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Academician A. E. ARBUZOV and Yu. P. KITAEV

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Abstract

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ON THE MECHANISM OF THE E. FISCHER REACTION AND ITS ANOMALOUS COURSE

Earlier (⁵) we showed that arylhydrazones can exist in three tautomeric forms:

$$\mathrm{ArN{=}N{-}CH(R){-}CH_2R'} \rightleftharpoons \mathrm{ArNH{-}N{=}C(R){-}CH_2R'} \rightleftharpoons \mathrm{ArNHNH{-}C(R){=}CHR'}$$

(1) (2) (3)

The polarographic activity of all these forms indicates the presence in their molecules of conjugation of bonds. We shall now determine the interaction of the bonds in the enehydrazine form (1-4).

Molecules of compounds built according to the enehydrazine type contain a system of two double bonds separated by two nitrogen atoms, i.e., in the present case there are two groups with πp-conjugation in each. The lone electron pairs of the nitrogen atoms act upon one another and upon the quality of the N—N bond, combining the πp-groups into a $\pi p \pi$-conjugated system, in which the activation energy of the bonds is approximately 15 kcal/mole lower than in the $\pi p \pi$-system of hydrazones, and 33.0 kcal/mole lower than in the $\pi\pi$-system of azo compounds (⁵). Entry of one of the multiple bonds into the aromatic ring disrupts the symmetry of the system and gives the direction of its polarization; alkyl substituents at the 6th carbon atom act in the same direction (conjugation C=C—C—H):

$$> \mathrm{C{=}C{-}N{-}N{-}C{=}C{-}C{-}H}$$

In this conjugation chain, the 1st and 6th atoms are the most reactive.

Conjugation of bonds in enehydrazines is characterized by a considerable exaltation of molecular refraction (see Table 1).

Table 1

Compound	Mol. wt.	n_D^{20}	d_4^{20}	MR, found	MR, calculated	$\Delta MR = MR_H - MR_B$
$C_6H_5NHNH-C(CH_3)=CH_2$	148.20	1.5880	1.0144	49.152	46.682	2.470
$C_6H_5NHNH-C(CH_3)=CHCH_3$	162.22	1.5718	1.0034	53.333	51.300	2.033
$C_6H_5NHNH-C(CH_3)=C(CH_3)_2$	176.35	1.5639	0.97514	58.779	55.918	2.861

Since arylhydrazones are compounds of basic character, an acid medium will have the strongest influence on their state. Thus, in the case of a hydrazone constructed according to type (2), in an acid medium 1,4-addition of the acid can proceed through the $\pi\sigma$-conjugated system:

$$\mathrm{Ar{-}NH{-}N{=}CH{-}C(H)(R){-}H + A'} \longrightarrow \mathrm{ArNH{-}N(H){-}CH{=}C(H)(R) + H^+ + A'}$$

As a result, the more basic enehydrazine is formed. The latter, adding a proton to the more nucleophilic nitrogen atom, becomes an anion in which the ethylene bond is strongly polarized, i.e., dienophilic; the $-NH-NH_2-$bond also becomes polar. The formation of a complex compound produces the same effect. On heating above the melting point, the hydrazone forms also apparently turn into enehydrazines.

In connection with what has been said, the action of catalysts in the Fischer reaction becomes understandable; these are acidic reagents, metals and their salts capable of forming complex compounds ($^{8-10}$). They shift the tautomeric equilibrium toward the enehydrazine and activate the bonds.

The most characteristic feature of 1–4-conjugated systems is their ability to enter into diene-synthesis reactions (^{1,3}). We believe that some 1–6-conjugated systems (and also, apparently, 1–8 and 1–10) are, under certain conditions, capable of a redistribution of electron densities with an intramolecular transformation of the diene-synthesis type. Such systems include, in particular, enehydrazine systems, in which atoms 1 and 6 acquire certain excess charges of opposite sign. If one takes into account that these atoms are spatially close, then their attraction as oppositely charged atoms and their interaction according to the following scheme may be considered quite probable:

$$\mathrm{(I)} \longrightarrow \mathrm{(II)} \longrightarrow \mathrm{(III)}$$

(In the scheme, structures I-III depict the intramolecular transformation of an enehydrazine system with atoms numbered 1-6; substituents R, R′, and K are shown, with K ⋯ NH interaction in II and III.)

The analogy of this transformation with the diene-synthesis reaction is complete. Atoms 1, 2, 3, 4 form a diene system: the double bond 1–2 is conjugated with the free electrons of the 3rd and 4th atoms—this is πpp-conjugation, in many respects similar to $\pi\pi$-conjugation, and it is strengthened by the action of the catalyst. The dienophilicity of bonds 5—6 has already been discussed. Diene-synthesis reactions are characterized by the formation of a multiple bond between the 2nd and 3rd atoms and of new bonds between the atoms of the dienophile and the 1st and 4th atoms of the diene, with cleavage of the 1—2 and 3—4 bonds. All this also occurs in the scheme written above, which is the first stage of the Fischer reaction. Further transformation of the intermediate *o*-[β-iminoalkyl]aniline, which can sometimes be isolated (^{11,12}), gives indole according to the scheme of R. and G. M. Robinson (^{13}) with the additions of Allen and Wilson (^{14}).

Thus, the generalized theory of conjugation has made it possible to reveal the "driving force" of the transformation taking place in the E. Fischer reaction and to clarify the reaction mechanism.

A scheme analogous to ours was proposed in 1948 by Carlin and Fischer (^{15}), who proceeded from a "formal analogy" of the first stage of the reaction with the Claisen rearrangement. We believe, however, that here the analogy is not formal but fundamental, since in both cases a transformation of 1—6-conjugated systems occurs.

The above mechanism of the Fischer reaction, which is a consequence of the generalized theory of conjugation and also applies to the syntheses of Brunner and Piloty (^{10}), agrees with all the experimental facts and, in particular, with the observations of V. V. Feofilaktov (^{16}).

In the molecule of the intermediate *o*-iminoquinone (II), as a result of $\sigma\pi\pi$-conjugation, hydrogen atom 8 acquires mobility, and an increased electron density arises on the nitrogen atom. The orientation and approach of molecules lead to a redistribution of electrons and the formation of aniline (III):

Reaction scheme: $R_2 = -\mathrm{CHR'CR{=}NH}$

A similar mechanism, apparently, is also followed by some tautomeric transformations. The preparation of 5,7-dichloroindoles from 2,6-dichlorophenylhydrazones (^{17}) can likewise be explained by using this mechanism.

One of us (^{18}), having shown at the time the catalytic character of the Fischer reaction, found that if cuprous chloride is used as the catalyst, then from arylhydrazones of aldehydes there is formed, along with indole (or even exclusively), the nitrile of the corresponding aldehyde acid and aniline. Acetone phenylhydrazone in the presence of Cu_2Cl_2 gives a complex product, ammonia, and aniline (^{19}):

$$2C_9H_{12}N_2 \to C_{12}H_{14}N_2 + C_6H_5NH_2 + NH_3$$

It was suggested that arylhydrazones of ketones that do not contain a methylene group adjacent to the carbonyl should also decompose abnormally with Cu_2Cl_2.

In the present work, using as examples the phenylhydrazones of acetone, methyl isopropyl ketone, pinacolone, pyruvic acid, acetophenone, *p*-chloroacetophenone, and also methylphenylhydrazone of acetone, it is shown that this assumption is correct. The amount of ammonia liberated in the reaction was always less than required by the equation for the normal reaction, and corresponded more closely to the equation for the abnormal reaction. From the phenylhydrazones of acetone and methyl isopropyl ketone abnormal products were obtained, for which structures (IV) and (V) are proposed. These substances change readily in air.

(IV)

b.p. 138–139°/10 mm
n_D^{20} 1.5801
n_{40}^{2} 1.0520
yield 21%

(V)

b.p. 144–145°/10 mm
yield 12%

In the remaining cases, aniline, ammonia, and resins not amenable to purification were obtained, while in the case of methylphenylhydrazone only resinification was observed.

The formation of nitriles and N-substituted indoles from arylhydrazones, as well as the decomposition of phenylhydrazine in the presence of a catalyst ([20,21]), we consider to be processes related in their mechanism and propose for them the following schemes (see (1)–(3) on p. 810):

In these schemes it is assumed that the hydrazine entering the complex reduces the free base. Such a mechanism agrees with the observations of Clusius ([21]), who decomposed phenylhydrazine labeled with the isotope N^{15}.

The disproportionation of hydrazobenzene ([22]), the formation of osazones ([23]), and the interaction of azobenzene and hydrazobenzene with phenylhydrazine ([24]) also have an analogous mechanism; and since they proceed without a catalyst, consequently free hydrazines too are capable of being reducing agents for molecules of their own kind.

$$(1)\quad C_6H_5{-}N{-}N{-}H \xrightarrow{Cu^+} C_6H_5{-}N{=}NH \longrightarrow C_6H_6 + N_2 + Cu^+$$
$$NH_2{-}NH{-}C_6H_5 \to NH_3 + NH_2C_6H_5$$

$$(2)\quad \mathrm{C_6H_5{-}NH{-}NH{-}CH{=}CHR \longrightarrow C_6H_5NH_2 + NH_2CH{=}CHR \rightleftharpoons NH{=}CHCH_2R}$$
$$\mathrm{+\ Cu^+ + RCH{=}CH{-}N{=}N{-}C_6H_5 \longrightarrow R{-}CH{=}CH{-}NH{-}NHC_6H_5 + N{\equiv}CCH_2R}$$
$$\mathrm{R{-}CH{=}CH{-}NH{-}NHC_6H_5} \xrightarrow{-\mathrm{NH_3}} \text{indole derivative}$$

$$(3)\quad \mathrm{2C_6H_5NHNH{-}C({=}CH_2)(CH_3) \rightarrow C_6H_5NH_2 + NH_2{-}C({=}CH_2)(CH_3)} \longrightarrow$$
$$\mathrm{CH_3{-}C({=}CH_2){-}NH \qquad C_6H_5N{=}N{-}C({=}CH_2)(CH_3)}$$
$$\mathrm{C_6H_5NH_2 + C_6H_5N{-}NH{-}C({=}CH_2)(CH_3)} \longrightarrow \text{indole derivative } \mathrm{N{=}C(CH_3)_2 + NH_3 + C_6H_5NH_2}$$

The abnormal Fischer reaction apparently occurs when the catalyst forms coordination bonds with both nitrogen atoms of the hydrazine; for example:

$$\mathrm{Cl^-} + \left[\begin{array}{c} \mathrm{C_6H_5{-}NH{-}NH{-}CR{=}CHR'} \\ \backslash\mathrm{Cu}/ \\ \mathrm{R'CH{=}CR{-}NH{-}NH{-}C_6H_5} \end{array}\right]^+$$

But it is still not clear why not all arylhydrazones undergo the abnormal reaction. We found that sulfanilic acid is also a good catalyst of the abnormal reaction. Its action is apparently based on its ability to form hydrogen bonds with hydrazines and to increase the nucleophilicity of the nitrogen atoms, i.e., its action on hydrazine is opposite to that of copper salts. In this case the free base acts as the reducing agent.

Kazan Chemical-Technological Institute
named after S. M. Kirov

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Note: Figure translations are in progress. See original paper for figures.

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