0.79 g. of a liquid which was identified as aniline by examination of its infrared spectrum and by conversion to benzanilide.

A yellow color persisted in the aqueous phase after extraction of the aniline. That this color was due to the presence of iron(II) salts was determined by oxidation with concentrated nitric acid, and finding a positive test for ferric ion with thiocyanate ion.

Decomposition of Ferrocenylphenylcarbinyl Azide (I) in Sulfuric Acid–Acetic Acid Solutions.—To 6.00 g. of I was added dropwise with stirring over a period of 10 min. 45 ml. of a 5 *M* solution of concentrated sulfuric acid in glacial acetic acid, the mixture being cooled in an ice-bath. The mixture was maintained at ice-bath temperature for 45 min. and then for 18 hr. at room temperature. The reaction mixture was then hydrolyzed by addition of 100 ml. of ice-water, the resulting deep blue solution was extracted exhaustively with benzene and each phase was filtered to remove resinous material. The deep yellow benzene solution was washed repeatedly with 5% sodium carbonate solution and then with water to remove acetic acid. The benzene solution was dried over anhydrous magnesium sulfate, then concentrated to a small volume and chromatographed on "grade II" alumina giving these compounds in the order listed.

Compound	Wt., g.	Eluent
Benzylferrocene	1.38	Skelly B solvent
II, m.p. 218–220°, plus II, m.p. 276–278°	0.09	Skelly B–benzene (1:1)
Ferrocenecarboxaldehyde	.05	Skelly B–ether (3:1)
Ferrocenylphenylcarbinol	.09	Ether

The deep blue aqueous phase was treated as described above for the decomposition of I in chloroform–sulfuric acid. In the chromatographic separation there was obtained

Compound	Wt., g.	Eluent
II, m.p. 218–220°	0.79	Skelly B solvent
II, m.p. 276–278°	.15	Skelly B–benzene (1:1)
Benzoylferrocene	.03	Benzene

The aqueous solution which remained after extraction with benzene was separated from excess zinc dust by filtration and the filtrate made strongly alkaline. A basic iron(III) acetate (0.86 g.) which precipitated was removed by filtration and extraction of the filtrate with ether afforded 0.09 g. of ferrocenylphenylcarbinylamine.

Ferrocenylphenylcarbinyl azide (15.0 g.) was next decomposed in 90 ml. of a 10 *M* solution of concentrated sulfuric acid in acetic acid. The reaction mixture was worked up as in the previous experiment, and the results were

Compound	Wt., g.	Eluent
Original benzene phase		
Benzylferrocene	0.70	Skelly B solvent
II, m.p. 218–220°, plus II, m.p. 276–278°	.32	Skelly B–benzene (1:1)
Ferrocenecarboxaldehyde	.37	Benzene
Ferrocenylphenylcarbinol	.15	Ether
Benzene phase (after extraction from reduced aq. phase)		
II, m.p. 218–220°	0.96	Skelly B solvent
II, m.p. 276–278°	.34	Skelly B–benzene (1:1)
Benzoylferrocene	.18	Skelly B–ether (3:1)

In addition to the compounds obtained from the benzene phases, there was isolated 0.64 g. of ferrocenylphenylcarbinylamine from the reduced aqueous phase after it had been made basic.

Decomposition of Ferrocenylphenylcarbinyl Azide (I) in Chloroform–Sulfuric Acid Containing Benzaldehyde.—A solution of 12 g. (0.038 mole) of I and 6 g. (0.057 mole) of benzaldehyde in 90 ml. of chloroform was added with mechanical stirring within 3 min. to a mixture of 25 ml. of concentrated sulfuric acid and 25 ml. of chloroform, the reaction mixture being cooled in an ice-bath. (It was noted that the rate of nitrogen evolution was much more rapid in this experiment than in the decompositions previously described.) The cooling bath was removed after 30 min., following which the reaction was allowed to proceed at room temperature for 15 hr. The reaction mixture was hydrolyzed with ice-water and then filtered to remove 3.8 g. of resinous material. The deep blue aqueous layer was separated from the yellow chloroform layer. Extraction of the latter layer with saturated sodium bisulfite solution gave 1.12 g. of benzaldehyde. The chloroform solution was evaporated to dryness, the residue dissolved in a minimum of benzene, and chromatographed on "grade II" alumina. The products were isolated.

Compound	Wt., g.	Eluent
Benzylferrocene	0.28	Skelly B solvent
II, m.p. 218–220°, plus II, m.p. 276–278°	.50	Skelly B–benzene (1:1)
Ferrocenecarboxaldehyde	.12	Skelly B–ether (3:1)
N-Benzoylferrocenylphenylcarbinylamine	.60	Skelly B–ether (3:2)

The N-benzoylferrocenylphenylcarbinylamine was identified by elemental analysis and by comparison with an authentic sample (see below). The m.p. of the compound was 184–186° (cor.).

Anal. Calcd. for $C_{24}H_{21}NOFe$: C, 72.92; H, 5.36; N, 3.54; Fe, 14.13; mol. wt., 395. Found: C, 73.19; H, 5.53; N, 3.54; Fe, 14.18; mol. wt., 359.

The blue aqueous layer was reduced and treated as described previously. There was obtained 3.90 g. of II, m.p. 218–220°; 1.50 g. of II, m.p. 276–278°; 0.04 g. of benzoylferrocene; and 0.13 g. of N-benzoylferrocenylphenylcarbinylamine. From the reduced aqueous phase which had been made basic there was isolated 0.47 g. of aniline. As in the previous decomposition reactions, evidence was found for the presence of iron(III) salts in the aqueous phase. These undoubtedly arise from break-up of the ferrocene moiety.

N-Benzoylferrocenylphenylcarbinylamine.—Ferrocenylphenylcarbinylamine was benzoylated by treatment of benzoyl chloride in pyridine solution. The amide was recrystallized from a benzene–Skelly B mixture and was found to have a m.p. of 184–186° (cor.). A mixed melting point test with the sample described above showed no depression.

Decomposition of Ferrocenylphenylcarbinyl Azide (I) in Chloroform–Sulfuric Acid Containing Benzaldehyde and Benzhydryl Azide.—A reaction of 6.0 g. (0.019 mole) of I, 3.0 g. (0.028 mole) of benzaldehyde and 4.0 g. (0.019 mole) of benzhydryl azide[18] in chloroform–sulfuric acid was carried out and the resulting mixture hydrolyzed in the same manner as for the reaction without benzhydryl azide present. After removal of 1.43 g. of resinous material, sodium bisulfite extraction of the chloroform layer gave 0.95 g. of benzaldehyde. Following evaporation of the chloroform, a benzene solution of the residue was placed on a "grade II" alumina column.

Elution with Skelly B solvent gave 2.2 g. of a pale red oil. This oil proved to be a mixture of diphenylmethane[10] and 1,1,2,2-tetraphenylethane. The latter compound, m.p. 213–215° (cor.), was isolated by dissolution of the red oil in benzene–Skelly B (1:3) and cooling the solution in an ice-bath. The tetraphenylethane was identified by a mixed m.p. test with an authentic sample of the compound,[22] and by the identity of the infrared spectra of the two samples in chloroform solution. The diphenylmethane was identified[10] by comparison of its retention time during vapor phase chromatography with that of an authentic sample. Also, the diphenylmethane was further characterized by oxidation to benzophenone.[10] Elution, next with benzene, gave unidentified oils. Further elution with ether afforded 0.35 g. of N-benzoylferrocenylphenylcarbinylamine.

The deep blue aqueous phase from the original decomposition was reduced with zinc dust, extracted with benzene, and the benzene extract placed on a "grade III" alumina

(22) G. Wittig and H. Witt, *Ber.*, **74**, 1474 (1941).

column. Elution with Skelly B solvent and then with Skelly B–benzene (1:1) gave, respectively, 0.94 g. of II, m.p. 218–220°, and 0.11 g. of II, m.p., 276–278°.

The aqueous phase remaining after extraction with benzene was made alkaline and extracted with ether. There was obtained 0.34 g. of aniline.

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The Conformation of Lysine on its Site of Biological Utilization[1]

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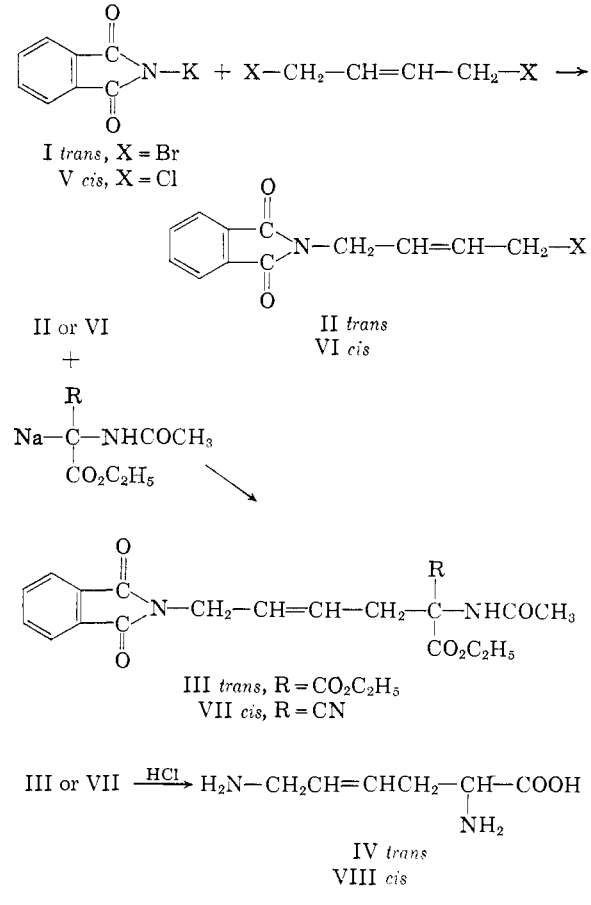
In order to study the conformation of lysine bound to its enzymic site of biological utilization, *cis*- and *trans*-2,6-diamino-4-hexenoic acids (4,5-dehydrolysines) were synthesized. The appropriate *cis*- or *trans*-1,4-dihalo-2-butene was treated with potassium phthalimide, and the resulting N-(4-halo-2-butenyl)-phthalimide was condensed either with ethyl acetamidocyanoacetate in the case of the *cis*- isomer or with ethyl acetamidomalonate in the case of the *trans*- isomer. Acid hydrolysis of the corresponding condensation products gave the isomeric 4,5-dehydrolysines. The biological activities of the two isomers indicate that the conformation of lysine in association with its enzymic site of utilization in several organisms is such that the β- and ϵ-carbons are in a *trans*-like configuration.

3-Aminocyclohexanealanine and 3-aminomethylcyclohexaneglycine both bind at the site of utilization of lysine and competitively inhibit its utilization in certain microörganisms.[3,4] In contrast, 4-aminocyclohexaneglycine apparently does not form such a complex since it is not antagonistic to lysine utilization in these assay systems.[4] The conformation of lysine in forming this enzyme-substrate complex may be such that the β- and ϵ-carbons are in a *trans*-like configuration since both of the active analogs, in contrast to the inactive derivative, can exist in an analogous *trans*-like configuration. Although substituents on either β- or ϵ-carbons of lysine as in the two active cyclohexane analogs did not prevent antagonism of lysine, the inactivity of 4-aminocyclohexaneglycine could possibly result from the effect of substituents on both of these carbons which might result in sufficient steric hindrance to prevent interaction with the enzyme utilizing lysine.

In order to demonstrate that a biologically active lysine analog must be able to conform to the structure in which the β- and ϵ-carbons are in a *trans*-like configuration, lysine analogs with no side chain substituents, but with restrictions on the relative positions of the β- and ϵ-carbons, would be required to eliminate the possibility of steric hindrance accounting for the inactivity of 4-aminocyclohexaneglycine. Accordingly, *trans*- and *cis*-4,5-dehydro-DL-lysine were prepared with the anticipation that the *trans*- but not the *cis*-isomer should prevent utilization of lysine.

trans-4,5-Dehydrolysine was prepared as indicated in the accompanying equations (I) to (VIII). Two equivalents of *trans*-1,4-dibromo-2-butene were treated with one equivalent of potassium phthalimide to yield N-(*trans*-4-bromo-2-butenyl)-phthalimide (II) which subsequently reacted



with the sodium salt of ethyl acetamidomalonate, and the resulting intermediate (III) was converted by acid hydrolysis to *trans*-4,5-dehydrolysine (IV).

As anticipated, the *trans* form of dehydrolysine inhibits utilization of lysine. The analog completely inhibits growth of *Leuconostoc dextranicum* 8086, *Lactobacillus arabinosus* 17–5 and *Streptococcus lactis* 8039 in media devoid of lysine at concentrations of 0.2, 0.6 and 0.6 μg. per ml., respectively. For each organism, the growth inhibition

(1) Presented at the 16th Southwest Regional American Chemical Society Meeting, December, 1960, Oklahoma City.

(2) Taken in part from the Ph.D. dissertation of A. L. Davis, The University of Texas, August, 1960.

(3) A. L. Davis, J. M. Ravel, C. G. Skinner and W. Shive, *Arch. Biochem. Biophys.*, **76**, 139 (1958).

(4) A. L. Davis, C. G. Skinner and W. Shive, *ibid.*, **87**, 88 (1960).