SYNTHESIS OF HETEROCYCLIC COMPOUNDS IN THE LIQUID PHASE AT HIGH PRESSURES (REVIEW)

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At the present time high pressures are widely used in organic chemistry both to determine the mechanisms of reactions and to realize processes which hardly occur at all at atmospheric pressure.

The dependence of the equilibrium constant K on the pressure is given by the thermodynamic equation

$$\left(\frac{\partial \ln K}{\partial P}\right)_T = -\frac{\Delta V}{RT}, \tag{1}$$

where ΔV is the change in volume during the reaction; R, the gas constant; and T, absolute temperature. The concentrations of the substances are expressed in mole fractions.

An analogous (quasithermodynamic) formula was derived [1] on the basis of the theory of the transition state (activated complex) for the variation in the reaction rate constant k:

$$\left(\frac{\partial \ln k}{\partial P}\right)_T = -\frac{\Delta V^{\neq}}{RT}, \tag{2}$$

where $\Delta V^{\neq}$ is the change in volume during the formation of 1 mole of the activated complex from the reactants (the volume effect of activation); the concentrations of the substances are expressed in molarities or mole fractions [2]. From Eq. (2) it follows that $\Delta V^{\neq}$ represents a fundamental quantity, the sign of which determines the direction of the kinetic effect of pressure ($\Delta V^{\neq} < 0$ corresponds to acceleration of the reaction; $\Delta V^{\neq} > 0$ corresponds to retardation), and its absolute value determines the degree of the effect of pressure.

A simple and as yet the soundest formula (3) was proposed [3, 4] for calculation of the volume effects of activation at atmospheric pressure and also for other calculations connected with the use of high pressures:

$$\lg \frac{(K)_P}{(K)_1} = -\frac{(\Delta V)_1 P}{(1+bP)RT \ln 10}, \tag{3}$$

where $(K)_P$ and $(K)_1$ are the equilibrium or rate constants (in molar units) measured at pressure P and at atmospheric pressure; $(\Delta V)_1$, change in volume (cm^3/mole) during the reaction or during the formation of the transition state at atmospheric pressure; in various units of pressure* b amounts to $9.32 \cdot 10^{-5}$ (atm, R = 82.06), $9.20 \cdot 10^{-5}$ (bar, R = 83.15), $9.02 \cdot 10^{-5}$ (kgf/cm^2, R = 84.80). In many cases Eq. (3) is suitable for quantitative calculations and is always extremely useful for assessing the possibility of synthesis at high pressures. Such assessment is sometimes facilitated further by the fact that the $\Delta V^{\neq}$ value for certain reactions (e.g., the Diels–Alder reaction) can be taken as equal to the change in volume during the reaction.

As seen from Eq. (3), log $(K)_P$ depends linearly on P/(1 + bP), so that Eq. (3) makes it possible, first, to determine the rate (equilibrium) constant from known values of the rate (or equilibrium) constant and volume effect of activation (or reaction) at atmospheric pressure; second, it makes it possible to determine the volume effect of activation (or reaction) and the rate (or equilibrium) constants at atmospheric pressure from the known values (not less than 2) of the rate (or equilibrium) constants at high pressures.

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*1 atm = 1.013 bar = 1.033 kgf/cm^2; subsequently, for uniformity, the pressure is expressed in kilobars (1 kbar = 1000 bar) or in bars without the corresponding conversions.

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Electrostriction effects are usually observed during the formation of a polar transition state. It is therefore customary to divide the experimentally determined $\Delta V^{\neq}$ value into two components $\Delta V^{\neq} = \Delta V^{\neq}_{i} + \Delta V^{\neq}_{s}$, where $\Delta V^{\neq}_{i}$ is the internal or structural and $\Delta V^{\neq}_{s}$ is the solvation component. The former represents the change in volume due to change in the arrangement of the atomic nuclei of the reacting particles in the transition state. The second component differs from zero in the case where there is a difference between the interactions of the transition state and initial particles with the solvent molecules. During the formation of a highly polar transition state from relatively nonpolar initial substances the nature of the solvent has a significant effect on the value of $\Delta V^{\neq}$ (e.g., see [5, 6]).

If $\Delta V^{\neq}_{s}$ is insignificant, $\Delta V^{\neq} = \Delta V^{\neq}_{i}$. For many chemical reactions $\Delta V^{\neq}_{i} < 0$, since they are bimolecular, and during the formation of the transition state the reacting particles approach to distances less than the sum of their van der Waals radii. Thus, acceleration of the reactions is the most often observed chemical effect of high pressure.* In principle, however, the magnitude of acceleration depends on the type of the reaction and, consequently, on the mechanism by which it occurs. For example [7], chloroprene dimerized to form mainly derivatives of cyclobutane and cyclohexene. The former are obtained as a result of 1,2-cycloaddition, occurring by a biradical mechanism with the formation of one C—C bond in the determining stage; the $\Delta V^{\neq}$ value for this reaction amounts to about -22 cm³/mole. The cyclohexene derivatives are obtained through a six-membered cyclic transition state (1,4-cycloaddition). For this reaction $\Delta V^{\neq} \approx -30$ cm³/mole, and the ratio of the cyclohexene derivatives to cyclobutane derivatives therefore increases appreciably with increase in pressure.

In researches devoted to the mechanism of Diels—Alder reactions on the basis of accurate kinetic measurements at high pressures it was shown that the above-mentioned reactions are characterized by large negative $\Delta V^{\neq}$ values between -30 and -45 cm³/mole [8].

In general, for many bimolecular reactions in the liquid phase $\Delta V^{\neq}$ is between -20 and -40 cm³/mole [9]. On the basis of this range of $\Delta V^{\neq}$ values and using a formula of type (3), El'yanov and Gonikberg [9] showed that the "synthetic effect" in reactions which hardly occurs at all at 1 bar can be achieved at pressures of 5-15 kbar.

The above-mentioned range of variation in $\Delta V^{\neq}$ applies to simple bimolecular reactions (although reactions with lower absolute $\Delta V^{\neq}$ values are frequently encountered), but organic reactions are often extremely complex, and the expressions for the rates of formation of the final products include not one but several rate and equilibrium constants, which are related to each other in various ways, depending on the mechanism. The overall volume effect of activation ($\Delta V^{\neq}_{c}$) is therefore determined from the dependence of the logarithm of the process rate on pressure. This also provides a valuable criterion for establishing the mechanisms of reactions or for predicting the effects of pressure on the basis of already known reaction schemes.

Papers published in the last 10 years illustrating the possibility of using high pressures in the synthesis of heterocyclic compounds are gathered below.

The theoretical and synthetic aspects of the use of high pressures in chemistry have been treated in a series of monographs and reviews [10-15].

DIELS—ALDER REACTION

The Diels—Alder reaction is sometimes reversible, and at normal pressure the equilibrium can be shifted largely toward the initial compound.

The heterodiene condensation of 1-methoxy- and 1-ethoxybutadiene with carbonyl compounds gives Δ^{3}-dihydropyrans (I) with yields of 40-90% in most cases (14 kbar, 80°C, 15 h) [16]. At atmospheric pressure (80°C, 5-6 h) the adducts were not detected; at 160-180°C aldehydes either do not react at all or form low yields of the adducts. The large effect of pressure in the investigated process is due to the considerable increase in the reaction rate constant and not to displacement of the equilibrium. For diene synthesis on the average $\Delta V^{\neq} = -33$ cm³/mole, and according to Eq. (3) and to the experimental results the reaction rate constant increases by almost 1000 times at 14 kbar.

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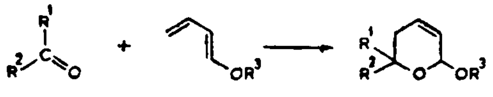
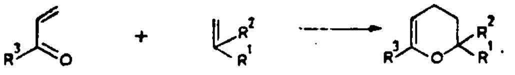
*Reactions normally retarded by pressure include monomolecular nonionic reactions involved in the decomposition of organic compounds.



I

At high pressures a mixture of the cis and trans isomers is usually obtained (except in the case of isobutyraldehyde and 2,3-isopropylidene-D-glyceraldehyde), and both aliphatic and aromatic aldehydes form the cis isomers preferentially. For aromatic aldehydes such a result is consistent with Alder's rule of maximum accumulation of unsaturation, while for aliphatic aldehydes it was unexpected. The preferential endo orientation of the diene and the dienophile in the transition state was explained by the presence of interaction between the partially protonated α-carbon atom of the aldehyde and the π system of the diene [17].

A comparative study was also made of the formation of Δ^2-dihydropyrans (II) from acrolein and unsaturated compounds (propylene, 1-hexene, methyl acrylate, methyl methacrylate, styrene, and vinyl acetate) at atmospheric and high pressures [18].



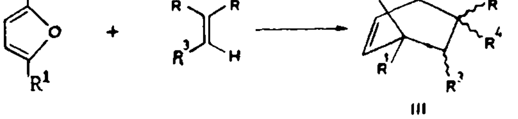
II

At atmospheric pressure and 150-230°C the yields of the dihydropyrans (II) after 1.5-5 h amount to only 1-8%; only with methyl methacrylate was a yield of 28% obtained. By reducing the temperature to 80°C and simultaneously increasing the pressure to 8-14 kbar it is possible to increase the yields of the dihydropyrans (II) considerably. Under these conditions acrolein reacts almost completely, and the acrolein dimer (II, $R^1 = R^3 = H$, $R^2 = CHO$) predominates in the mixture of adducts. The proportion of the dimer decreases when an excess of the dienophile is used.

The analogous reactions with acrolein, methyl vinyl ketone, and crotonaldehyde as dienes and with methyl acrylate, acrylonitrile, and methacrylonitrile as dienophiles were investigated at pressures of 1 and 2750 bar and at 145 and 130°C, respectively [19]. After 48 h under pressure the overall yields of the Diels—Alder products were 25-90% when the first two dienes were used, and this is significantly higher than the yields obtained at atmospheric pressure. In these cases the cyclic dimers of the diene component also predominate in the mixture of adducts. The reaction of crotonaldehyde with the above-mentioned dienophiles hardly goes at all under the investigated conditions. Only with methyl acrylate and methyl methacrylate were low yields of the adducts obtained (up to 7%).

Quantitative data on the effect of pressure on the rate constants in the range of 1-11,280 bar at 70°C were obtained for four reactions of the type under discussion [20]. The $\Delta V^{\neq}$ values calculated according to Eq. (3) were practically identical, i.e., -36 ± 1 cm^3/mole.

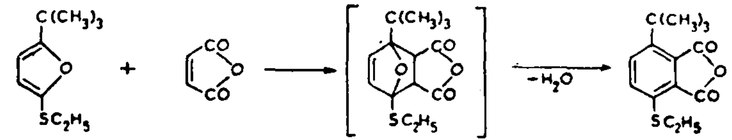
Syntheses based on the Diels—Alder reaction with furan and its derivatives are of great interest, since this is the most direct route to the creation of the 7-oxabicyclo[2.2.1]-heptene system widely used in organic chemistry. At atmospheric pressure it is not possible to realize this reaction on account of the thermal instability of the adducts, due to the strain in the bicyclic ring. However, at 15 kbar and room temperature compounds of type (III) are obtained with yields of 7-97% (4-14 h) [21]. Comparison of these data with results obtained at atmospheric pressure shows that high pressure gives a significant advantage in these reactions. The reasons for the different reactivities of the investigated compounds have been discussed, and it has been emphasized that in some cases the process is characterized by high stereoselectivity [21]. Thus, only the endo-cis isomer is obtained from furan and dimethyl maleate, and the only product from the reaction of furan with dimethyl fumarate is the trans isomer.



III

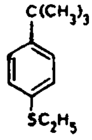
R^1, $R^2 = H$, CH_3; $R^3 = H$, CH_3, CO_2R; $R^4 = CN$, CO_2R, CHO, $COCH_3$. An adduct was not obtained for $R^1 = R^2 = H$, $R^3 = CH_3$ and $R^4 = CN$

A characteristic feature of the reaction of 2-alkylthiofurans with maleic anhydride and acrylic acid is the instability of the Diels–Alder adduct containing the semithioacetal fragment, which is readily aromatized with elimination of water. At atmospheric pressure in boiling toluene for 5 h the sulfide (IV) does not react with maleic anhydride, but in the presence of oxalic acid after boiling in benzene for 25 h the adduct (V) was obtained with a yield of about 3% [22]. At 10 kbar its yield amounted to 20%.

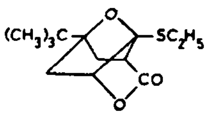


IV V

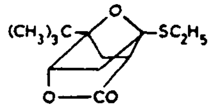
With acrylic acid at atmospheric pressure 22% of the sulfide (VI) (elimination of H_2O and CO_2), 0.8% of a mixture of compounds (IIa, b), and 2.3% of compound (VIII) were obtained, and the initial furan (IV) reacted to the extent of 43%. At 10 kbar the yields of the compounds increased to 33, 13, and 4%, respectively. [Here the furan (IV) does not react fully.]



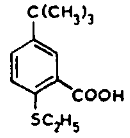
VI



VIIa



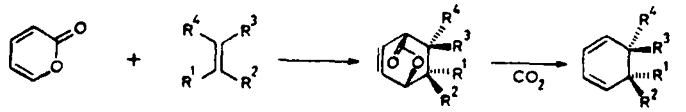
VIIb



VIII

The significant increase in the fraction of the lactone at 10 kbar was explained by the fact that the establishment of an equilibrium between the endo and exo forms of the unstable intermediate Diels–Alder adduct is retarded under pressure [22].

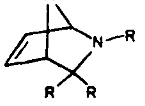
The prospects for the synthesis of polyfunctional cyclic compounds with the pyrone system at high pressures was demonstrated in [23]. Under normal conditions (100-200°C) the reaction does not stop at the stage of formation of the diene synthesis product (IX), which rapidly eliminates carbon dioxide and gives the cyclohexadiene (X).



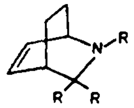
IX X

The strong accelerating effect of pressure during cycloaddition made it possible to realize the reaction at room temperature (20-40 kbar), as a result of which a series of compounds of type (IX) were obtained with quantitative yields after about 24 h. 3-Hydroxy-2-pyrone was used as diene, and methyl vinyl ketone, methyl methacrylate, methyl crotonate, and α-chloroacrylonitrile were used as dienophiles. Dimethyl acetylenedicarboxylate also gives a bicyclic adduct, but this soon decomposes at room temperature after removal of the pressure with the release of carbon dioxide and the formation of dimethyl 3-hydroxyphthalate. Consequently, the adduct is stable at room temperature only at a sufficiently high pressure, which thus prevents decarboxylation.

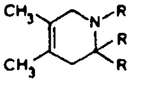
The condensation of ethyl azomethinetricarboxylate with 1,3-dienes has been investigated [24]. The process was realized at 10 kbar and 100-110°C in tetrahydrofuran. Cyclopentadiene enters into condensation at atmospheric pressure, whereas the other employed dienes react only at high pressure giving 23-72% yields of the adducts (after reaction times of up to 36 h). Cyclopentadiene and furan give derivatives of series (XI), 1,3-cyclohexadiene (XII), 2,3-dimethyl-1,3-butadiene (XIII), and 1-phenyl-1,3-butadiene (XIV).



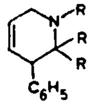
XI



XII



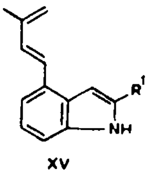
XIII



XIV

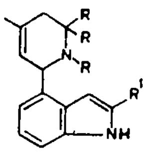
XI X=CH$_2$, O ; XI-XIV R=CO$_2$C$_2$H$_5$

The successful synthesis of the dihydropyridine (XIV) made it possible to hope to obtain compounds of the ergoline series in the same way. However, when indolylisoprene (XV) was brought into the reaction, the isomer (XVII) was obtained instead of the expected adduct (XVI).


XV

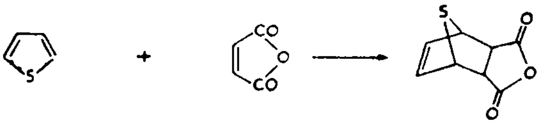
$R^1 = H$


XVI


XVII

The direction of the reaction was not changed by variation of the electron density distribution in the indole skeleton by the introduction of an ester group ($R^1 = CO_2C_2H_5$) or by increase in the steric hindrances at the nitrogen atom in the azomethinetricarboxylic ester (R at the nitrogen atom = $CO_2C_4H_9$-t).

Quite recently it was possible to bring thiophene into the Diels–Alder reaction. With maleic anhydride (at 100°C, 15 kbar, 3 h, in methylene chloride) it forms the adduct (XVIII) (the exo form) with yields of 37-47% [25]. However, adducts were not obtained with other dienophiles (dimethyl maleate, methyl acrylate, etc.) under the same conditions.

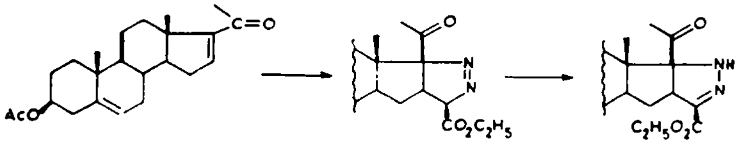

XVIII

1,3-DIPOLAR CYCLOADDITION

The quantitative effect of pressure on reactions of this type has been studied for the case of the cycloaddition of diphenyldiazomethane to 5,6-diethoxycarbonyl-5,6-diazabicyclo-[2.2.1]hept-2-ene in toluene at 24.5°C [26]. The obtained $\Delta V^{\neq}$ value of −30 cm^3/mole is close to the average value of $\Delta V^{\neq}$ for the Diels–Alder reaction.

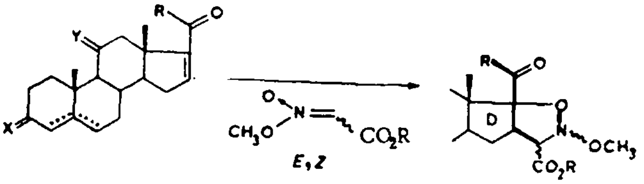
Successful syntheses of pyrazolines and triazolines by addition of diazomethane to nine dipolarophiles at 20°C and 5 kbar in ether have been described [27]. trans-Stilbene, cis-stilbene, and methyl α-phenylcinnamate do not enter into the reaction at all under normal conditions, but for the others a multiple increase in the yields of the adducts was observed with increase in the pressure to 5 kbar.

An interesting example of a significant change in the composition of the products from the reaction of ethyl diazoacetate with 16-dehydropregnenolone acetate under high pressure conditions was described in [28]. Previously the only product from these compounds at 1 bar and 120°C had been Δ^2-pyrazoline (XX).


XIX XX

In [28] the authors supposed that the pyrazoline (XX) was a secondary product and that the migration of the double bond in the initially formed pyrazoline (XIX) was due to the high reaction temperature. Since pressure greatly accelerates the cycloaddition reaction, it was realized at 20°C and 14 kbar. It was found that a mixture of the pyrazolines (XIX) and (XX) in a ratio of 3:2 was formed with a 75% yield under these conditions.

The production of the products from 1,3-dipolar addition of nitronic esters to conjugated olefins of the 16-dehydro-20-oxosteroid series at 14 kbar and 22°C has been described [29]. At atmospheric pressure this reaction does not occur to the extent of more than 2%. Increase in temperature does not lead to an increase in the yield on account of the thermal instability of the nitronic esters. The addition of Lewis acids accelerates the reaction but at the same time gives rise to side transformations in the isoxazolidines. It is known that nitronic esters represent mixtures of two geometric isomers in a Z:E ratio of 60:40, and the Z isomer is chemically more reactive than the E isomer. With a large excess of the nitronic esters, therefore, only the Z form reacts. In [29] the reactions were realized with both forms under pressure. With each of the isomers (Z and E) the majority of the investigated dipolarophiles give stereoisomeric pairs of cyclic adducts. It was shown that the four obtained compounds were stereoisomers only with respect to the C_3' and N centers.



It was concluded that this process is mainly controlled by kinetic factors.

CYCLOTRIMERIZATION OF NITRILES

In the presence of alcohols and weak bases at pressure of up to 8 kbar (60-150°C) acetonitrile, propionitrile, n-valeronitrile, α,α-dichloropropionitrile, and benzonitrile give s-triazines [30]. Acetonitrile, when mixed with an equivalent amount of methanol at 6.4-7.2 kbar and 60°C, gives 39% of 2,4,6-trimethyl-1,3,5-triazine after 65 h. The s-triazine is not formed in the absence of methanol.

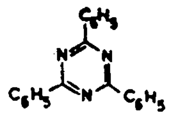
During the trimerization of acetonitrile 4-amino-2,6-dimethylpyrimidine is formed in addition to s-triazine, and its yield may be high under the appropriate conditions. For example, in the presence of ammonia the yield of the pyrimidine amounts to 68%. The s-triazine is also capable of being converted into its isomeric aminopyrimidine in methanol saturated with ammonia at 8.5 kbar and 150°C. This process occurs even more readily in the case of 2,4,6-triethyl-1,3,5-triazine.

The following scheme has been proposed for the trimerization of benzonitrile [31-33]:

$$C_6H_5CN + ROH \underset{k_2}{\overset{k_1}{\rightleftharpoons}} C_6H_5C(=NH)OR$$

$$2C_6H_5C(=NH)OR \xrightarrow[\text{slow}]{k_3} [C_6H_5C(OR)=N-C(=NH)C_6H_5] + ROH$$

$$[C_6H_5C(OR)=N-C(=NH)C_6H_5] + C_6H_5C(=NH)OR \xrightarrow[\text{fast}]{k_4}$$



$$+2ROH$$

According to this mechanism, the trimerization rate (W_T) can be expressed in the following form:

$$W_T = k_3 \cdot K \cdot N_n^2 \cdot N_a^2, \tag{4}$$

where K is the equilibrium constant for the formation of the imidic ester

$$K = \frac{N_e}{N_n \cdot N_a}, \tag{5}$$

and N represents the mole fractions of the imidic ester, nitrile, and alcohol.

If it is supposed that N_n and N_a vary little with pressure (compared with K), logarithms are taken, and the expression for W_T is differentiated with respect to pressure; the following equation is obtained for the overall volume effect of activation of trimerization ($\Delta V_c^{\neq}$):

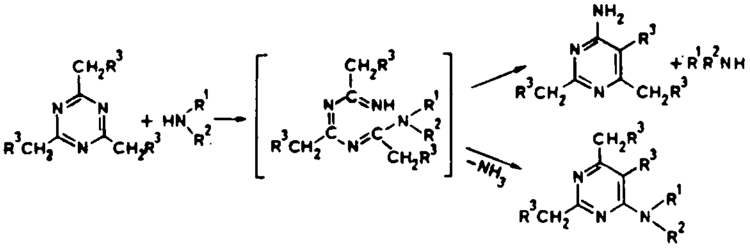
$$\Delta V_c^{\neq} = \Delta V_3^{\neq} + 2\Delta V_{ie}. \tag{6}$$

i.e., the $\Delta V_c^{\neq}$ value is equal to the sum of the volume effect of activation of the condensation reaction (k_3) and the two volume effects of the imidic ester formation reaction.

Analysis of data on the effect of pressure on the equilibrium constant for the formation of the imidic ester from methanol and benzonitrile [31, 33] with due regard to the fact that the k_3 reaction must be accelerated by pressure gave reason to conclude [34] that $\Delta V_c^{\neq}$ must be negative and must be greater than 60 cm³/mole in absolute value. This conclusion was confirmed by calculation of $\Delta V_c^{\neq}$ from data on the dependence on pressure and from Eq. (3) for the trimerization of both acetonitrile [34, 35] and benzonitrile [31, 33]. Calculation gives

$\Delta V_c^{\neq}$ values between −64 and −69 cm^3/mole. Such a large negative value for $\Delta V_c^{\neq}$, due to characteristics of the mechanism of trimerization of nitriles, leads to an unusually strong effect from pressure. Thus, it was shown [34, 35] that the trimerization of acetonitrile in the presence of an equimolar amount of methanol and 1% of diethylamine occurs to the extent of 90% after 1 h at 14 kbar (80°C). At this pressure the reaction goes fairly rapidly even in the presence of extremely small amounts of methanol (2.5%). Calculation by means of Eq. (3) shows that with $\Delta V_c^{\neq} \approx -60$ cm^3/mole about 1 year would be required for the production of a few percent of the triazine under normal conditions, i.e., the process cannot be realized at low pressures. Thus, the large effect of pressure during the trimerization of nitriles in alcohols is actually due to displacement of the equilibrium under pressure toward the imidic esters, the equilibrium concentration of which at 1 bar is so small that the condensation occurs extremely slowly.

At 14 kbar and 80°C nitriles with longer aliphatic radicals (propionitrile, butyronitrile, valeronitrile, and capronitrile) also react considerably more rapidly [34]; after 3-10 h 60-80% yields of the s-triazines were obtained. At 7 kbar and 100°C only 7% of the s-triazine was obtained from valeronitrile after 18 h [31].



Attention should be paid to the formation of side products during the trimerization of nitriles, since the contribution from concurrent reactions depends on the temperature, the composition of the initial mixture, and the structure of the nitriles. There are grounds for supposing that side products and, primarily, 2,5,6-trisubstituted 4-aminopyrimidines are obtained as a result of rearrangement of the s-triazines catalyzed by nitrogen bases [33, 36].

The reactions of nitriles in alcohol can also occur in the absence of the base; in this case the role of the base may be played by the imidic ester. On the basis of the scheme given above unsymmetrically substituted triazines were synthesized from a mixture of the s-triazine with various nitriles and alcohol. By appropriate selection of the ratio between the initial compounds it is possible to obtain a predominant yield of a mixed triazine with given structure [33, 36].

The significant (and possibly predominant) formation of the aminopyrimidines is explained by the fact that under the conditions for the synthesis of s-triazines the β-alkoxypropionitriles give high-molecular-weight compounds containing s-triazine and aminopyrimidine groups in the structure. The respective individual compounds were identified only in small quantities. Polymeric substances here are formed as a result of condensation processes involving the amino and alkoxy groups of the aminopyrimidines and s-triazines formed at the initial stages [34].

Acrylonitrile in a mixture with alcohol at 14 kbar also gives polymers close in structure to those described above. This is explained by the formation of β-alkoxypropionitriles in the first stage of the process as a result of addition of the alcohols at the double bond of acrylonitrile [34, 37].

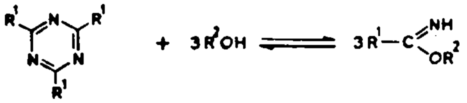
Successful syntheses of s-triazines with yields of up to 95% in the presence of alcohols were realized at 8-17 kbar and 150-240°C from the nitriles of benzoic, cyclopropanecarboxylic, 2-thiophenecarboxylic, and 2-furancarboxylic acids [38].

It should be noted that the presence of the alcohol is not always essential for the reaction. Thus, at pressures up to 40 kbar and 400°C trimerization of aromatic nitriles occurs [39]. Under these conditions benzonitrile reacts quantitatively after a few minutes, but aliphatic nitriles form resins. 2-Thiophenecarbonitrile forms s-triazine in such solvents as piperidine and sulfolane [38]. Perfluoro-2-methyl-3-oxahexane- and perfluoro-2,5-dimethyl-3,6-dioxanonanecarbonitriles are converted into s-triazines at 10-14 kbar and 80°C with yields of 40-55% after 5 h in the presence of catalytic amounts of triethylamine and water. The yield of s-triazine increases with increase in temperature, reaching 70% at 200°C even in the absence of a catalyst [40].

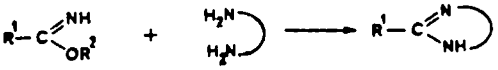
All these data show that the mechanism of trimerization can differ and depends both on the nature of the solvent and on the reaction conditions. Proposed mechanisms are discussed in [38].

OTHER SYNTHESES OF HETEROCYCLES

s-Triazines with aliphatic substituents and, in particular, those containing two hydrogen atoms at the α position of the alkyl substituent react in a mixture with alcohol even in the absence of bases, forming aminopyrimidines [38]. From this it was concluded that an equilibrium of the following type exists:

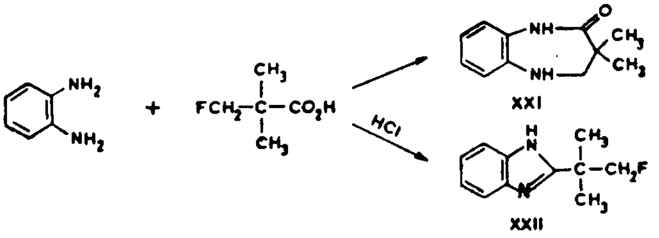


The presence of the imidic ester in such a scheme was confirmed by the synthesis of imidazole derivatives by the addition of diamines to the reaction mixture. The yields of the imidazoles amounted to 45-95% at 9-13 kbar and 180-210°C after 10-40 h in the presence of methanol or ethanol.



The idea of combining the intermediate unstable imidic esters for the purposes of synthesis was used more rationally in [33], where mixtures of a nitrile with methanol and substituted amines capable of condensation with the imidic ester were used as starting materials. In this way rings containing N, S, and O heteroatoms were obtained.

Benzimidazoles have been obtained by the condensation of carboxylic acids with o-phenylenediamines at pressures of up to 8 kbar [41]. This reaction is often used in syntheses at atmospheric pressure, but certain acids, 2,2-dimethylpropionic and 1-adamantanecarboxylic, in particular, either do not react at all under normal conditions or give low yields of the benzimidazoles. At 8 kbar and 112°C in aqueous alcohol these acids give the corresponding imidazoles with good yields. Unexpected results were obtained in the reaction of 2,2-dichloro- and 3-fluoro-2,2-dimethylpropionic acids with o-phenylenediamine under analogous conditions. In the first case only 2-acetylbenzimidazole was detected, and the authors explain this by rapid hydrolysis of the initially formed 2-(1,1-dichloroethyl)benzimidazole. In the second case it is possible to obtain either 3,3-dimethyl-1,3,4,5-tetrahydro-1,5-benzodiazepin-2-one (XXI) or, in the presence of an equimolar amount of hydrogen chloride, 2-(2-fluoromethyl-2-propyl)benzimidazole (XXII).

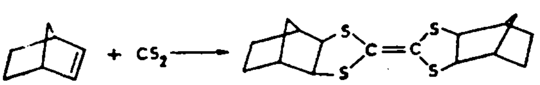


XXI

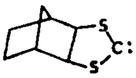
XXII

It was concluded that the strong acid suppresses nucleophilic substitution of the labile fluorine atom and favors the reaction leading to the formation of the benzimidazole.

The reactions of carbon bisulfide with unsaturated hydrocarbons, amines, and amides at 8-10 kbar and 100°C were studied in [42]. The strained norbornene gives 83% of the adduct (XXIII), which has the exo,exo configuration.



XXIII

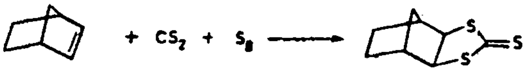


XXIV

endo-Dicyclopentadiene reacts similarly. If norbornadiene is used in the reaction, a polymer is obtained almost exclusively with an excess of carbon bisulfide. In an excess of the olefin 18% of a compound similar in structure to that obtained from endo-dicyclopentadiene was isolated in addition to the polymer. It is supposed that the reaction takes place by a mechanism of 1,3-dipolar addition with the intermediate formation of the carbene (XXIV), which then rapidly dimerizes.

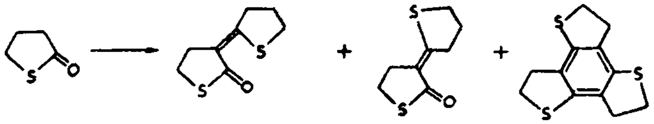
Normal (unstrained) olefins do not react with carbon bisulfide under the investigated conditions. In the presence of sulfur, however, cyclohexene forms thiocarbonic esters (the cis and trans isomers) with very low yields (~1%).

Norbornene also reacts with carbon bisulfide and sulfur, but the yield of the trithiocarbonic ester (XXV) amounts to 70% (2.5% at 6 kbar) [44].



XXV

In contrast to lactones and lactams, which form polymeric substances, γ-thiobutyrolactone gives a mixture of (XXVI-XXVIII) at 15-20 kbar and 170-200°C [44].



XXVI XXVII XXVIII

It is known that radical-chain processes are usually accelerated by pressure, although cases are known where pressure has a retarding effect on such processes. In this connection it is expedient to mention [45], in which the synthetic possibilities of free-radical addition of alcohols to α,β-unsaturated acids to form γ-lactones at pressures of up to 10 kbar at 150°C were studied. Reactions which occur very slowly or do not occur at all at atmospheric pressure were mainly chosen. For instance, the addition of 3-pentanol to β,β-dimethylacrylic acid hardly occurs at all at 100 bar, while at 6 and 10 kbar the yields of the γ-lactone amount to 25 and 60%, respectively.

The presented results make it possible to reach the following brief conclusion. High pressure favors the occurrence of synthetic reactions which in most cases are characterized by fairly large negative values for the volume effects of activation and reaction. If it is possible to isolate a small amount of the desired product as a result of reaction at atmospheric pressure, it is possible to predict with certainty an increase of tens and sometimes hundreds and even thousands of times in the yield at 10-15 kbar. Such a considerable effect from pressure makes it possible to realize reactions at lower temperatures than the temperatures at which they occur at atmospheric pressure, and, consequently, to use thermally unstable compounds as starting materials. In addition, the use of high pressures makes it possible to vary the selectivity or even the direction of the process, if an intermediate compound which decomposes or isomerizes at increased temperature but is stable at a comparatively low temperature is used; here the required reaction rate is achieved by the use of high pressure. The selectivity of the process also varies in the case where parallel reactions are characterized by different volume effects of activation. This usually arises when the transition states have different "chemical" structures.

The use of pressures in the order of 15 kbar in organic synthesis is becoming a normal occurrence in scientific practice, and the volumes of the reaction mixtures amount to 3-40 cm^3. The realization of reactions at pressures higher than 15 kbar is most frequently inexpedient for a number of reasons. For example, when $\Delta V^{\neq} = -30$ cm^3/mole the reaction rate constant increases by almost 2000 times in the range of 1-15 kbar and by only 15 times in the range of 15-30 kbar. In addition, the apparatus for the creation of pressures higher than 15 kbar is considerably more complex and less readily available. Finally, in the range of pressures under discussion it becomes extremely difficult to prevent the solidification of organic substances, the melting points of which increase considerably with increase in pressure, while reactions in the solid phase usually go extremely slowly.

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