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NEW VIEWS ON HYDRAZONE–ENEHYDRAZINE TAUTOMERISM

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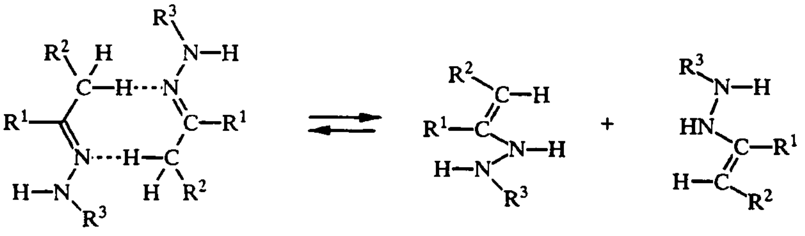
A new proton transfer mechanism is proposed for hydrazone–enehydrazine tautomerism through the cyclic dimer of the phenylhydrazones that take part in the E. Fischer indolization process. The energy, structural, and electronic indices of the proposed dimers were calculated by the AM1 quantum-chemical method. The calculated data were used to derive a new equation for the constant of the hydrazone–enehydrazine tautomeric equilibrium in terms of the orders of the breaking and forming bonds.

Hydrazone–enehydrazine tautomerism plays a special role in the chemistry of nitrogen-containing heterocyclic compounds. In particular, this process is considered to be the controlling stage in the E. Fischer indolization of arylhydrazones [1]. Although we do not share this opinion [2], there is no doubt about the importance of the hydrazone–enehydrazine tautomeric transformation for the planned synthesis of indole derivatives. The results from investigations devoted to this problem have mostly been qualitative in nature [3]. With the exception of a few isolated cases [4, 5] experimental difficulties and, in particular, the isolation and description of the enehydrazine tautomer have not made it possible to analyze the tautomeric process quantitatively. This is due either to the instability of the enehydrazine tautomers or to the inadequacy of the experimental technique.

In this connection it was extremely interesting to investigate theoretically the possibility of obtaining a quantitative description of the hydrazone–enehydrazine tautomeric transformation. As in the case of keto–enol tautomerism [6, 7], proton transfer in this process must take place by means of an inter- and intramolecular hydrogen bond. The mobility of the proton, as leaving particle, is actuated under the influence of the neighboring functional groups, temperature, catalyst, solvent, and the concentration of the solution [8]. In the absence of external promoting factors, however, the description of the mechanism of the tautomeric process requires a different approach. In this case it is tacitly assumed that the proton transfer results from a redistribution of electron



A B

I $R^1 = R^2 = H$, $R^3 = C_6H_5$; II $R^1 = CH_3$, $R^2 = H$, $R^3 = C_6H_5$; III $R^1 = C_2H_5$, $R^2 = H$, $R^3 = C_6H_5$; IV $R^1 = COOC_2H_5$, $R^2 = H$, $R^3 = C_6H_5$; V $R^1 = C_6H_5$, $R^2 = H$, $R^3 = C_6H_5$; VI $R^1 = p\text{-}CH_3C_6H_4$, $R^2 = H$, $R^3 = C_6H_5$; VII $R^1 = p\text{-}O_2NC_6H_4$, $R^2 = H$, $R^3 = C_6H_5$; VIII $R^1 = C_6H_5$, $R^2 = H$, $R^3 = p\text{-}CH_3C_6H_4$; IX $R^1 = C_6H_5$, $R^2 = H$, $R^3 = p\text{-}O_2NC_6H_4$; X R^1,R^2 = cyclo C_4H_8 (cyclohexanone residue), $R^3 = C_6H_5$

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density in the molecule. We suppose that the contribution from the electronic effects of the neighboring atoms and functional groups in the proton transfer process becomes effective if an additional condition is imposed. Such a condition may be the formation of a cyclic dimer by means of an intermolecular hydrogen bond between two molecules of the same compound. (See the scheme for the transformation of the phenylhydrazone dimer into the respective enehydrazine.)

The participation of the methyl hydrogen atoms in the formation of a hydrogen bond is not now subject to doubt [9]. We recently demonstrated by IR spectroscopy the existence of an intermolecular hydrogen bond in acetophenone [10]. In order to interpret the formation of the cyclic dimer of phenylhydrazine as transitional complex in the hydrazone–enehydrazine tautomeric transformation we calculated the energy, structural, and electronic indices of the phenylhydrazone derivatives dimers I-X by the semiempirical AM1 quantum-chemical method [11]. The advantages of the AM1 method among the various MO methods for the description of tautomeric equilibria was demonstrated recently in [12, 13].

The calculations were carried out in the reaction coordinate regime, where all the geometric parameters are optimized except for the C–H and N–H bonds participating in the formation of intermolecular hydrogen bonds. A scan was made from R_{CH} = 0.80 and R_{NH} = 1.90 Å to R_{CH} = 1.90 and R_{NH} = 0.80 Å at steps of 0.05 Å. Greatest attention was paid to calculation of the change in enthalpy (ΔH) and the orders of the breaking C–H and C=N bonds and forming N–H and C=C bonds (P_{CH}, P_{CN}, P_{NH}, and P_{CC}) during transfer of the proton by means of an intermolecular hydrogen bond.

Figure 1 shows the energy diagrams of the hydrazone–enehydrazine tautomeric transformation of the phenylhydrazones I-X – the dependence of the enthalpy (ΔH) on the reaction coordinate (R_{CH}). The first term for R_{CH} = 1.10 Å (R - 1.60 Å) relates to the hydrazone form (A), while the second term for R_{CH} = 1.70 Å (R = 1.00 Å) relates to the enehydrazine form. The transition state has the cyclic structure of the phenylhydrazone dimer (A). From this figure and also from Table 1 it is seen that acetaldehyde phenylhydrazone has the highest activation energy $\Delta\Delta H/^{\neq}$, while cyclohexanone phenylhydrazone X has the lowest. The heats of reaction ΔΔH vary directly with $\Delta\Delta H/^{\neq}$. This agrees fully with data on indolization, according to which the phenylhydrazone I cyclizes under very stringent conditions [14, 15], while the phenylhydrazone X cyclizes under mild conditions [16]. The activation barriers $\Delta\Delta H/^{\neq}$ of the hydrazones II-IX also adequately describe their capacity for indolization. Here it should be noted that the isoentropic approximation $\Delta\Delta G/^{\neq} \approx \Delta\Delta H/^{\neq}$ is sufficiently accurate for the tautomeric transformations [17].

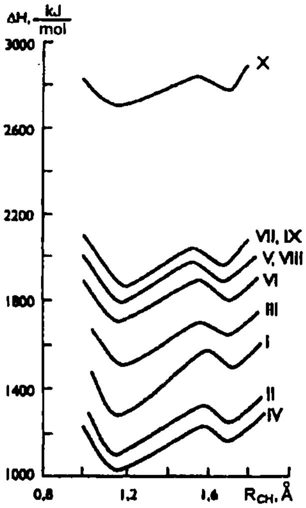

Fig. 1. The dependence of the enthalpy ΔH of the hydrazone–enehydrazine tautomeric transformation of the phenylhydrazones I-X on the reaction coordinate R_{CH}.

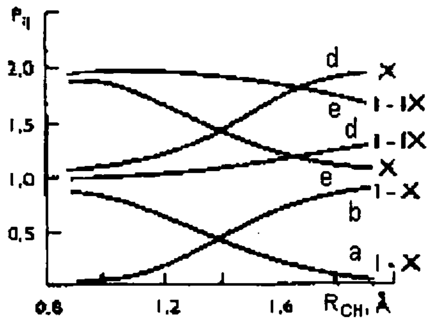

Fig. 2. The dependence of the bond orders P_{CH} (a), P_{NH} (b), P_{NC} (c), and P_{CC} (d) on the reaction coordinate R_{CH} of the tautomeric transformation of the phenylhydrazones I-X.

It is seen from Fig. 2 that in the tautomeric transformation through the cyclic dimer P_{CH} decreases to zero as the proton is transferred, i.e., the bond is broken, while $P_{N=C}$ decreases to P_{N-C}, i.e., the imine bond N=C is transformed into the N–C bond. At the same time P_{NH} increases from zero to 0.900, i.e., the optimum N–H bond is formed. The bond order P_{C-C} also increases to $P_{C=C}$. Thus, as a result of cleavage of the old (C–H and C=N) and the formation of the new (N–H and C=C) bonds the hydrazone form (A) changes completely into the enehydrazine form (B).

The orders of the bonds under discussion (P_{CH}, P_{NH}, and P_{CC}) must change adequately with change in the content of the hydrazone and enehydrazine forms. In the transition from the first term to the transition state the content of the hydrazone and enehydrazine forms can be described by the equation:

$$\frac{P^{\neq}{}_{CH}}{P^{1}{}_{CH}} H + \frac{P^{\neq}{}_{NH}}{P^{1}{}_{NH}} E = \frac{P^{\neq}{}_{CN}}{P^{1}{}_{CN}} H + \frac{P^{\neq}{}_{CC}}{P^{1}{}_{CC}} E , \qquad (1)$$

and in the transition from the transition state to the second term it is described by the equation:

$$\frac{P^{2}{}_{CH}}{P^{\neq}{}_{CH}} H + \frac{P^{2}{}_{NH}}{P^{\neq}{}_{NH}} E = \frac{P^{2}{}_{CN}}{P^{\neq}{}_{CN}} H + \frac{P^{2}{}_{CC}}{P^{\neq}{}_{CC}} E, \qquad (2)$$

where *H* and *E* are the hydrazone and enehydrazine forms respectively; $P^1{}_{CH}$, $P^1{}_{NH}$, $P^1{}_{CN}$, $P^1{}_{CC}$ and $P^2{}_{CH}$, $P^2{}_{NH}$, $P^2{}_{CN}$, $P^2{}_{CC}$ are the bond orders in the first and second terms respectively; $P^{\neq}{}_{CH}$, $P^{\neq}{}_{NH}$, $P^{\neq}{}_{CN}$, and $P^{\neq}{}_{CC}$ are the values of the bond orders in the transition state.

Dividing the sum of Eqs. (1) and (2) by *H* and taking account of the fact that *K* = *E/H*, we obtain an expression for the equilibrium constant of the hydrazone–enehydrazine tautomerism:

$$K_1 = \frac{P^1{}_{CC}P^{\neq}{}_{CC}P^1{}_{NH}P^{\neq}{}_{NH}[P^1{}_{CH}P^{\neq}{}_{CH}(P^{\neq 2}{}_{CN} + P^1{}_{CN}P^2{}_{CN}) - P^1{}_{CN}P^{\neq}{}_{CN}(P^{\neq 2}{}_{CH} + P^1{}_{CH}P^2{}_{CH})]}{P^1{}_{CH}P^{\neq}{}_{CH}P^1{}_{CN}P^{\neq}{}_{CN}[P^1{}_{CC}P^{\neq}{}_{CC}(P^{\neq 2}{}_{NH} + P^1{}_{NH}P^2{}_{NH}) - P^1{}_{NH}P^{\neq}{}_{NH}(P^{\neq 2}{}_{CC} + P^1{}_{CC}P^2{}_{CC})]}, \qquad (3)$$

Equation (3) describes the equilibrium constant of the hydrazone–enehydrazine tautomeric equilibrium taking into account the energy barrier of the proton transfer process. In the case of proton tunnelling it is possible to construct analogous relationships for the terms in place of Eqs. (1) and (2), and as a result of adequate algebraic transformations the equilibrium constant for the tunnel transfer of the proton is obtained:

$$K_2 = \frac{P^1{}_{NH}P^1{}_{CC}(P^2{}_{CN}P^1{}_{CH} - P^2{}_{CH}P^1{}_{CN})}{P^1{}_{CH}P^1{}_{CH}(P^2{}_{NH}P^1{}_{CC} - P^2{}_{CC}P^1{}_{NH})} . \qquad (4)$$

TABLE 1. The Constants of the Hydrazone–Enehydrazine Tautomeric Equilibrium in the Phenylhydrazones I-X (K_1 and K_2), the Energy Barrier ($\Delta\Delta H^{\neq}$), and the Heats of Reaction ($\Delta\Delta H$, kJ/mol)

Compound	R^1	R^2	R^3	K_1	K_2	$\Delta\Delta H^{\neq}$	$\Delta\Delta H$
I	H	H	C_6H_5	0.14	0.05	185.2	171.3
II	CH_3	H	C_6H_5	0.11	0.04	150.0	130.4
III	C_2H_5	H	C_6H_5	0.13	0.04	124.1	92.0
IV	$COOC_2H_5$	H	C_6H_5	0.15	0.05	145.5	128.4
V	C_6H_5	H	C_6H_5	0.12	0.05	134.2	98.2
VI	p-$CH_3C_6H_4$	H	C_6H_5	0.13	0.05	133.3	97.0
VII	p-$O_2NC_6H_4$	H	C_6H_5	0.11	0.05	140.0	107.8
VIII	C_6H_5	H	p-$CH_3C_6H_4$	0.12	0.04	133.8	98.0
IX	C_6H_5	H	p-$O_2NC_6H_4$	0.12	0.05	134.8	98.0
X	C_4H_8		C_6H_5	0.35	0.09	83.2	46.0

The calculated equilibrium constants (*K*) and also the activation energies ($\Delta\Delta H^{\neq}$) and heats of reaction ($\Delta\Delta H$) are given in Table 1. From this it is seen that the equilibrium constant of cyclohexanone phenylhydrazone X is 2-3 times larger than for the other phenylhydrazones, which have almost identical *K* values. In addition, it is seen from Fig. 2 that the phenylhydrazone is converted more completely into the enehydrazine form, i.e., the N=C and C–C bonds are converted completely into N–C and C=C bonds. For other phenylhydrazones this transformation is not complete. This fact confirms the published data cited above on the indolization of the phenylhydrazone (X) with high yields under mild conditions [16].

It is seen from Table 1 that electron-accepting (NO_2) and electron-donating (CH_3) substituents at the *para* position of the benzene ring in the hydrazine and carbonyl fragments of VI-IX have a very weak effect on the values of *K* and $\Delta\Delta H$, whereas their effect on the kinetics and energy of indolization is substantial [2]. This shows once again that the hydrazone–enehydrazine tautomeric transformation is not the controlling stage in the Fischer indolization of arylhydrazones.

In conclusion we mention that the proposed equations for the constants of the hydrazone–enehydrazine tautomeric equilibrium, which were derived for the isolated molecule, can also be applied to the calculation of condensed media.

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REFERENCES

1. N. M. Przheval'skii, M. E. Kletskii, I. I. Grandberg, and L. Yu. Kostromina, *Khim. Geterotsikl. Soedin.*, No. 6, 779 (1985).
2. Dzh. A. Kereselidze, Sh. A. Samsoniya, and M. A. Tsikoliya, *Khim. Geterotsikl. Soedin.*, No. 8, 1092 (1995).
3. S. I. Yakimovich and K. N. Zelenin, *Zh. Obshch. Khim.*, **65**, 705 (1995).
4. N. N. Suvorov, N. P. Sorokina, and Yu. N. Sheinker, *Zh. Obshch. Khim.*, **28**, 1090 (1959).
5. H. Ahlbrecht and M. Th. Heib, *Tetrahedron Lett.*, **12**, 549 (1971).
6. M. L. Huggins, *Angew. Chem.*, **83**, 155 (1971).
7. L. M. Epshtein, *Usp. Khim.*, **48**, No. 9, 1600 (1979).
8. A. I. Kol'tsov and G. M. Kheifets, *Usp.Khim.*, **40**, 1646 (1971).
9. V. M. Bilborov, *The Hydrogen Bond* [in Russian], Naukova Dumka, Kiev (1991).
10. Dzh. A. Kereselidze, *Zh. Fiz. Khim.*, **72**, 144 (1998).
11. J. S. Dewar, E. G. Zoebisch, E. F. Healy, and J. J. P. Stewart, *J. Am. Chem. Soc.*, **107**, 3902 (1985).

12. I. F. Tupitsyn, A. S. Popov, and A. Yu. Shibaev, *Zh. Obshch. Khim.*, **63**, 2350 (1993).
13. U. Maron, M. Karelson, and A. R. Katritzky, *Int. J. Quant. Chem.*, **60**, 41 (1996).
14. G. I. Zhungietu, V. A. Budylin and A. N. Kost, *Preparative Chemistry of Indole* [in Russian], Shtiinitsa, Kishinev (1975), p. 32.
15. Yu. A. Kitaev and T. V. Troepol'skaya, *Khim. Geterotsikl. Soedin.*, No. 8, 1011 (1978).
16. N. N. Suvorov, V. P. Mamaev, and V. M. Rodionov, *Reactions and Methods of Investigation of Organic Compounds* [in Russian], Book 9, Goskhimizdat, Moscow-Leningrad (1959), p. 7.
17. V. A. Pichko and B. Ya. Simkin, *Izv. Sev.-Kavk. Nauch. Tsentra Vysshei Shkoly. Est. Nauki*, **2**, 107 (1989).