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NEW SCHEME OF THE MECHANISM OF FISCHER INDOLIZATION

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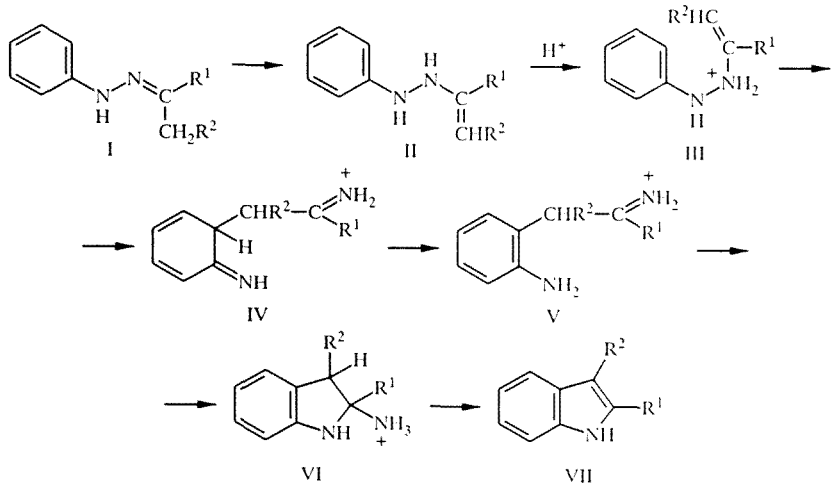
An expanded and fundamentally new scheme of the mechanism of Fischer indolization has been constructed on the basis of quantum chemical calculations of the energetic, electronic, and structural indices, as well as a study of the regioselectivity, kinetic and spectrometric characteristics of some phenylhydrazones.

The Fischer indolization of arylhydrazones is one of the reactions in the chemistry of heterocyclic compounds that are convenient for the synthesis of indole derivatives and of great importance, and for which the fine mechanism has been worked out. The main steps in the acid-catalyzed Fischer reaction were proposed in the studies of G. and R. Robinson [1], as well as by Allen and Wilson [2]:

Scheme 1



The validity of these steps was subsequently demonstrated experimentally by many researchers, among whom we might single out the studies of Pleninger [3], Douglas [4], Clusius [5], Suvorov [6], and Geller [7].

The study of the step of cleavage of the N–N bond and the formation of a new C–C bond is of special interest. In 1949 Pousacker and Schubert [8] suggested on the basis of the production of cross-cyclization products of a mixture of two different phenylhydrazones that the N–N bond is broken homolytically, and the new C–C bond is formed according to an intermolecular radical addition mechanism. However, their idea was immediately criticized [9] — the formation of cross-products was explained by hydrolysis of the phenylhydrazones; when the formation of cross-products was also detected in anhydrous medium, the process was explained by "transhydrazonization" [10] — and the bold hypotheses of Pousacker and Schubert were forgotten. Continuing a study of this step of the Fischer reaction, Arbuzov and Kitaev [11] proposed that the

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TABLE 1. Kinetic Characteristics of the Fischer Reaction for Phenylhydrazones VIII-X

Phenyl-hydrazone	R	Rate constant k, liter$^{0.5}$·mole$^{-0.5}$sec^{-1}	$E^{\neq}$, kJ/mole	Order of the Fischer reaction, n
VIII	H	0,060	109,9	1,5
IX	Cl	0,043	155,9	1,5
X	CH_3	0,700	64,4	1,5

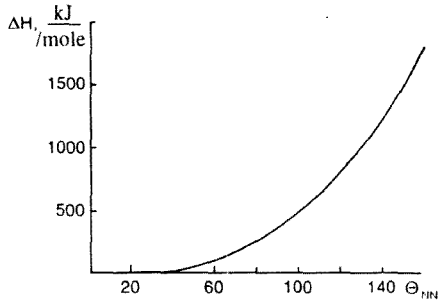


Fig. 1

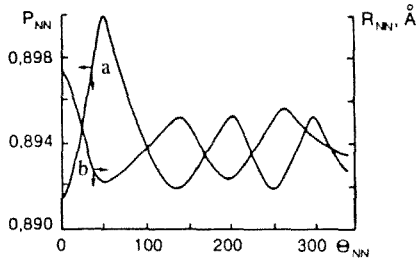


Fig. 2

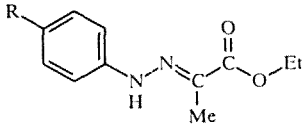
Fig. 1. Enthalpy (ΔH) of the enehydrazine tautomer of acetaldehyde phenylhydrazone XXI as a function of the angle of rotation around the N−N bond.

Fig. 2. Order (P_{NN}) (a) and bond length (R_{NN}) (b) in the protonated enehydrazine XXII as a function of the angle of rotation around the N−N bond (Θ_{NN}).

formation of a new C−C bond be considered as intramolecular electrophilic addition, but this mechanism was refuted on the basis of the kinetic data [12]. In 1972 Grandberg advanced the idea of (3,3)-sigmatropic rearrangement, based on the principle of conservation of orbital symmetry [13]. In his opinion, this is an intramolecular synchronous process, in which the N−N bond is not broken completely, and the new C−C bond is not completely linked. For an experimental confirmation of this hypothesis the indolization of para-substituted α,α-diphenylhydrazones of cyclohexanone was investigated [14], and it was shown that the electronic effects of substituents have little influence on the direction of formation of the C−C bond. However, both in this study and in the work of other authors [15], a favorable influence of electron-donor substituents on the formation of a C−C bond was noted systematically, which makes the concept insufficiently convincing. In our opinion, the mechanism under consideration is of a general nature and does not describe all the complexity of the step of cleavage of the N−N bond and formation of a new C−C bond.

To construct an expanded scheme of the mechanism of Fischer indolization of arylhydrazones we investigated the kinetics [16], spectrophotometric [17], and quantum-chemical [18] characteristics of some phenylhydrazones, as well as their regioselectivity [19, 20] and reactivity [21, 22].

The rate constants (k), activation energy ($E^{\neq}$) and order of the Fischer reaction (n) of para-substituted phenylhydrazone derivatives of the ethyl ester of pyruvic acid (PAEE):



VIII–X

VIII R = H; IX R = Cl; X R = Me

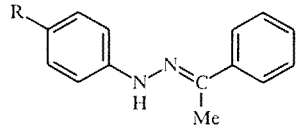
were determined by UV spectrometry.

TABLE 2. Enthalpy (ΔH) (kJ/mole) of Phenylhydrazones XXIIIa-h and Their Enehydrazine Tautomers XXIVa-h and XXVa-h, Enthalpy Changes of the Hydrazone–Enehydrazine Tautomeric Conversion (ΔΔH), Reaction Yields at Room Temperature in the Presence of PCl_3, and Ratio of Products of Fischer Indolization XXVI:XXVII

Phenylhydrazone	ΔH			ΔΔH		Yield, %	Ratio XXVI: XVII
	XXIII	XXIV	XXV	XXIII — XXIV	XXIII — XXV		
a	200,2	269,2	275,9	69,0	75,6	74 (XXVIa)	48 : 0
b	-103,2	-62,7	-48,1	40,5	55,1		
c	-135,4	-96,1	-86,1	39,3	49,3		
d	318,5	380,4	369,5	61,9	51,0	61 (XXVI d) 10 (XXVIId)	0 : 52
e	290,1	332,3	342,3	42,2	52,2	65 (XXVI e)	47 : 15
f	147,5	188,1	198,1	40,6	50,6	61 (XXVIf)	Complex in solution
g	120,4	159,3	174,7	38,9	54,3	58 (XXVI g)	51 : 0
h	90,7	135,0	145,0	44,3	54,3	41 (XXVI h) 36 (XXVIIh)	Complex in solution

The values of the kinetic characteristics (Table 1) are evidence that the electron-donor substituent in the para-position of the phenyl ring substantially decreases the activation energy of the reaction ($E^{\neq}$) in comparison with the unsubstituted phenylhydrazone VIII, whereas in the case of an electron-acceptor substituent it increases by a factor of 1.4. The order of the reaction n for all three phenylhydrazones is 1.5 (the non-whole-number value, in our opinion, is an indication of a more complex reaction pathway than is provided for by the synchronous mechanism of intramolecular (3,3)-sigmatropic rearrangement). Since the principle of conservation of orbital symmetry on which the (3,3)-sigmatropic rearrangement is based is observed for a first-order reaction, the noncorrespondence created in the approaches to the description of the mechanism of indolization of arylhydrazones serves as grounds for further theoretical and experimental investigation of individual steps of the complex Fischer reaction. From Table 1 it is also evident that an electron-donor substituent accelerates the Fischer reaction in comparison with the unsubstituted phenylhydrazone VIII, and an electron-acceptor substituent slows it down.

To study the influence of a substituent in the phenyl ring of the hydrazine fragment on the properties of the N=C bond we recorded the IR spectra of the phenylhydrazone of acetophenone (XI) and its p-NO_2- (XII) and p-CH_3- (XIII) derivatives in DMSO [17].



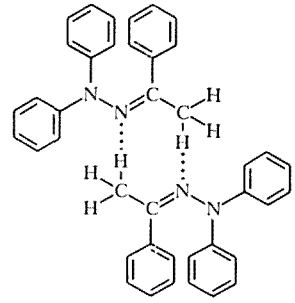
XI–XIII

XI R = H; XII R = NH_2; XIII R = Me

It was established that the frequency of the stretching vibration of the imine group N=C is the same for all the derivatives (1691 cm^{-1}), while the intensity of the absorption band decreases sharply in the series p-CH_3 > H > p-NO_2. Since hydrazone–enehydrazine conversion is directly related to the ability for conversion of the imine bond N=C to a N–C bond, it can be concluded that the electron-donor substituent hinders the tautomeric conversion, whereas an electron-acceptor substituent promotes it. Comparing this conclusion with the conclusion drawn above, that an electron-acceptor substituent slows down indolization, we can conclude that the hydrazone–enehydrazine tautomeric conversion cannot be the limiting step of the Fischer reaction.

The IR spectrum of acetophenone diphenylhydrazone (XIV) was examined in more detail. The integral intensity of the band of the N=C group in this hydrazone is rather low (A_{NC} = $0.5 \cdot 10^4$ liters/mole·cm^2), which is an indication of its increased ability for conversion to the enehydrazine form. As we go from chloroform (solvent) to KBr tablets, the half width of the absorption band of the deformational asymmetric vibration of the methyl group ($\Delta\nu_{1/2}\delta_{CH_3}^{as}$) decreases almost by half

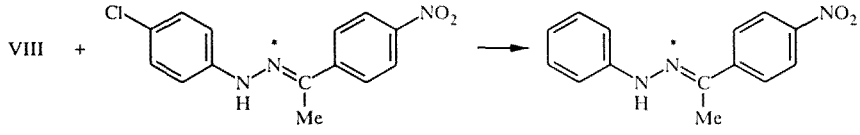
(30 and 17 cm^{-1} in chloroform and KBr, respectively), and the width of this band is determined by the vibrational and rotational movement of the methyl group. The decrease in the half-width of the absorption band is due to disappearance of its rotational structure, which, in our opinion, is explained by the formation of an intermolecular hydrogen bond between the hydrogen atom of the metal group and the unshared pair of electrons of the imine nitrogen [23].



XIVa

As a result of the proposed association, favorable conditions are created for a shift of the tautomeric equilibrium in the direction of the enehydrazine form. This is also essentially the mechanism of the hydrazone–enehydrazine conversion.

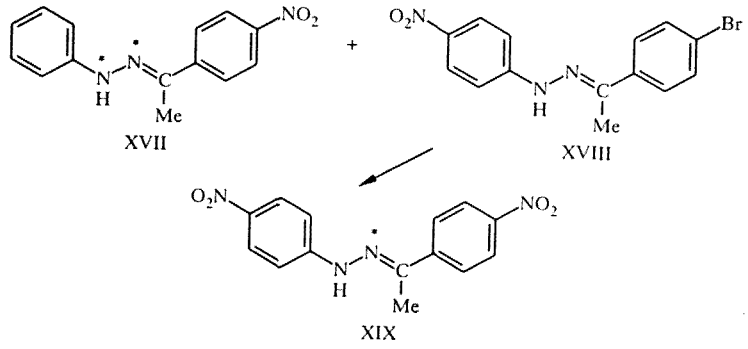
To study the process of cleavage of the N–N bond we investigated a mixture of the hydrazone of PAEE (VIII) and p-nitroacetophenone p-chlorophenylhydrazone, labeled at the imine nitrogen atom with the stable isotope ^{15}N (XV).



XV XVI

By heating this mixture to 60°C in polyphosphoric acid we obtained a cross phenylhydrazone of p-nitroacetophenone, labeled on the imine nitrogen atom (XVI), which can be formed only as a result of cleavage of the N–N bond. Consequently, there is a possibility of cleavage of the N–N bond without the formation of a new C–C bond.

To reproduce the results cited, an experiment on the detection of a different surface product from a mixture of p-nitroacetophenone phenylhydrazone, labeled on both nitrogen atoms (XVII), and p-bromoacetophenone p-nitrophenylhydrazone (XVIII), was proposed.



XVII XVIII XIX

As a result we obtained a cross p-nitrophenylhydrazone of p-nitroacetophenone, labeled on the imine nitrogen atom (XIX). Here, just as in the preceding case, the formation of a cross phenylhydrazone XIX is possible only as a result of cleavage of the N–N bond. The cross phenylhydrazones XVI and XIX were isolated preparatively, and their structures were established by spectrometric methods.

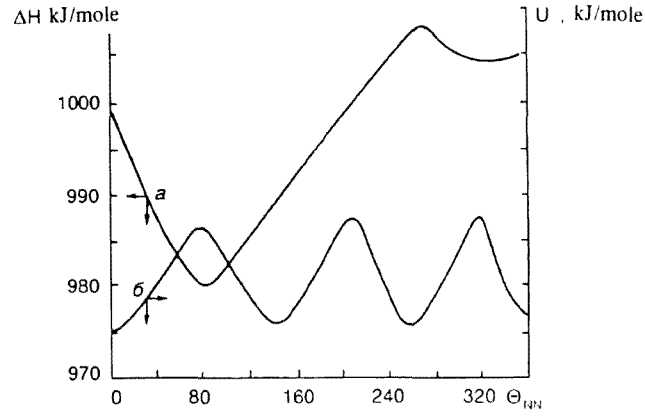
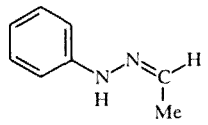


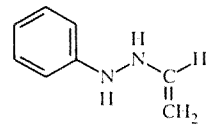
Fig. 3. Enthalpy (ΔH) (a) and energy of electrostatic attraction between nitrogen atoms U_e (b) in the protonated enehydrazine XXII as a function of the angle of rotation around the N−N bond (Θ_{NN}).

Thus, cleavage of the N−N bond without the formation of a new C−C bond is theoretically possible in the Fischer reaction. Consequently, this step of the investigated reaction is of a stepwise nature, and the formation of a new C−C bond is preceded by cleavage of the N−N bond, which contradicts the existing theory of a synchronous occurrence of this process [13].

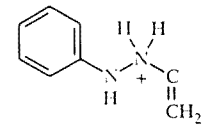
The order (P_{NN}) and length (R_{NN}) of the N−N bond, the enthalpy of the molecule (ΔH), and the energy of electrostatic attraction between nitrogen atoms (U_e) at different values of the rotation around the N−N bond (Θ_{NN}) for the enehydrazine tautomer XXI of acetaldehyde phenylhydrazone XX and its protonated form XXII



XX



XXI



XXII

were subsequently calculated by a quantum-chemical semiempirical MNDO AM1 method [24].

From Fig. 1 it is evident that at small angles Θ_{NN} the enthalpy of the enehydrazine XXI increases slightly; beginning with Θ_{NN} = 80° it increases sharply, and at Θ_{NN} = 150° the rotation is inhibited. In the protonated enehydrazine XXII at Θ_{NN} = 140°, a favorable condition is created for breakdown of the N−N bonds, since in this phase of the rotation R_{NN} takes a maximum value, while P_{NN} and U_e are minimal (Figs. 2 and 3). From Fig. 2 it is evident also that the stablest state of the enehydrazine XXII corresponds to the conformation for which Θ_{NN} = 80°. It was established as a result of the analysis that protonation promotes cleavage of the N−N bond. The phase of the angle Θ_{NN}, at which the N−N bond is broken, gives the theoretical value from the standpoint of formation of a new C−C bond. The most favorable conformation for this is the one in which Θ_{NN} = 180°. In this phase, however (see Fig. 2), the N−N bond is not broken. Taking into consideration the fact that at Θ_{NN} = 140°, the molecule is closer to the coplanar state, we can assume that the mechanism of formation of the C−C bond is of a "partial intramolecular" nature (considering that the formation of a new C−C bond is preceded by cleavage of the N−N bond).

To study the regioselectivity of the indolization of arylhydrazones, we calculated the enthalpy (ΔH) and enthalpy change (ΔΔH) of some phenylhydrazones of nonsymmetrical carbonyl compounds (XXIIIa-h) and their enehydrazine tautomers (XXIVa-h, XXVa-h) [19, 20] (Table 2). It is known that these phenylhydrazones form chiefly 3-substituted 2-methylindoles [12]. The formation of 3-unsubstituted 2-alkylindoles is rarely observed. Although the corresponding reaction pathway is characterized by a comparatively high value of the enthalpy change, it is unprofitable from the energy standpoint.

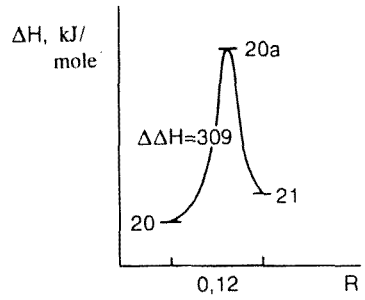


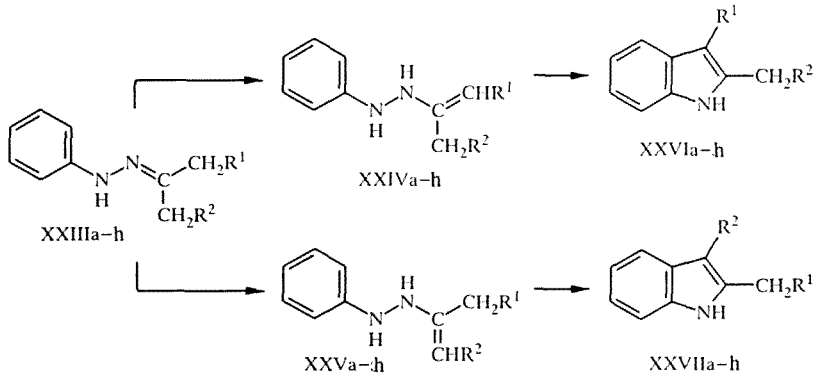
Fig. 4. Energy diagram of the tautomeric conversion of acetaldehyde phenylhydrazone XX to the corresponding enehydrazine XXI (R is the reaction coordinate).

Originally we considered the phenylhydrazones of methyl ethyl ketone (XXIIIa), acetoacetic (XXIIIb) and levulinic acid (XXIIIc) and their enehydrazine tautomers (XXIVa-c, XXVa-c).

As can be seen from Table 2, the minimum values of the enthalpy change ($\Delta\Delta H$) are characteristic of the tautomeric conversions that occur through the methylene groups XXIIIa-c → XXIVa-c, resulting in the formation of 3-substituted 2-methylindoles (XXVIa-c), which is in full agreement with the experimental data [12].

The regioselectivity of the indolization of phenylhydrazones XXIIIa,d-h at room temperature in the presence of PCl_3 was studied by Baccolini et al. [25]. The predominant formation of 2,3-disubstituted indoles (structures XXVIa,d-h) was demonstrated on the basis of the yield of the indolization products and basically corresponds to our calculated data on $\Delta\Delta H$ and the ratios of the products of Fischer indolization XXVI:XXVII. An exception is the phenylhydrazone of 1-phenylbutan-2-one (XXIIId), for which, of the two possible end products, primarily 2-ethyl-3-phenylindole (XXVIb) is formed, whereas only 2-methylphenyl-3-methylindole (XXVIId) is formed according to the Fischer reaction. Judging by the values of $\Delta\Delta H$ that we calculated, in the case of the compound XXIIId the reaction proceeds through the enehydrazine XXVd to the indole XXVIId, which agrees with the data of the Fischer reaction.

Scheme 2



a $R^1 = CH_3$, $R^2 = H$; b $R^1 = COOH$, $R^2 = H$; c $R^1 = CH_2COOH$, $R^2 = H$; d $R^1 = C_6H_5$, $R^2 = CH_3$; e $R^1 = C_6H_5$, $R^2 = C_2H_5$; f $R^1 = CH_3$, $R^2 = C_2H_5$; g $R^1 = CH_3$, $R^2 = C_3H_7$; h $R^1 = C_2H_5$, $R^2 = C_3H_7$

Thus, the results of a comparison of the yields of the end products of indolization of phenylhydrazones of nonsymmetrical carbonyl compounds with the values of the enthalpy change ($\Delta\Delta H$) of the conversion of the phenylhydrazones permit us to conclude that the latter can serve as a reliable parameter of the regioselectivity of the Fischer reaction.

On the basis of quantum chemical calculations in the system of the reaction coordinates on the example of the phenylhydrazone of acetaldehyde XX, which is simplest in structure, an expanded scheme of the mechanism of Fischer indolization

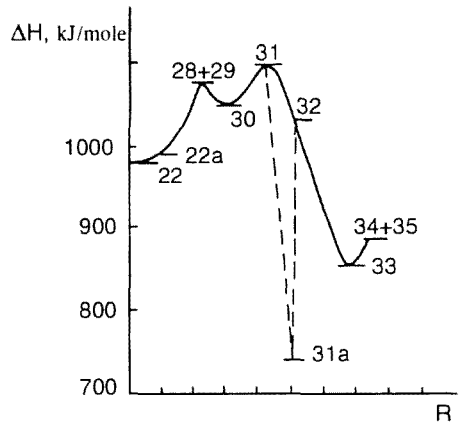
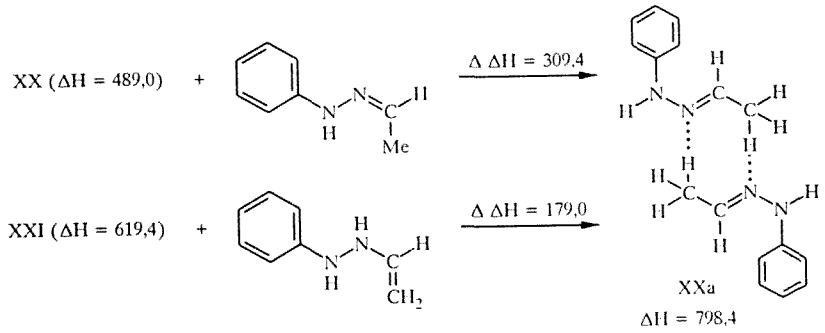


Fig. 5. Energy diagram of the conversion of the protonated enehydrazine XXII to the indole XXXIV (R is the reaction coordinate).

was constructed in [18]. The entire scheme formally consists of two parts, one of which includes the formation of a crystalline dimer XXa of two molecules of acetaldehyde phenylhydrazone XX, its breakdown into enehydrazine tautomers XXI, and their protonation XXII. In essence this is also hydrazone–enehydrazine tautomeric conversion through the dimer XXa.

Scheme 3

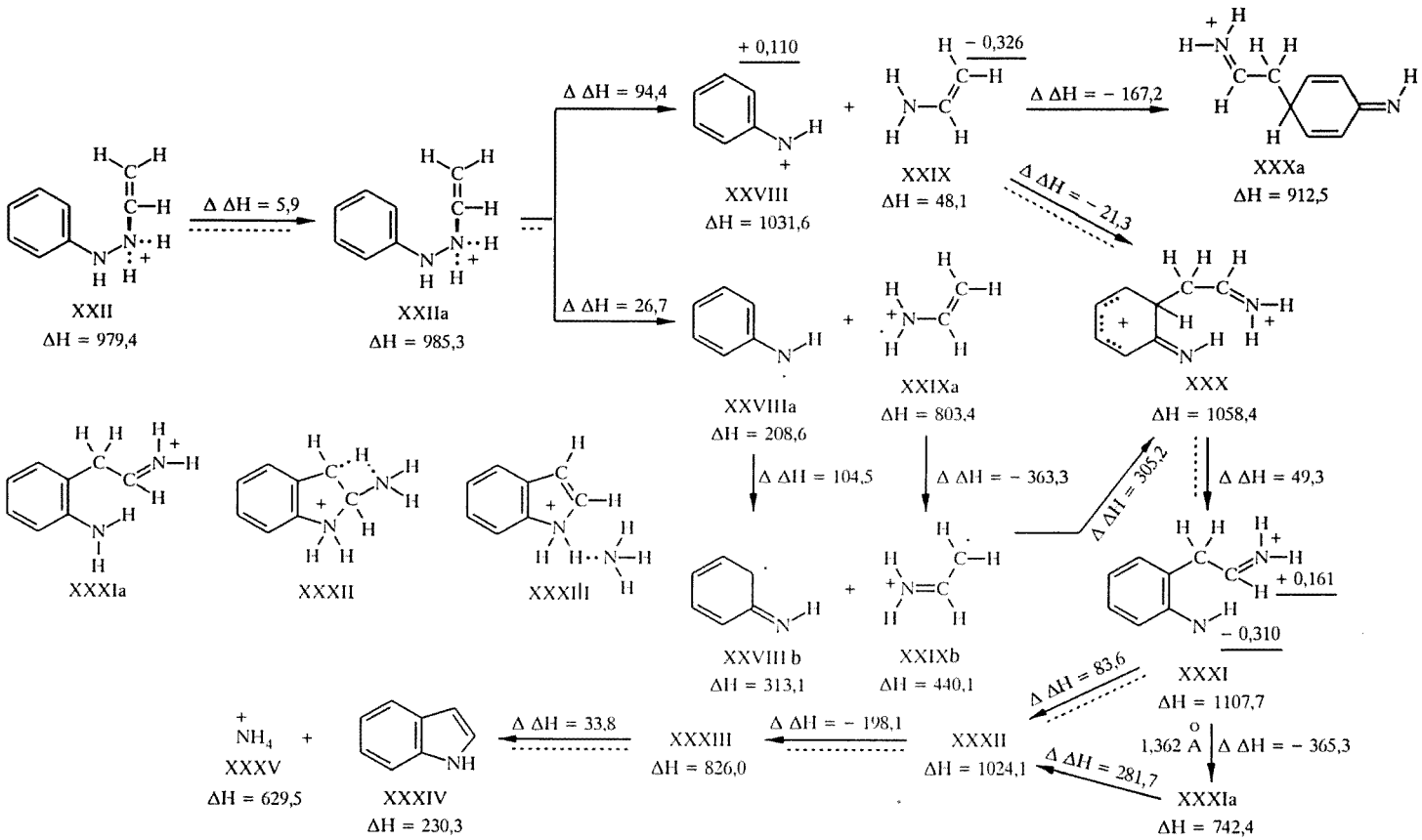


From Scheme 3 and Fig. 4 it is evident that the energy of tautomeric conversion reaches 309.4 kJ/mole, whereas, according to kinetic measurements, the activation energy of the Fischer reaction ranges from 60 to 160 kJ/mole. Such a high and narrow (0.12 Å) energy barrier indicates the possibility of tunneling of the methyl proton. The tunneling energy, considering the frequency of the asymmetrical deformational vibration of the methyl group (δ_{CH3}^{as} = 1470 cm^{-1}), is ~20 kJ/mole, and according to the theory of German and Dogonadze [26], the proton may act like a quantum particle.

On the basis of what has been outlined and the experimental data, we can suggest that the hydrazone-enehydrazine tautomeric conversion is a quantum process, proceeding on account of the thermal motion of the reacting particles according to an intermolecular hydrogen bond mechanism.

Under the conditions of the Fischer reaction, the enehydrazine tautomer XXI undergoes protonation; the Nβ nitrogen atom can be considered as the site of protonation without limiting its generality. The protonation energy is 669.7 kJ/mole, which is characteristic of nitrogen-containing compounds, i.e., the protonated enehydrazine XXII, which we shall arbitrarily take as the initial compound of the second part of the scheme that we have proposed (Scheme 4), becomes the next intermediate of the reaction under investigation. The enehydrazine XXII has a conformation rotated through an angle Θ_{NN} = 80° around the N–N bond, with an enthalpy of 979.4 kJ/mole. As a result of rotation through another 60° the energy is increased by only 5.9 kJ/mole, and in this state (XXIIa) the N–N bond is broken, as was described above.

Scheme 4


XXII
ΔH = 979,4
Δ ΔH = 5,9
XXIIa
ΔH = 985,3
Δ ΔH = 94,4
Δ ΔH = 26,7
+ 0,110
XXVIII
ΔH = 1031,6
XXVIIIa
ΔH = 208,6
− 0,326
XXIX
ΔH = 48,1
XXIXa
ΔH = 803,4
Δ ΔH = − 167,2
XXXa
ΔH = 912,5
Δ ΔH = − 21,3
XXX
ΔH = 1058,4
Δ ΔH = 104,5
Δ ΔH = − 363,3
Δ ΔH = 305,2
Δ ΔH = 49,3
XXVIII b
ΔH = 313,1
XXIXb
ΔH = 440,1
+ 0,161
− 0,310
XXXI
ΔH = 1107,7
Δ ΔH = 83,6
XXXII
ΔH = 1024,1
Δ ΔH = − 198,1
XXXIII
ΔH = 826,0
Δ ΔH = 33,8
XXXIV
ΔH = 230,3
XXXV
ΔH = 629,5
1,362 Å
Δ ΔH = − 365,3
Δ ΔH = 281,7
XXXIa
ΔH = 742,4
XXXIa
XXXII
XXXIII

Scheme 4 presents two versions of cleavage of the N−N bond: heretolytic and homolytic. As can be seen, homolytic cleavage is preferable from the energy standpoint, although in heterolytic cleavage the enthalpy also changes within reasonable limits ($\Delta\Delta H$ = 94.4 kJ/mole). To detect radical products of the homolytic cleavage of the N−N bond we took the ESR spectrum of PAEE phenylhydrazone (VIII) under the conditions of the Fischer reaction and demonstrated the presence of an aniline radical by the spin trap method (nitrosodurol) [27]. To verify the radical pathway of the reaction we conducted the cyclization of PAEE phenylhydrazone (VIII) in the presence of nitrosodurol as an inhibitor of radicals in various molar ratios; in all cases the formation of the cyclization product — 2-carbethoxyindole — was observed. Consequently, it can be assumed that the reaction does not develop along the radical pathway. Actually, for the formation of a new C−C bond according to a mechanism of radical addition, the aniline radical XXVIIIa and the enamine radical cation XXIXa should be preliminarily converted to the radicals XXVIIIb and XXIXb, respectively, and for radical addition 305.2 kJ/mole of energy should be absorbed, which is unrealistic in practice both from the quantitative and from the qualitative standpoints, since energy should be liberated in the formation of a molecule from two particles.

Thus, of the two versions of cleavage of the N−N bond in the protonated enehydrazine XXIIa, heterolytic cleavage becomes acceptable. As can be seen from Scheme 4, a positive charge is concentrated on the carbon atom in the ortho-position of the aniline cation XXVIII, and a rather high negative charge on the extreme carbon atom of the allyl group of the enamine XXIX. As a result of this distribution of charges in the products of heterolytic cleavage of the N−N bond, a new C−C bond should be formed according to a nucleophilic addition mechanism, which, according to the calculations, occurs with a release of energy (21.3 kJ/mole). As can be seen from Fig. 5, the process considered corresponds to passage through the first energy barrier of the Fischer reaction, which we constructed on the basis of quantum chemical calculations in the system of the reaction coordinates. On the basis of the intermolecular nature of this process, in addition to the intermediate XXX, we should also have expected the formation of the product of para-rearrangement XXXa; however, we were unable to detect it (a single case of its formation from an unsubstituted phenylhydrazone has been described in the literature [28]). In one way or another, there should be no doubt of the possibility of an intermolecular process forming the new C−C bond. Why the products of para-rearrangement are formed more rarely than the products of ortho-rearrangement is another question. The answer, in our opinion, lies in the fact that the N−N bond is broken in the phase Θ_{NN} = 140°, when the extreme carbon atom of the allyl group is spatially close to the carbon atom in the ortho-position of the phenyl ring. From this standpoint the formation of a new C−C bond may be of a "partially intramolecular" nature, considering the fact that the formation of the C−C bond is preceded by cleavage of the N−N bond.

In the intermediate XXX, R_{CC} — 2.928 Å, and for the length of this bond to reach the optimum value and for aromaticity to arise, an additional energy of 49.3 kJ/mole is required. As a result of the difficult intramolecular transfer of a proton to the amine group, the intermediate XXX is converted to the molecule XXXI, which is also an activated complex of the Fischer reaction (Fig. 5). On account of the energy liberation (365 kJ/mole), the activated complex XXXI may be converted to an intermediate product — the aminoimine XXXIa, the existence of which was demonstrated by ^{15}N NMR spectrometry [4]. However, as can be seen from Fig. 5, the aminoimine XXXIa falls into a deep energy well with a height of 281.7 kJ/mole, and its participation in the reaction is unrealistic. From Scheme 4 it is evident that in the activated complex the imine carbon atom has a positive charge q_C = +0.161, while the amine nitrogen atom has a negative charge q_N = −0.310. At the closest possible mutual approach of these atoms, a pyrrole ring is closed, and, with the liberation of 83.6 kJ/mole of energy, a new intermediate XXXII is formed, the existence of which was demonstrated by other authors by the methods of graph theory [29]. The ammonia molecule split out of the intermediate XXXII attacks a hydrogen atom of the pyrrole amine XXXIII, and as a result of stripping of a proton with the absorption of a small amount of energy (33.8 kJ/mole), the indole XXXIV and the ammonium ion XXXV are formed.

From Fig. 5 it is evident that the energy curve has two maxima, i.e., the process described consists of two main steps: cleavage of the N−N bond with the formation of a new C−C bond and closing of a pyrrole ring to form an indole. These two steps constitute the second part of the scheme that we have proposed for the mechanism of the Fischer reaction, with activation energy 128.3 kJ/mole.

The first part of the scheme, which was discussed above, consists of spontaneous processes: thermal motion, hydrazone−enehydrazine tautomeric conversion through a crystalline dimer, and protonation of the enehydrazine tautomer. The combination of these two parts represents one whole scheme of the mechanism of Fischer indolization of arylhydrazones.

EXPERIMENTAL

The IR spectra were recorded on a UR-20 spectrometer in DMSO and chloroform (ν, cm^{-1}); the UV spectra were recorded on a Specord UV-VIS spectrometer in formic acid and acetonitrile (λ, nm, log ε); the mass spectra were recorded on a Ribermag R10-10B spectrometer (m/e); the PMR spectra were recorded on a Bruker WH-200 spectrometer in deuterated formic acid with an HMDS internal standard (δ scale); the ESR spectra were recorded on an RÉ-1306 spectrometer in a solution of dichloromethane and PPK using the spin trap method (nitrosodurol).

The data of elementary analysis for C, H, and N correspond to those calculated.

Phenylhydrazone of Pyruvic Acid Ethyl Ester (VIII). A 6 g portion of phenylhydrazine hydrochloride was dissolved in the minimum amount of water, heated to 50°C, pH 5. After cooling of the solution, 4 g of pyruvic acid ethyl ester was added. The mixture was mixed for 45 min at room temperature. Then two to three drops of acetic acid (pH 3) were added to the oily mass formed. The white curdled precipitate was filtered, washed with water, dried, and crystallized from ethanol. Mp 105-107°C. IR spectrum: 3430 (NH), 1720 (C−O), 1697 (N=C), 1250 (C−O−C) (in chloroform). UV spectrum (in acetonitrile): 221 (3.76); 290 (3.82); 316 (4.05).

p-Methylphenylhydrazone of Pyruvic Acid Ethyl Ester (X). A 29 g portion of p-tolylhydrazine hydrochloride (pH 3) was dissolved in warm water and adjusted to pH 3 by alkalinization with dilute KOH. Then 21 g of pyruvic acid ethyl ester was added to the reaction mass, the mixture was mixed for 1 h, and acetic acid was added. The precipitate formed was filtered and crystallized from isopropyl alcohol. Mp 83-84°C. IR spectrum (in chloroform): 3430 (NH), 1720 (C=O), 1687 (N=C), 1250 (C−O−C).

p-Nitrophenylhydrazone of Acetophenone (XIII). A 1 g portion of p-nitrophenylhydrazine was dissolved in 50 ml of warm water, 0.8 g of acetophenone dissolved in 50 ml of ethanol was added, and the mixture was mixed and heated for 30 min at 50°C. The precipitate formed was filtered and dried. Mp 164-165°C. IR spectrum (in DMSO): 3350 (NH), 1693 (N=C), 1550 (NO_2).

Diphenylhydrazone of Acetophenone (XIV). A 9 g portion of diphenylhydrazine hydrochloride and 4.5 g acetophenone were dissolved in isopropyl alcohol. The solution was boiled, then cooled and left in a refrigerator for 24 h (pH 3). The white precipitate formed was crystallized several times from isopropyl alcohol. T_m 96-97°C. IR spectrum (in chloroform): 1632 (N=C). UV spectrum (in acetonitrile): 254 (3.99), 405 (3.66).

p-Chlorophenylhydrazone of p-Nitroacetophenone with a Labeled (^{15}N) Imine Nitrogen Atom (XV). Diazotization of 5.08 g p-chloroaniline was performed in 30 ml of HCl under conditions of cooling, constant mixing, and addition of a mixture of 3.08 g NaN^*O_2, labeled with the stable isotope ^{15}N, in 25 ml of water. The diazo-compound obtained was reduced with 20 g of $SnCl_2 \cdot H_2O$ in 35 ml of HCl with constant mixing and cooling. To the reaction mass we added 3.8 g of p-nitroacetophenone in 50 ml of isopropyl alcohol (pH 3). The reaction was conducted at 40-50°C for 5 min with constant mixing. The reaction mixture was filtered, the precipitate washed with water, dried, and crystallized from isopropyl alcohol. Mp 85-86°C. IR spectrum (in DMSO): 3350 (NH), 1690 (N=C), 1540 (NO_2). Mass spectrum: 289 (M^+), 290 (M + 1), 291 (M + 2). Found, %: C 58.0, H 4.5, N 15.0. Gross formula $C_{14}H_{12}N_3O_2Cl$. Calculated, %: C 57.9, H 4.3, N 14.8.

Phenylhydrazone of p-Nitroacetophenone with Labeled (^{15}N) Imine Nitrogen Atom (XVI). To a mixture of 0.3 g of the p-chlorophenylhydrazone of p-nitroacetophenone with a ^{15}N-labeled imine nitrogen atom (XV) and 0.2 g of the phenylhydrazone of PAEE (VIII) we added 5 g of PPK. The reaction mixture was heated at 60°C for 5 min, and a threefold excess of water was added with mixing. The reaction products were extracted with ether. The ether was distilled off and the residue dried. The mixture obtained was separated by thin-layer chromatography in the system hexane−ether, 1:1. The cross phenylhydrazone XVI was isolated preparatively by elution of the corresponding spot. The eluent was ether. Yield 0.06 g (42%). Mp 265-267°C (with dec.). IR spectrum (in DMSO): 3350 (NH), 1685 (N=C), 1540 (NO_2). PMR spectrum: 2.63 (3H, s), 7.15-7.32 (aromatic protons, m), 7.86 (1H, d, $J_{aa'}$ = 8.0), 8.15 (1H, d, $J_{BB'}$ = 8.0), 8.04 (1H, d, J_{aB} = 10.0), 8.24 (1H, d, $J_{a',B'}$ = 10.0). Mass spectrum 255 (M^+), 256 (M + 1). Found, %: C 66.0, H 5.2, N 17.0. Gross formula: $C_{14}H_{13}N_3O_2$. Calculated, %: 65.9, H 5.1, N 16.8.

Phenylhydrazone of p-Nitroacetophenone with Labeled (^{15}N) Nitrogen Atoms (XVII). Nitration of 4.5 ml of benzene was performed with 5 ml of nitric acid, labeled with ^{15}N. To 5 g of the nitrobenzene obtained we added 5 g of hydrazine hydrate in 50 ml of isopropyl alcohol. The mixture was heated to 30-40°C, and an alcohol suspension of Raney nickel was added in small portions until the evolution of nitrogen ceased. The precipitate was dissolved in 15 ml of hydrochloric acid, cooled to −4°C, and 1.5 g NaN^*O_2 in 15 ml of water was added dropwise with constant mixing. The diazo-compound obtained was reduced to the phenylhydrazine with 10 g $SnCl_2 \cdot 2H_2O$ in 17.5 ml of HCl, and 6.6 g of p-nitroacetophenone in

alcohol (pH 3) was added. The phenylhydrazone of p-nitroacetophenone obtained, containing labeled nitrogen atoms (XXVII), was recrystallized from isopropyl alcohol. Mp 265-266°C, IR spectrum (in DMSO): 3350 (NH), 1685 (N=C), 1540 (NO_2). PMR spectrum: 2.63 (3H, s), 7.15-7.32 (aromatic protons, m), 7.86 (1H, d, $J_{aa'}$ = 8.0), 8.15 (1H, d, $J_{BB'}$ = 8.0), 8.04 (1H, d, J_{aB} = 10.0), 8.24 (1H, d, $J_{a',B'}$ = 10.0). Mass spectrum 255 (M^+), 257 (M + 2). Found, %: C 65.5, H 5.0, N 17.0. Gross formula: $C_{14}H_{13}N_3O_2$. Calculated, %: C 65.6, H 5.1, N 17.1.

p-Nitrophenylhydrazone of p-Bromoacetophenone (XVIII). A 1 g portion of p-nitrophenylhydrazine was dissolved in 50 ml of hot water, and 1.33 g of p-bromoacetophenone was dissolved in 50 ml of ethanol. The solutions were mixed and heated to 50°C for 30 min. The precipitate was filtered and dried. Mp 246-247°C. IR spectrum (in DMSO): 3350 (NH), 1692 (N=C), 1540 (NO_2).

p-Nitrophenylhydrazone of p-Nitroacetophenone with Labeled (^{15}N) Imine Nitrogen Atom (XIX). To a mixture of 0.65 g p-nitroacetophenone phenylhydrazone with labeled nitrogen atoms (XVII) and 0.85 g p-bromoacetophenone p-nitrophenylhydrazone (XVIII) we added 1.5 g of PPK and heated for 5 min at 90°C. A threefold excess of water was added to the reaction mixture with constant mixing. The product was extracted with ether, the ether distilled off, and the residue dried. The mixture obtained was separated by thin-layer chromatography in the system hexane–ether, 1:1. The cross phenylhydrazone XIX was isolated preparatively by elution of the corresponding spot; the eluent was ether. Yield 0.031 g (40%). Mp 284-285°C. IR spectrum (in DMSO): 3350 (NH), 1693 (N=C), 1540 (NO_2). PMR spectrum: 2.58 (3H, s), 8.06 (1H, d, J_{aB} = 10.0), 8.18 (1H, d, $J_{aa'}$ = 8.0), 8.30 (1H, d, $J_{a'B'}$ = 10.0), 8.32 (1H, d, $J_{B,B'}$ = 8.0). Mass spectrum: 300 (M^+), 301 (M + 1). Found, %: C 55.8, H 4.1, N 19.0. Gross formula: $C_{14}H_{12}N_4O_4$. Calculated, %: C 55.6, H 4.0, N 18.9.

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