RESEARCH IN THE CHEMISTRY OF PYRAZOLIDINE

XX.* EFFECT OF THE STRUCTURE OF 3,5-DIOXOPYRAZOLIDINES ON THE RATE OF HYDROGENATION OF THE N–N BOND IN THE PRESENCE OF RANEY NICKEL

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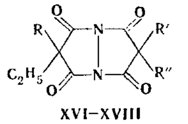
The rate of hydrogenolysis of 3,5-dioxopyrazolidines at the N–N bond is determined by the number, position, and nature of the substituents in the heteroring. The introduction of a phenyl group into the 1 and 2 positions increases the rate of hydrogenation, while a phenyl group in the 4 position lowers it. On the other hand, an alkyl substituent in the 1 and 2 positions lowers the rate of hydrogenation, while an alkyl substituent in the 4 position increases it. It is assumed that the effect of substituents is a consequence of an increase or decrease in the adsorption of a molecule by the β-dicarbonyl or hydrazine fragments; this is in agreement with the results of calculation of the charges on the heteroring atoms. The hydrogenation of 4-alkyl-1,2-diphenyl-3,5-dioxopyrazolidines is limited by their activation, while the hydrogenation of the 4-phenyl derivative is limited by the activation of hydrogen.

The hydrogenation of various compounds that contain a N–N bond in the presence of Raney nickel is used quite widely, but the dependence between the structure of these compounds and the rate of their hydrogenolysis has not been adequately studied. It is difficult to make any correlation on the basis of the available literature data, since various authors have carried out the process under incomparable conditions and have not studied the interaction of the substance undergoing hydrogenation with the catalyst surface.

The present communication is a continuation of previous investigations [2] and is devoted to a study of the effect of the structure of 3,5-dioxopyrazolidines (3,5-DOP) on the rate of hydrogenolysis of the N–N bond in the presence of a Raney nickel catalyst. A potentiometric method [3], which makes it possible to measure the catalyst potential directly during hydrogenation, was used in this study. The selection of the standard reaction conditions was made on the basis of a study of the effect of various factors on the rate of hydrogenation of 1,2-diphenyl-4-butyl-3,5-DOP (butadione). The starting materials (Table 1) were 3,5-DOP that are capable of keto–enol (I-VIII), lactim–lactam (IX-XI), and (simultaneously) keto–enol and lactim–lactam tautomerization (XII-XIV) and 3,7-di- (XVI), 3,3,7-tri- (XVII), and 3,3,7,7-tetra-substituted (XVIII) 2,4,6,8-tetraoxo-1,5-diazabicyclo[3.3.0]octane [4].



XVI–XVIII

XVI $R = R'' = H$, $R' = C_2H_5$;
XVII $R = C_2H_5$, $R' = H$, $R'' = i\text{-}C_3H_7$
XVIII $R = R' = C_2H_5$, $R'' = i\text{-}C_5H_{11}$

The experimental data (Table 1) provide evidence that the number, position, and nature of the substituents in the ring affect the rate of hydrogenation of 3,5-DOP at the N–N bond. In this case, the rate of hydrogenation of 1,2-diphenyl-substituted I-VI, which are capable of keto–enol tautomerization, decreases in

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* See [1] for communication XIX.

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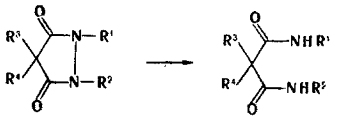
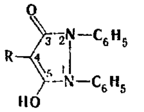
TABLE 1. Effect of Substituents on the Shift in the Catalyst Potential (ΔE) and Reaction Rate (W) in the Hydrogenation of 3,5-DOP



I-XIV XV

Compound	R^1	R^2	R^3	R^4	Exptl. temp., °C	ΔE, mV	W, ml/min, (half consump. of H_2)
I[5]	C_6H_5	C_6H_5	H	H	30	215	2,4
II[6]	C_6H_5	C_6H_5	CH_3	H	30	230	6,7
III[7]	C_6H_5	C_6H_5	C_4H_9	H	30	210	4,2
IV[6]	C_6H_5	C_6H_5	i-C_5H_{11}	H	30	220	4,7
V[8]	C_6H_5	C_6H_5	$C_6H_5CH_2$	H	30	190	0,5
VI[9]	C_6H_5	C_6H_5	C_6H_5	H	30	320	1,7
VII	CH_3	CH_3	$C_6H_5CH_2$	H	30	125	0
VIII[10]	$C_4H_4SO_2NH_2$-p	$C_4H_4SO_2NH_2$-p	C_4H_9	H	30	225	0
IX[5]	H	H	C_2H_5	C_2H_5	50	90	0
X[11]	H	H	C_6H_5	C_2H_5	50	150	0
XI[5]	C_6H_5	H	C_2H_5	C_2H_5	50	125	0,5
XII[12]	C_6H_5	H	H	H	30	155	2,0
XIII[13]	C_6H_5	H	C_6H_5	H	50	225	0,6
XIV[14]	H	H	i-C_5H_{11}	H	30	145	0

TABLE 2. Effect of Substituents in the 4 Position on the Electronic Charges on the Atoms of the Heteroring of 1,2-Diphenyl-3,5-DOP



Compound	R	N_1	N_2	C_3	C_4	C_5	W, ml/min, for half consump. of H_2
II	CH_3	+0,261	+0,273	+0,219	−0,155	+0,128	6,7
I	H	+0,264	+0,273	+0,234	−0,192	+0,170	2,4
VI	C_6H_5	+0,270	+0,274	+0,240	−0,169	+0,181	1,7

the following order, as a function of the character of the substituents in the 4 position of the heteroring: $CH_3 >$ iso-$C_5H_{11} > C_4H_9 > H > C_6H_5 > C_6H_5CH_2$. This order is retained at 20-40°. Compounds I-IV, which are homologs, induce a shift of 190-230 mV in the catalyst potential (ΔE) in the anode direction and are hydrogenated at slightly variable steady-state potentials of the catalyst, which is shifted in the cathode direction by 50-60 mV only at the end of the hydrogenation without reaching the saturation potential (Fig. 1). The potential curve of V has the same character. In contrast to I-V, VI causes a considerably greater shift in the catalyst potential (320 mV), and at the end of the hydrogenation its value does not reach that of the starting potential by 200 mV; this attests to considerable adsorption of the hydrogenation products.

Some differences in the ΔE values are observed in series I-V, and the greatest difference in the ΔE values in II and V (230 and 190 mV, respectively) is also accompanied by the greatest difference in the rate of hydrogenation (6.7 and 0.5 ml/min, respectively).

The reason for the different adsorbability of I-VI on the catalyst surface may be the electronic effect of the substituent in the 4 position and steric factors.

It is known that the surface of Raney nickel is negatively charged[15], and a molecule of substance undergoing hydrogenation should therefore be adsorbed at the expense of atoms with a reduced electron density. The nitrogen and carbon atoms in the 1, 2, 3, and 5 positions of the heteroring are atoms of this sort in the 3,5-DOP molecule. Proceeding from this, it can be assumed that alkyl substituents in the 4 position by reducing δ^+ on C_3 and C_5 promote a decrease in adsorption due to the β-dicarbonyl portion of the molecule. The latter should lead to an increase in the rate of hydrogenolysis as compared with 4-unsubstituted 3,5-DOP (I) or 3,5-DOP with an electron-acceptor substituent in the 4 position (VI). Similarly, a phenyl substituent in the 4 position, by increasing δ^+ on C_3 and C_5, promotes intensification of adsorption due to

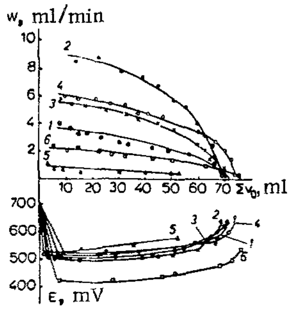


Fig. 1

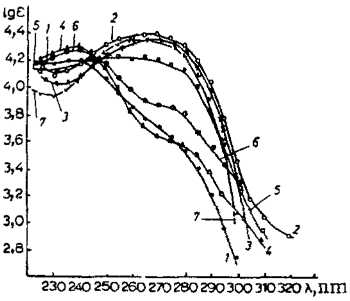


Fig. 2

Fig. 1. Kinetic and potential curves of the hydrogenation of I-VI in 100 ml of 96% ethanol at 30°C: 1) I; 2) II; 3) III; 4) IV; 5) V; 6) VI.

Fig. 2. UV spectra of III: 1) in 0.1 N HCl in 96% ethanol; 2) in 96% ethanol; 3) in 0.001 N KOH in 96% ethanol; 4) in heptane; 5) in heptane–absolute ethanol (10 : 1); 6) in heptane–absolute ethanol (1 : 1); 7) in absolute ethanol.

the β-dicarbonyl portion of the molecule; this should lead to a decrease in the rate of hydrogenation as compared with 4-unsubstituted (I) or 4-alkyl-substituted (II-IV) compounds. These assumptions are in good agreement with the experimental data.

In order to make a theoretical verification of the assumption regarding the electronic effect of substituents, we calculated molecules of I, II, and VI with the Hückel π-electron approximation. The calculation was made for the keto–enol form, since, according to the UV-spectroscopic data (Fig. 2), I-VI in ethanol exist in the keto–enol form, stabilized by interaction with the solvent and apparently partially ionized.

As seen from the data presented in Table 2, while the charges on the atoms of N–N groups in I, II, and VI are almost identical, the electron deficit on C_3 and C_5 increases in the series II, I, and VI; a decrease in the rate of hydrogenolysis in this same order is also observed.

From the point of view of steric hindrance, alkyl substituents in the 4 position should hinder adsorption of a molecule due to a decrease in the interaction with the catalyst surface of both the β-dicarbonyl and (to a lesser degree) hydrazine fragments. Moreover, a methyl substituent in the 4 position should interfere with adsorption due to the hydrazine fragment of the molecule to a lesser extent than benzyl, butyl, and isoamyl substituents. This may also explain the greater rate of hydrogenation of II as compared with III-V. The relatively low rate of hydrogenation of I is explained by intensification of adsorption due to the β-dicarbonyl fragment, which is promoted by the absence of a substituent in the 4 position. The considerably higher (than in other 3,5-DOP) adsorption of VI is favored not only by the electron-acceptor character of the phenyl group in the 4 position but also by its coplanarity with the plane of the heteroring; this is clearly seen on examination of a molecular model of this compound.

Replacement of phenyl groups in the 1 and 2 position by alkyl groups should, by reducing δ^+ on the nitrogen atoms, decrease the interaction of them with the catalyst surface and lead to a decrease in the rate of hydrogenation. In fact, 4-benzyl-1,2-dimethyl-3,5-DOP (VII), in contrast to V, causes a shift in the catalyst potential by only 110 mV and is not hydrogenated at 30° (Table 1). Hydrogenolysis occurs only when an ethanol solution of VII is refluxed with excess catalyst. At the same time, introduction of strong electron acceptors – sulfamide groups – into the phenyl radicals of III causes an intensification of adsorption ($\Delta E = 255$ mV), which leads to hindrance of the hydrogenation.

4,4-Disubstituted (IX, X) and 1,4,4-trisubstituted 3,5-DOP (XI), which are capable of lactim–lactam tautomerization (Table 1), exist in the dicarbonyl form in ethanol solution, judging from the spectral data [16]. Compounds IX and X, which do not contain substituents in the 1 and 2 positions, are not hydrogenated at 20-50°, and hydrogenolysis of the N–N bond was observed only when ethanol solutions of these compounds were refluxed in the presence of catalyst. Introduction of a phenyl group into the 1 position of IX promotes the reaction: at 50°, XI is hydrogenated, although at a very low rate. The decrease in the rate of hydrogenation associated with the decrease in the adsorption of these compounds as compared with I and VI is apparently due to steric hindrance created by the two substituents in the 4 position and also by a reduction in δ^+ on the nitrogen atom because of the absence of phenyl groups.

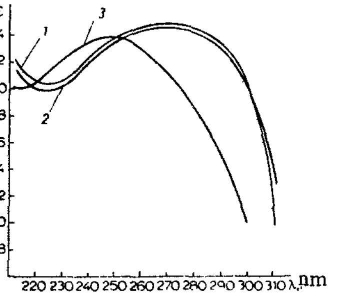


Fig. 3

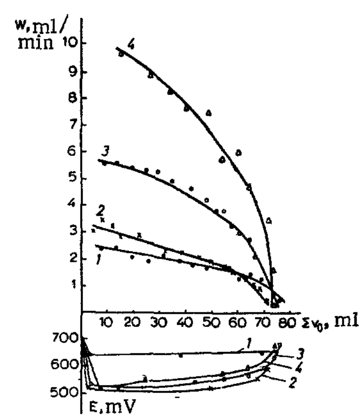


Fig. 4

Fig. 3. UV spectra of XIII: 1) in 96% ethanol; 2) in 0.001 N KOH solution in 96% ethanol; 3) in 0.1 N HCl in 96% ethanol.

Fig. 4. Kinetic and potential curves of hydrogenation of 3.25 mmole of III at 30°C in the presence of 4 g of Raney nickel in 100 ml of solvent: 1) in benzene–absolute ethanol (3 : 1); 2) in absolute ethanol; 3) in 96% ethanol; 4) in 80% ethanol.

Compounds XII-XIV, which are simultaneously capable of keto–enol and lactim–lactam tautomerization, exist in the keto–enol form in ethanol solution, according to the spectral data (Fig. 3). 1-Phenyl-3,5-DOP (XII) is hydrogenated at the highest rate: ~2 ml/min (Table 1). Replacement of the hydrogen in the 4 position by a phenyl group increases adsorption and sharply retards the reaction rate: XIII is hydrogenated only at 50° at a rate of ~0.6 ml/min, and ΔE in this case increases from 155 to 225 mV.

Thus the introduction of a phenyl group into the 4 position of XII leads to an intensification of the adsorbability and a decrease in the rate of hydrogenation, just as in the case of the introduction of a phenyl group into the 4 position of I.

Since steric hindrance to approach of the β-dicarbonyl fragment in XIV to the catalyst surface is less than in IX, the ΔE value of this compound is also higher (145 and 90 mV, respectively). However, the increase in the adsorption by the β-dicarbonyl fragment does not promote an increase in the rate of hydrogenolysis. The considerable increase in the rate of hydrogenation and the ΔE value on passing from 1,4,4-trisubstituted 3,5-DOP (XI) to 1-monosubstituted compound XII is evidence that two substituents in the 4 position hinder adsorption of the molecule. The change in the rate of hydrogenation as a function of the number, position, and character of the substituents is associated with the change in the limiting step under the conditions used for the hydrogenation. In ascertaining the effect of the reaction conditions on the rate of hydrogenolysis of the N–N bond of butadione by carrying out experiments with different amounts of the latter, it was found that the reaction rate and the ΔE value increase with increasing concentration of substance undergoing hydrogenation. An investigation of the effect of the solvent made it possible to establish that the rate of hydrogenolysis increases with decreasing solubility of the substance undergoing hydrogenation* in the order: DMF < benzene–absolute ethanol (3 : 1) < absolute ethanol < 96% ethanol < 80% ethanol (Fig. 4). In DMF, in which the solubility is greatest, hydrogenation does not proceed at all at 30°. The increase in the reaction rate in aqueous ethanol cannot be explained by an increase in the hydrogen concentration on the catalyst surface, since the solubility of hydrogen in water is less than in ethanol [17]. In all cases involving an increase in the rate of hydrogenation, the change in the coefficient of partition of butadione between the solvent and catalyst in favor of the latter – the so-called "salting-out" effect of the solvent [17] – apparently plays the decisive role. The reaction rate increases as the temperature rises, while the shift in the catalyst potential decreases.

The increase in the reaction rate as the concentration of the substance undergoing hydrogenation increases and its solubility decreases and the decrease in ΔE as the butadione concentration decreases make it possible to suppose that the limiting step in the hydrogenation of butadione and its homologs under the given conditions is activation of the substance undergoing hydrogenation. On the other hand, since a ΔE

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* The solubilities of III in grams per 100 ml of solvent are as follows: DMF 80.0, benzene 50.0, absolute ethanol 3.92, 70% ethanol 0.85, water 0.02.

value of 320 mV is characteristic for VI, in this case hydrogenation is apparently limited by activation of hydrogen rather than by activation of the compound undergoing hydrogenation, since, according to the data in [17], the Raney nickel surface is devoid of hydrogen when ΔE is 300 mV.

Hydrogenolysis of the N—N bond of XVI-XVIII was not observed under the conditions of the hydrogenation of 3,5-DOP. The difference in the ΔE values induced by these compounds is extremely significant. While tetra-substituted XVIII shifts the catalyst potential by only 40 mV, which indicates very weak adsorption of the substance because of steric hindrance, XVI and XVII, which are capable of keto—enol tautomerization, shift the catalyst potential by 330-335 mV, i.e., they are adsorbed very strongly, displacing all of the hydrogen from the catalyst surface. This is apparently a consequence of the considerable increase in the electron deficit on the nitrogen atom created by the second malonyl residue.

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EXPERIMENTAL

The hydrogenation was accomplished in a thermostated flask equipped with a stirrer and an adapter with a platinum electrode and a comparison electrode (a saturated calomel electrode), an adapter with a funnel for introduction of substances, and a device for selection of catalyzate samples during the reaction. The catalyst potential was measured with respect to a compensated scheme relative to the comparison electrode. The Raney nickel was prepared under standard conditions [18] immediately prior to each experiment. The conditions for hydrogenation of III, under which dissolving of hydrogen and diffusion of the reaction components do not limit the process, were determined by a change in the amount of catalyst and stirring rate, and all of the experiments were subsequently carried out with 3.25 mmole of substance to be hydrogenated and 4 g of catalyst in 100 ml of 96% ethanol at a stirring rate of 300 rpm at 20 to 50°. The hydrogen-consumption curve coincided with the curve of the decrease in butadione concentration in the catalyzate (determined spectrophotometrically), in connection with which the rate of hydrogenation in other cases was determined from the hydrogen consumption. The reproducibility of the kinetic curve was estimated by statistical treatment (the probable relative error was ±8.8%). The catalyzate composition was established by means of thin-layer chromatography (TLC), and the reaction products (in all cases, the corresponding amides of malonic acid, obtained in 80-90% yields) after isolation were identified on the basis of elementary analysis, UV and IR spectroscopy, and comparison with authentic substances.

The conditions for chromatography on activity-II aluminum oxide were as follows (starting compound, solvent system, $R_f \cdot 100$ of the starting substance; $R_f \cdot 100$ of the hydrogenation product, and reference to its preparation): II,* ethanol—chloroform (1 : 2), 62, 83 [20]; IV, benzene—chloroform (3 : 1), 12, 42 [21]; XI,* benzene—chloroform (5 : 1), 6, 19 [22]; XII, ethanol—25% ammonia (15 : 2), 16, 77 [23]; XIII,* ethanol—chloroform (1 : 2), 15, 90. The conditions for chromatography of I, III, V, VI, and their hydrogenation products were described in [2].

1,2-Dimethyl-4-benzyl-3,5-dioxopyrazolidine (VII). A 0.761-g (3.25 mmole) sample of 1,2-dimethyl-4-benzylidene-3,5-DOP [19] was hydrogenated in the presence of 4 g of Raney nickel in 100 ml of 96% ethanol at 30° for 30 min. The catalyst was separated, and the alcohol was removed by distillation to give a liquid residue, which began to crystallize on standing in air to give 0.4 g (53%) of a product with mp 59-63° (softens at 55°). The product was quite soluble in organic solvents. IR spectrum, ν, cm^{-1}: 1742, 1700, 1611, 1586, 1332, 1270, and 1212. UV spectrum: λ_{max} 258 nm, log ε 4.04. Found: N 12.8%. $C_{12}H_{14}N_2O_2$. Calculated: N 13.2%.

Benzylmalonic Acid N,N'-Dimethylamide (XV, $R^1 = R^2 = CH_3$, $R^3 = H$, $R^4 = C_6H_5CH_2$). A mixture of 0.3 g (1.3 mmole) of VII and 3 g of Raney nickel in 30 ml of 96% ethanol was refluxed for 5 h. The catalyst was removed by filtration, and the alcohol was removed by distillation to give 0.2 g (67%) of a substance with mp 183-184° (from ethanol). IR spectrum, ν, cm^{-1}: 1687, 1658, 1600, 1550, 1500, 1325, and 1280. UV spectrum: λ_{max} 245 nm, log ε 4.11. Found: N 12.2%. $C_{12}H_{16}N_2O_2$. Calculated: N 12.8%.

Phenylmalonic Acid Anilide (XV, $R^2 = R^3 = C_6H_5$, $R^1 = R^4 = H$). A mixture of 0.25 g (1 mmole) of XIII and 4 g of Raney nickel in 50 ml of 96% ethanol was refluxed for 1.5 h. The catalyst was removed by filtration, and the alcohol was partially removed by distillation to give 0.23 g (92%) of a crystalline precipitate with mp 184-185°. IR spectrum, ν, cm^{-1}: 1673, 1555, 1496, 1416, 1350, 1307, 1260. UV spectrum, λ_{max}, nm (log ε): 260 (2.26), 290 (1.47). Found: N 11.2%. $C_{15}H_{14}N_2O_2$. Calculated: N 11.0%.

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* Activity-II aluminum oxide containing 2% CH_3COOH was used.

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