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Decomposition products of tetrazoles as starting reagents of secondary chemical and biochemical reactions †

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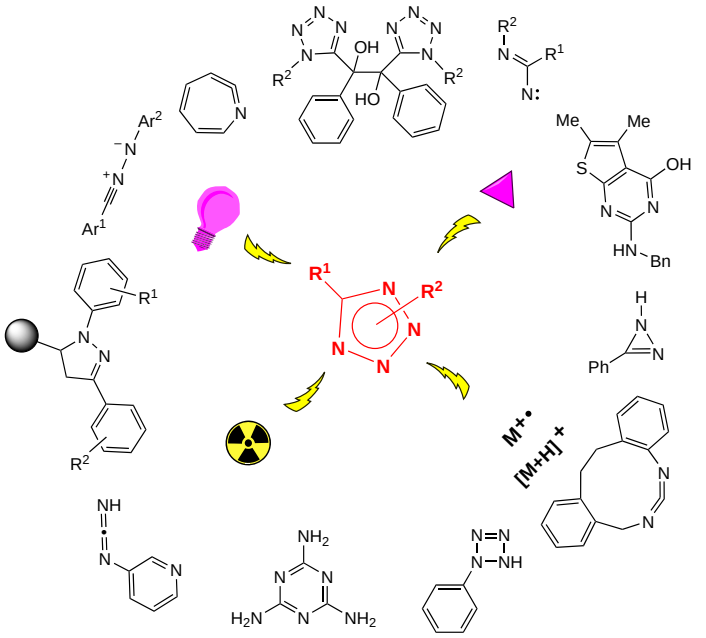
Rapid processes of tetrazole decomposition serve as sources of chemical energy stored in the five-membered ring, as well as gaseous products, primarily molecular nitrogen. Due to these properties, energetic tetrazole derivatives have found applications in various fields of science, engineering and technology, for example as components of energetic materials and products, as well as in emergency rescue equipment. The review presents an alternative view of the processes of tetrazoles decomposition, focusing on the diversity, differences, and similarities of the mechanisms and degradation products formed under the action of external energy sources. Some of these products are valuable reagents for the synthesis of previously inaccessible substances, as well as promising objects of analytical, medical, and bioorthogonal chemistry.
The bibliography includes 140 references.
Keywords: tetrazoles, thermolysis, pyrolysis, photolysis, radiolysis, mass spectrometric fragmentation, decomposition products, mechanisms, application.



Contents

1. Introduction

Tetrazole **1**(N[1]*H*) and some of its derivatives were first synthesized by Bladin [1] in 1885 (see also anniversary article [2]).‡ Herein, compounds bearing an unsubstituted nitrogen atom are indicated by NH next to the number in parentheses; for tautomers, the position of this moiety is given as the top index). Among the simplest stable azoles, this heterocycle has the highest nitrogen content and the highest enthalpy of formation (ΔH_f°) (Fig. 1).[3,4]

The unsubstituted pentazole (HN_5), unlike its salts and N-aryl derivatives, has not yet been obtained in free form and has only been studied by computational methods.[5]

Since the second half of the 20th century, the rapid processes of decomposition of tetrazole and its energetic derivatives, such as combustion and detonation, have been the subject of systematic studies by leading scientific schools, led by prominent scientists and specialists in the synthesis and chemical physics of energy-rich substances and materials. Tetrazole derivatives have received considerable attention in a number of monographs devoted to the chemistry, thermal decomposition, thermochemistry, combustion and detonation of energy-rich compounds and materials.[6–10] Below, in chronological order, are selectively cited original publications that reflect the important trends in the

† Dedicated to the memory of Professor Rolf Huisgen (1920–2020).
‡ Herein, compounds bearing an unsubstituted nitrogen atom are indicated by NH next to the number in parentheses; for tautomers, the position of this moiety is given as the top index).

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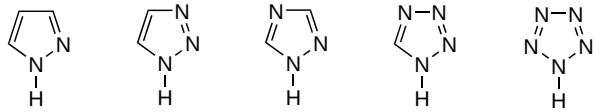

			1(N^1H)	
41.2	61.0	61.0	80	98.5
(1733)	(2690)	(2345)	(3370)	(>6000)

Figure 1. The nitrogen content (%) and ΔH_f° (in parentheses, kG kg^{-1}) for the simplest representatives of azoles.

chemistry of energetic tetrazoles and the contribution of their authors to the development of this subject, which has not lost its relevance since the end of the XIX century and up to the present day.[11–31]

The review articles and chapters of monographs[32–38] are devoted to the analysis and generalization of the findings in the chemistry and chemical physics of energetic tetrazoles, and also in the processes of tetrazole decomposition.[32–38] The topics of the traditional areas of chemistry and chemical physics of energetic tetrazoles related to thermal decomposition processes are still topical, as shown by the works published in recent years.[31,39,40] Figure 2 presents the exemplary formulas of typical energetic tetrazoles, with the name of the author and the year of preparation given below.

The chemistry of energetic tetrazoles, as evident from the above, goes back to the 19th century, but continues to develop intensively in the 21st century. The main trend is the search for novel compounds, the properties of which allow a compromise between the high energy amount released during rapid combustion or detonation and safe handling, which is determined by sensitivity to mechanical effects (impact, friction), fire beam, electrical discharge, coherent light sources and other primary impulses.[40]

In addition to the traditional research area, a new, alternative vector of development in tetrazole chemistry, focused on the

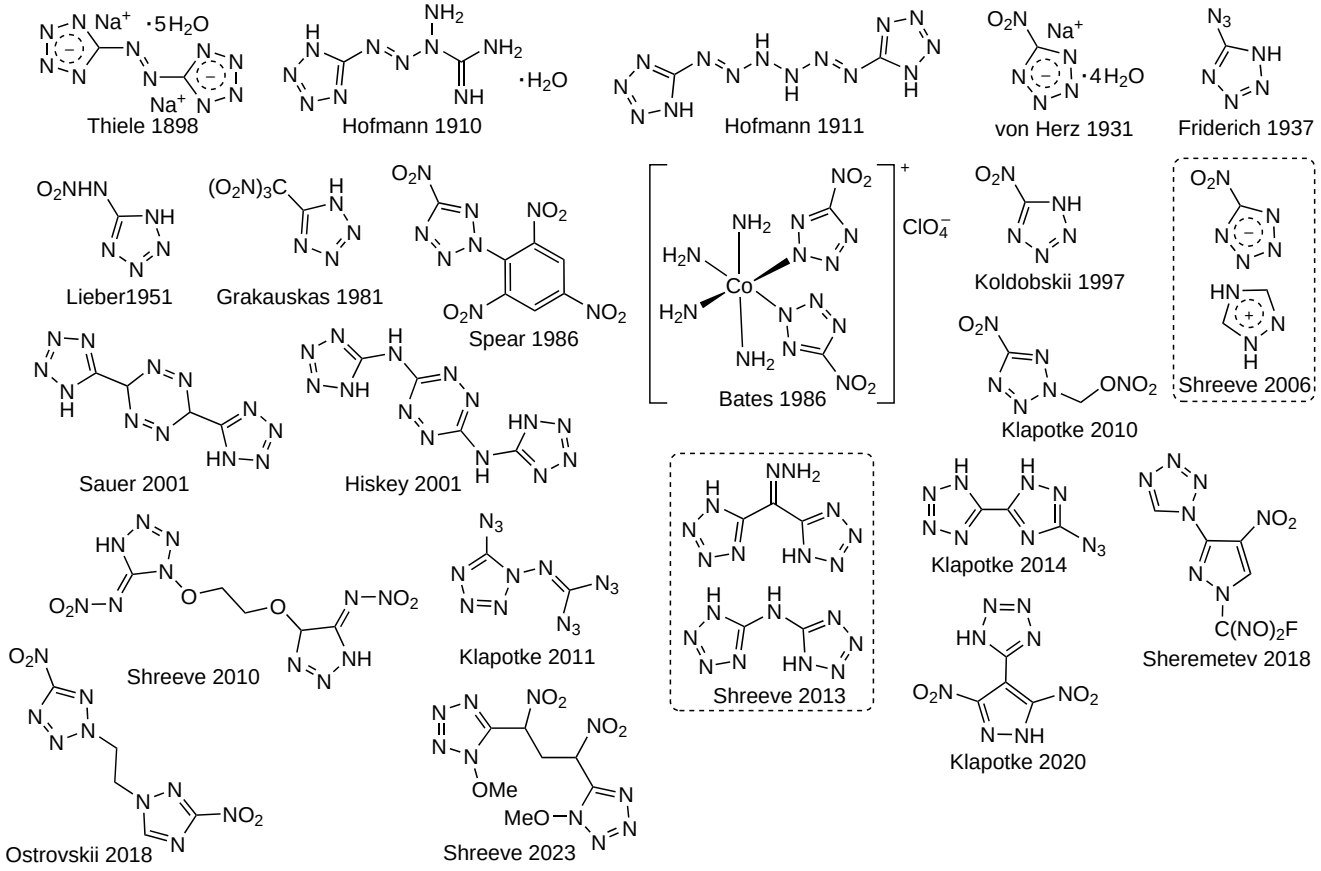

Figure 2. Structures and years of discovery of energetic tetrazoles.

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Current research interests: high-nitrogen heterocyclic compounds, synthesis, properties, reactivity, flexible small-scale production.
E.N.Chernova. Senior Researcher, PhD (Chemistry).
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Current research interests: instrumental methods of analysis, mass-spectrometry.
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Current research interests: environmental analysis, mass-spectrometry.
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M.A.Ilyushin. Professor, DrSci (Chemistry).
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Current research interests: nitrogen-containing heterocycles, synthesis, physicochemical properties and reactivity, medicinal chemistry, chemistry of natural compounds.

Translation: N.M.Vinogradova.

synthesis and identification of decomposition products of the tetrazole ring initiated by external energy sources, has been intensively formed in recent decades. The great Rolf Huisgen (1920–2020) was at the origin of this scientific field.[41] This area has recently received additional impetus with the award of the Nobel Prize in Chemistry in 2022 to a group of scientists, Carolyn Bertozzi, K.Barry Sharpless, Morten Meldal, who have explored click and bioorthogonal chemistries. Obviously, it is practically impossible to use rapid thermal decomposition of energetic tetrazoles for synthesis and study of further product transformations. The risk of an uncontrolled transition from decomposition to detonation of such compounds should be considered. However, exceptions are known. For example, a successful synthesis of bis(1,2,4-triazolo[1,5-b;5′,1′-*f*])-1,2,4,5-tetrazine by thermocyclization of the energetic 3,6-bis(1*H*–1,2,3,4-tetrazol-5-ylimino)–1,2,4,5-tetrazine (BTATz) has been described.[39] Astakhov *et al*.[42] managed, although not without difficulty, to find conditions for studying the kinetics and mechanism of decomposition of the energetic 5-nitraminotetrazole. Nevertheless, tetrazole derivatives bearing no explosophoric substituents are undoubtedly more suitable models. It is known that the replacement of explosophoric groups on endocyclic nitrogen and carbon atoms, such as NO_2, $NHNO_2$, $C(NO_2)_3$, N_3, N=N, *etc*. (see Fig. 2), with aryl, certain hetaryl, alkyl, alkoxyl substituents in non-annulated heterocycles[38] makes these tetrazole derivatives not only safe to handle but also in demand as active ingredients of modern drugs.[43] Despite the still sporadic and scarce publications on this subject, studies of processes involving annulated tetrazole compounds and their degradation products[44,45] are also of considerable interest in this context (Fig. 3).

This review highlightes the findings on tetrazole decomposition where the authors have been able to detect, identify and in some cases isolate the decomposition products of non-annulated and annulated tetrazoles initiated by external energy sources. These processes occur without catalysts under the action of high temperature (thermolysis, pyrolysis), light (photolysis), radiation (radiolysis). A separate Section of this review is devoted to studies in which the fragmentation of the tetrazole ring occurs under mass spectrometric conditions.

2. Thermal decomposition of tetrazoles

The research findings on the thermal decomposition of unsubstituted tetrazole, its N- and C-derivatives, both non-annulated and annulated, and polyvinyl tetrazoles published before 1992 are summarized in the fundamental review by Gaponik and co-workers.[33] The data presented demonstrate the diversity of mechanisms, intermediates and products of thermal decomposition of tetrazoles, as well as the dependence of their rate and activation parameters on the nature of the substituents, temperature, solvent polarity and other factors. Special mention should be made of the pioneering work of Huisgen and co-workers[46–48] on the mechanisms and products of thermal decomposition of tetrazoles, cited in the review.[33] It was on the basis of these works that the idea of nitrile imines as key reagents (1,3-dipoles) for 1,3-dipolar cycloaddition was formed. Huisgen's ideas enabled a systematic approach of a number of researchers to the interpretation of the results of quantitative studies of the above process.

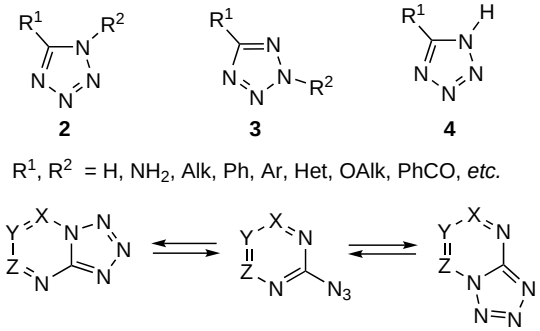
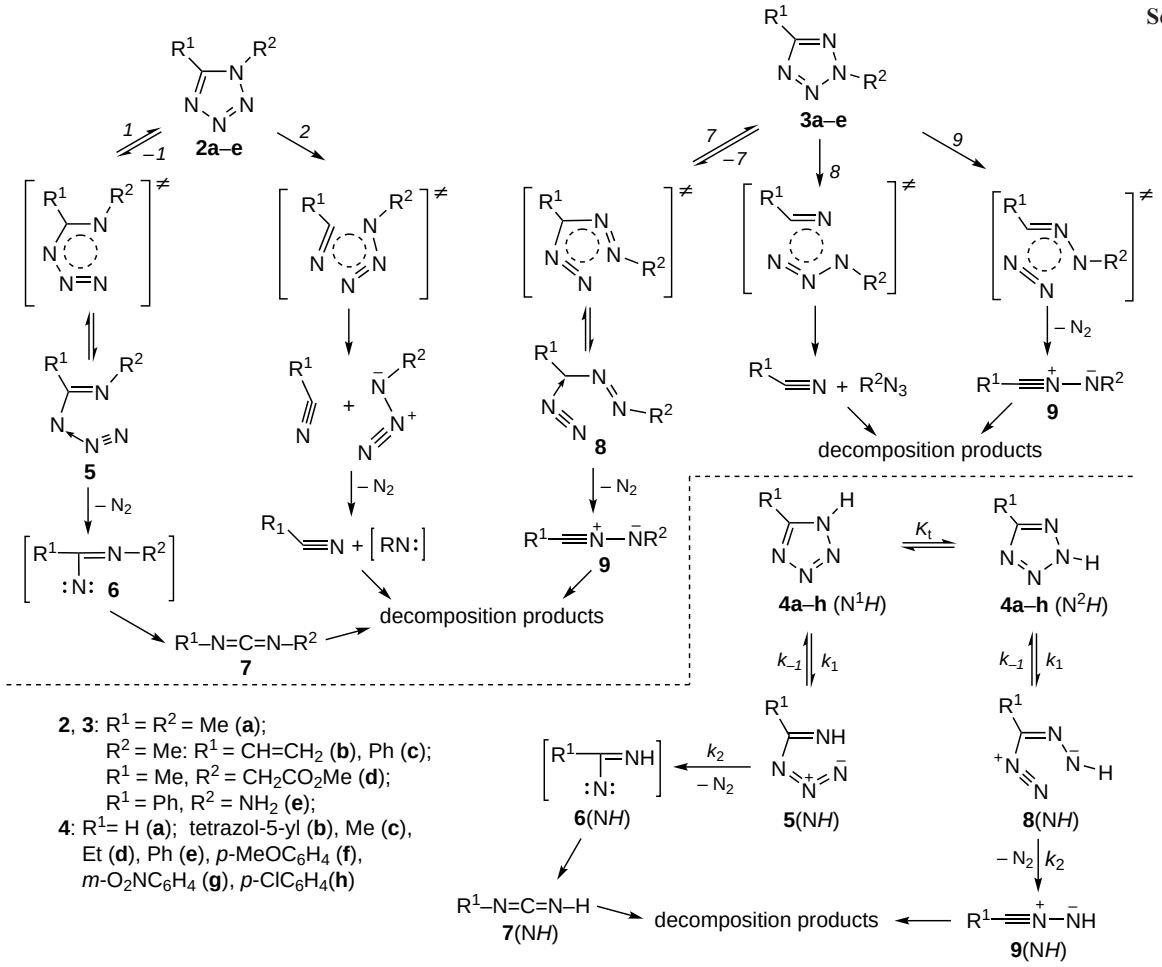


Figure 3. Structures of non-annulated (**2**–**4**) and annulated tetrazoles as promising objects for the study of degradation processes initiated by external energy sources.

The results of a manometric study of the kinetics of the thermal decomposition of 2,5-diaryltetrazoles in 1-chloronaphthalene at 165.8 °C are described.[49] The reaction rate was monitored by the amount of nitrogen released. Based on the value of the parameter ρ of the correlation dependence of the logarithms of the observed first-order rate constants on the electronic constants of the Hammett substituents, as well as on the estimation of the activation entropy, the authors suggested that there is no symmetrical transition state of the retro–1,3-cycloaddition type in the mechanisms of the high temperature-induced nitrogen cycloelimination from 2,5-diaryltetrazole. First, the N(2)–N(3) bond is cleaved to generate an open-chain intermediate followed by elimination of the nitrogen molecule. Differential Scanning Calorimetry (DSC) has also been used to determine the kinetic and activation parameters of the thermal decomposition of tetrazoles.[50,51] As the authors have shown, the activation parameters of tetrazole decomposition depend rather strongly on the conditions of the experiment, especially on the heating rate.

In later studies,[52,53] the kinetic and activation parameters of the thermal decomposition of 1,5-disubstituted (**2a**–**e**), 2,5-disubstituted (**3a**–**e**) and NH-tetrazoles **4a**–**h** have been quantified (Scheme 1). The studies were carried out by the manometric method under isothermal conditions in Bourdon vessels in the gas phase (at 180–230 °C) and in solution in nitrobenzene (150–190 °C). It was shown that the thermal decomposition of 1,5-disubstituted tetrazoles **2a**–**e** occurs predominantly *via* pathway *1* with the ring opening to afford azidoazomethine **5** (see Scheme 1). Release of N_2 from the azidoazomethine **5** leads to nitrene **6**, the subsequent sextet rearrangement of which gives carbodiimide **7**. In the case of 2,5-disubstituted tetrazoles **3a**–**e**, pathways *7*–*9* are realized, yielding compounds **8**, but the preferred direction of thermal decomposition is pathway *9*, leading to reactive nitrile imines **9**, which often act as 1,3-dipoles in 1,3-dipolar cycloaddition reactions.[47] The unimolecular decomposition of the NH-unsubstituted tetrazoles **4a**–**h** initially involves the rapid reversible interconversion of the 1*H* and 2*H* tautomeric forms, each of which decomposes by a specific mechanism. The 1*H* tautomeric form of such compounds is characterized by the reversible formation of azidoazomethine **5**(N*H*) and further elimination of N_2 to give nitrene **6**(N*H*). The subsequent sextet rearrangement of this nitrene gives the corresponding carbodiimide **7**(N*H*). The reversible ring opening in the tautomeric 2*H*-form of NH-unsubstituted tetrazoles leads in the limiting step to the diazo compound **8**(N*H*) and in the next rapid step to its decomposition with loss of N_2 and formation of the corresponding nitrile imine **9**(N*H*) (see Scheme 1).

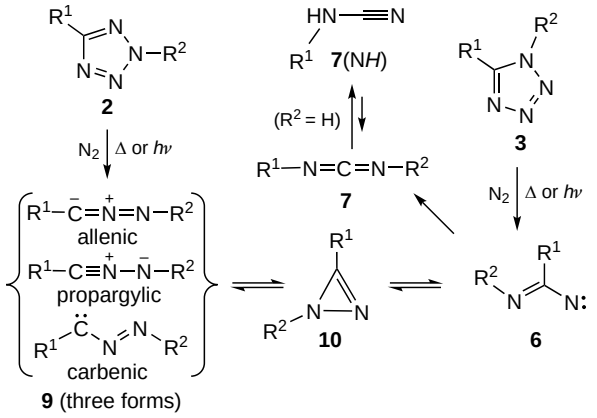
Scheme 1



Analysis of the effect of substituents on the rate of thermal decomposition of tetrazoles indicates the crucial role of prototropic ($N^1H \leftrightarrow N^2H$) tautomerism as a factor affecting the mechanism of thermal decomposition of NH-unsubstituted tetrazoles[53] (see Scheme 1). The authors of an earlier study on the kinetics of thermal decomposition of 5-aryltetrazoles take a different view. In their opinion, the acid dissociation of NH-unsubstituted tetrazoles furnishing the corresponding anion, tetrazolide, contributes more significantly to this process.[54] The Section 'Stability of tetrazoles' of the well-known monograph[7] is based on the findings described in publications[52,53] cited above. This monograph, which is well known to those skilled in the art of combustion and explosion, supports the conclusion of the authors of the study[53] who pointed out the determining influence of the prototropic tautomerism on the mechanism of thermal decomposition of NH-unsubstituted tetrazoles. The analysis of the activation parameters of tetrazole degradation presented in the above papers is of independent interest. However, given the diversity of tetrazole degradation mechanisms, it is practically impossible to summarize this problem within the scope of this review. The activation parameters of this process are analyzed in the monograph by Manelis *et al*.[7] and also in a series of articles by Kiselev and Sinditskii *et al*.[55–57]

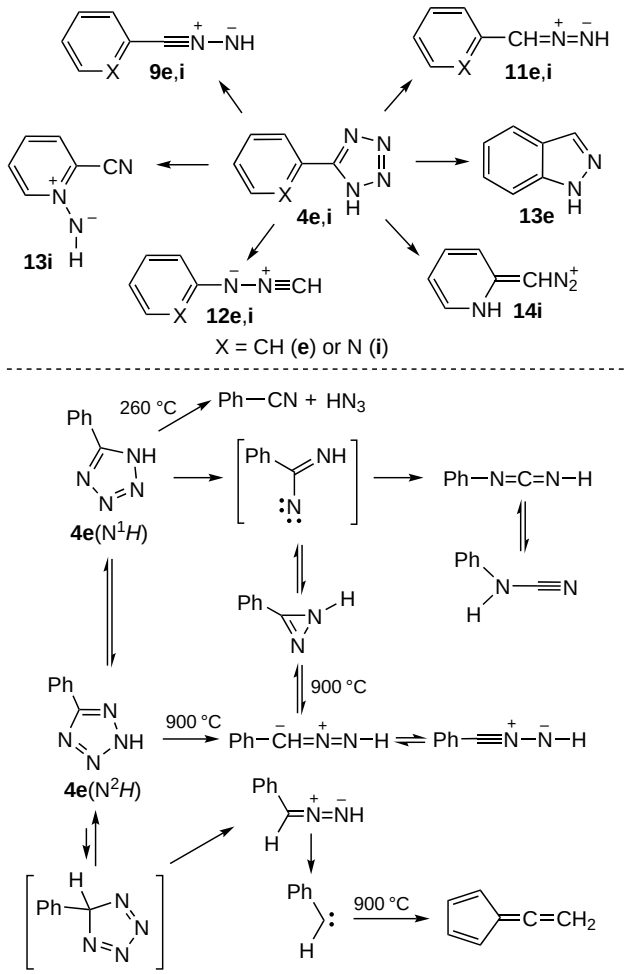
In recent years, an increasing number of papers have been devoted to the study of the thermal decomposition of tetrazoles using flash vacuum pyrolysis (FVP).[58] Flash vacuum pyrolysis, despite very high operating temperatures, often reaching 600 °C and higher, is a promising method for the generation and control of decomposition products, including reactive intermediates capable of participating in secondary chemical and biochemical reactions, due to specific engineering solutions and hardware design.[59] FVP data allow us to significantly extend and deepen previously established ideas about the mechanism of thermal decomposition of tetrazoles. For example, it was shown[60] that nitrile imines,[9] including those with R^2 = H (see Scheme 1), can exist in three isoergic forms, namely, allenic, propargylic and carbenic (Scheme 2). Carbenic nitrile imines have maximum energy and are stabilized by electron-donating substituents. In addition to nitrile imines **9**, 1*H*-diazirines **10**, imidoyl nitrenes **6** and carbodiimides **7**, including cyanamides **7**(N*H*), are also involved in the general decomposition scheme (see Scheme 2).[60–62]

Scheme 2



Flash vacuum pyrolysis of tetrazoles **4e**,**i** is a convenient source of reactive compounds such as nitrile imines **9e**,**i**, aryl diazo compounds **11e**,**i**, *N*-nitrile imines **12e**,**i**, indazoles **13e**, cyanopyridine *N*-imides **14e**,**i**. Theoretical studies using Density Functional Theory (DFT) at the CASPT2 level revealed the possibility of a transfer of the hydrogen atom from the pyrrole-type tetrazole **4i** to the pyridine nitrogen atom with subsequent loss of N_2 and formation of 1*H*-2-(diazomethylidene)pyridine **14i** with an energy barrier of ~26 kcal mol^{-1} (Scheme 3).[62] This simple pathway has not been considered before.

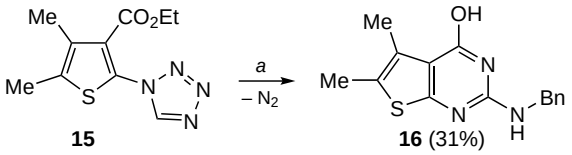
Scheme 3



Study[59] presented the results of the research of NH-unsubstituted 5-phenyltetrazole (**4e**) under FVP conditions. The authors showed that in addition to the expected intermediates and products, benzonitrile and HN_3 are also formed (see Scheme 3).

The decomposition of 1-(thiophen-2-yl)-1*H*-tetrazoles under microwave (MW) activation and FVP conditions has been studied.[63] The composition and yield of the thermolysis products depend strongly on the process conditions. Two examples from the extensive material of publication[63] are given below. Notably, despite the low yields, this work clearly demonstrates the possibility of synthesizing annulated pyrimidines and imidazoles as the main products of FVP. The thermolysis of ethyl 4,5-dimethyl-2-(1*H*-tetrazol-1-yl)-thiophene-3-carboxylate (**15**) was carried out at 165 °C in 1,2,4-trichlorobenzene (1,2,4-TCB) under microwave irradiation in the presence of benzylamine. As a result, 2-benzylamino-5,6-dimethylthieno[2,3-*d*]pyrimidin-4-ol (**16**) was obtained in moderate yield (Scheme 4).[63]

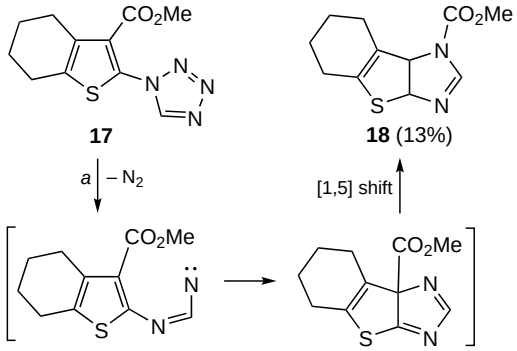
Scheme 4



(*a*) $BnNH_2$ (1.05 equiv.), 1,2,4-TCB, MW, 165 °C, 12 min

The FVP of methyl 2-(1*H*-tetrazol–1-yl)-4,5,6,7-tetrahydrobenzo[*b*]thienophen-3-carboxylate (**17**) gives methyl 5,6,7,8-tetrahydro–1*H*-benzo[4,5]thieno[2,3-*d*]imidazol-1-carboxylate (**18**) in low yield.[63] A possible mechanism for this reaction involves elimination of N_2 from the tetrazole and further intramolecular attack of the terminal nitrogen of imidoyl nitrene on the carbon atom at the 3-position of the thiophene ring, followed by electrocyclization. The process is completed by the [1,5]-sigmatropic shift of the methoxycarbonyl group (Scheme 5).

Scheme 5



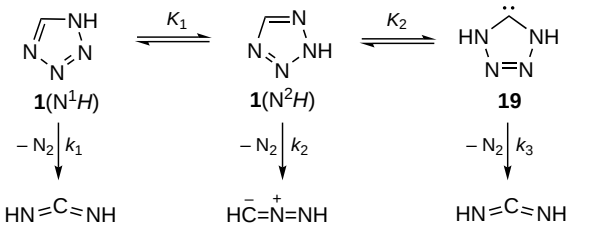
(*a*) FVP, 600 °C, 10^{-5} mbar, 7 h

In view of the development of new methods for the study of tetrazoles and areas of application of their decomposition processes, the results of theoretical work are in demand, which allow the interpretation of the experimental data already obtained, as well as the prediction of new knowledge in this field of chemistry. The tetrazole tautomers **1**(N^1*H*) and **1**(N^2*H*) (see Fig. 1), as well as the NH-unsubstituted 5-R-tetrazoles **4**(*N*^{1}*H*), **4**(N^2*H*), bearing simple substituents (R = H, Me, NH_2, NO_2, Cl, *etc*.) at the endocyclic carbon atom are versatile models for the theoretical and experimental study of the thermal decomposition patterns of the five-membered ring. The relationship between ring tautomerism and the thermal decomposition patterns of NH-unsubstituted tetrazoles was already pointed out in early experimental work (see, *e.g.*,[7]).

The tetrazoles **1**(N^1*H*), **1**(N^2*H*), and the carbene **19** were the objects of theoretical calculations carried out using high-level *ab initio* quantum chemical methods.[55] The authors suggest that not only the tautomers of the unsubstituted tetrazole **1**(N^1*H*) and **1**(N^2*H*) (see Fig. 1 and Scheme 1), but also the carbenoid structure **19** are involved in the thermal decomposition, the latter apparently being the most active (Scheme 6).[55] This study presents the results of calculations of the energy parameters of the equilibrium constants (K_1, K_2) between different tautomeric forms of N*H*-unsubstituted tetrazole, the values of the rate constants k_1, k_2, k_3 of monomolecular thermal decomposition, and also the parameters of the Arrhenius equation (E_a, log A) for the corresponding transformations.

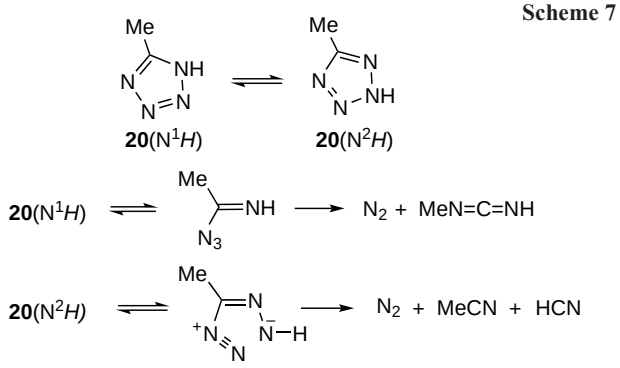
The thermal decomposition of the prototropic tautomeric forms of 5-methyltetrazole **20**(N^1*H*) and **20**(N^2*H*) has been

Scheme 6



studied by experimental and theoretical methods.[64] The experiments involved the UV photoelectron spectroscopy monitoring of the thermal decomposition products of a sample of 5-methyltetrazole subjected to rapid and slow (< 60 °C per min) heating from room temperature to 500 °C. The theoretical study was carried out using data from quantum chemical calculations by the MP2/6-311++G(d,p) method and taking into account the earlier concepts[55] (see Scheme 6). It was found that the thermal decomposition of the tautomer **20**(N^2H) prevailing in the equilibrium mixture starts in the gas phase at 195 °C and gives low-molecular-weight compounds, N_2, MeCN and HCN (Scheme 7).

Scheme 7



The nitrogen molecule is formed by two competing pathways from the 5-methyltetrazole tautomers **20**(N^2H) and **20**(N^1H) with activation barriers to isomerization of 150.2 and 126.2 kJ mol^{-1}, respectively. Two competing pathways with activation energies of 218.3 kJ mol^{-1} from the **20**(N^2H) tautomer and 198.6 kJ mol^{-1} from the **20**(N^1H) tautomer also lead to acetonitrile. According to quantum chemical calculations, the formation of HCN results from the secondary reactions with thermal decomposition products, MeCN and MeN=C=NH.[64]

The problem of activation of thermal decomposition of tetrazoles has been considered on the example of 2,5-dimethyltetrazole (**21**), 2-methyl-5-phenyltetrazole (**22**), 5-methyl-2-phenyltetrazole (**23**) and 2,5-diphenyltetrazole (**24**), as well as other substituted tetrazoles.[65] The data obtained using the M06-2x functional and the 6-31+G(d,p) level of theory with the solvation model (SMD) corrections, indirectly indicate the possibility of a significant (~80 kJ mol^{-1}) lowering of the activation barrier for the thermal decomposition of tetrazoles using the most suitable solvents and introducing an electron-withdrawing moiety in the substituent at the N(2) tetrazole atom.[65]

The thermal decomposition of 5-aminotetrazole (**25**) has received close attention.[4] This nitrogen-rich representative of the azoles has a high enthalpy of formation but is safe to handle.[4,6] Both tautomeric forms **25**(N^1H), **25**(N^2H), and 1,4-dihydro-5*H*-tetrazol-5-imine (**26**) may be involved in its thermal decomposition (Fig. 4).

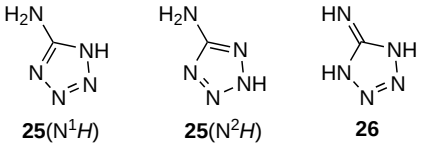
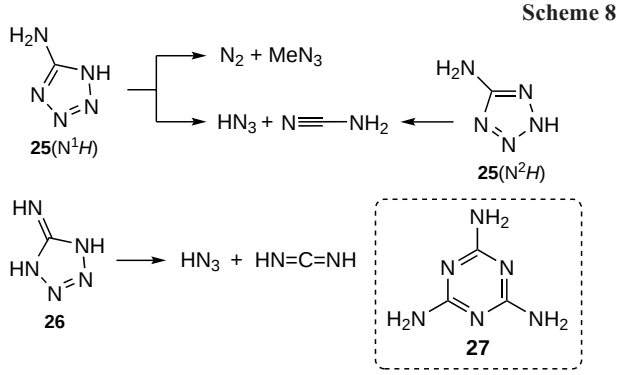


Figure 4. Structures of prototropic tautomeric forms of 5-aminotetrazole **25** and their isomer, 1,4-dihydro-5*H*-tetrazole-5-imine (**26**).

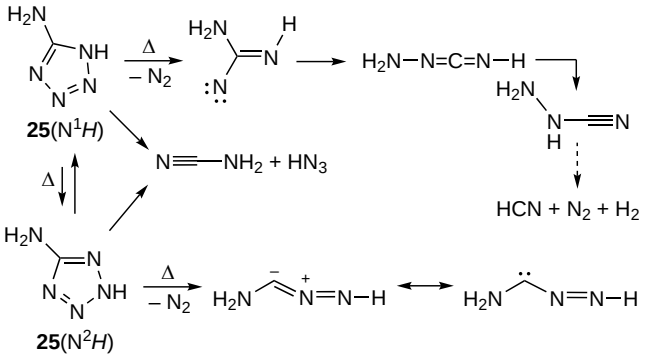
As noted by Paletsky *et al.*[66] with reference to studies,[67,68] the mechanism of thermal decomposition of 5-aminotetrazole implies the involvement of both prototropic tautomeric aminoforms **25**(N^1H) and **25**(N^2H), and the isomeric imino-form **26**, which converts to the tautomer **25**(N^1H) on melting. The above forms give rise to gaseous (HN_3, N_2, NH_2CN, NH_3, HCN) and condensed (melamine **27**) products. Hydrazoic acid, in turn, decomposes with the release of energy which intensifies the decomposition of the starting sample of 5-aminotetrazole (**25**). Such a process can be achieved by self-sustained combustion of compound **25** under pressurised conditions (Scheme 8).[66]

Scheme 8



A generalized mechanism for the thermal decomposition of 5-aminotetrazole, which complements the results of studies[66,67,69], is reviewed[59] (Scheme 9).

Scheme 9



The results of a theoretical study (DFT B3LYP technique) of the thermal decomposition of 5-aminotetrazole **25** in the gas phase and in the melt (simplified model) are reported.[70] As can be seen from the analysis of the energy diagrams and the values of the activation parameters, the thermolysis of the imino form **26** in the condensed phase (melt) cannot be described only by the traditional concept of the unimolecular mechanism. The formation of intermediate reactive dimers should be considered. The dimers **28** and **28′** can be formed with the participation of hydrogen atoms from both the NH_2 group of compound **28** and the endocyclic NH group of tetrazole **28′**. In the latter case, the

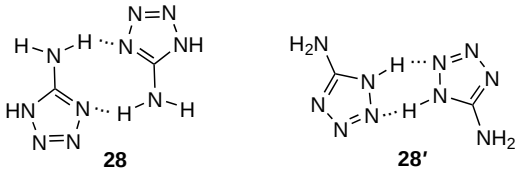


Figure 5. Structures of dimers **28** and **28′** formed by two molecules of 5-aminotetrazole (**25**) involving hydrogen atoms of an amino group or endocyclic NH groups of tetrazole rings, respectively.

hydrogen bond is formed with a pyrrole-type nitrogen atom (Fig. 5).

The thermolysis of 5-aminotetrazole (**25**), 5-amino-1-methyltetrazole (**29a**), 1,5-diaminotetrazole (**30**) and the sodium salt of 5-aminotetrazole **31** was studied using a set of complementary experimental methods: thermogravimetric analysis (DSC, DTA), thermal volumetric analysis (TVA), evolved gas analysis (EGA), infrared spectroscopy, mass spectrometry, and gas chromatography.[67,68] Data from kinetic experiments are also included in the discussion. For 5-aminotetrazole (**25**), two main routes of thermal decomposition, determined by the involvement of amino and imino forms, were confirmed. Thus, heating of compound **25** increases the content of imino form **26**, the melting and decomposition of which occur simultaneously to give hydrogen azide and carbodiimide. The polymerization products of carbodimiimide and melamine **27** were detected in the condensed phase. Subsequent heating leads to the decomposition of the corresponding amino form **25**(N^1*H*), accompanied by nitrogen release. It is shown that secondary reactions allow the range of products of thermal decomposition of 5-aminotetrazoles to be significantly extended.[67,68] It should be stressed again that the above experimental data[67,68] are consistent with the mechanism presented in the study.[66]

The thermal decomposition of 1-(R-phenyl)tetrazoles, where R = H (**32**), 2-Cl (**33**), 4-Cl (**34**), 4-OH (**35**), 4-OMe (**36**), 4-NO_2 (**37**), 1-(3-pyridyl)tetrazole **38** and 1,4-bis(tetrazol–1-yl) benzene (**39**) has been studied by theoretical (B3LYP/cc-pVDZ level of theory) and experimental methods (TGA, DSC and IR spectroscopy).[69] The *ortho*- and *para*-substituted 1-aryltetrazoles **33**, **34** (R = Cl) and **36** (R = 4-OMe) have been shown to decompose at 190–240 °C with energy release and formation of the corresponding aryl isonitriles and a binary mixture of gaseous products consisting of 1.5 mol of N_2 and 0.5 mol of H_2. The regularities of thermal decomposition of 1-phenyltetrazole (**32**) and its 4-nitro derivative **37** differ from those mentioned above. According to the authors, this is due to the different nature of the electron density delocalization. For example, in the case of compound **37** (R = NO_2), the nitro group is reduced during decomposition. The presence of two tetrazole units in 1,4-bis(tetrazol–1-yl)benzene (**38**) leads to a loss of 95% of the molecular mass during decomposition.[71]

The chemistry of tetrazole-containing polymers and materials based thereon has traditionally attracted the attention of researchers.[35] As an example, we present the results of the decomposition of the tetrazole ring in polyvinyltetrazoles. The thermal decomposition of poly(1-vinyl-5-methyltetrazole) **39** and poly(1-vinyl-5-phenyltetrazole) **40** has been studied using high-resolution thermogravimetry, DSC and thermometry methods.[72] As the temperature increases, the polymers **38** and **39** decompose stepwise and the process begins, as expected, with the degradation of the tetrazolyl moieties. Subsequent transformations are due to the formation of active intermediates such as azides **41**, imidoyl nitrenes **42**, as well as products of

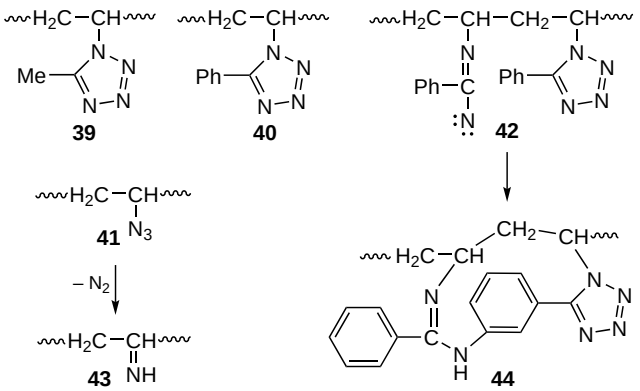
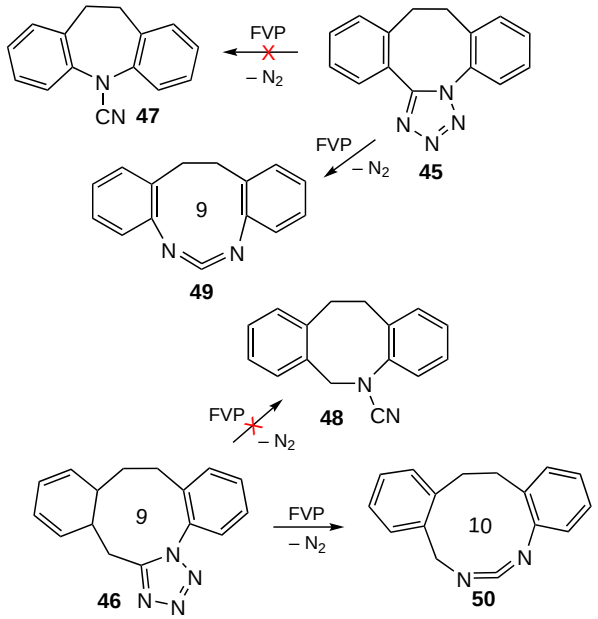


Figure 6. Structures of poly(1-vinyl-5-methyltetrazole) **39**, poly(1-vinyl-5-phenyltetrazole) **40** and products of their thermal decomposition **41**–**44**.[72]

subsequent transformations of macromolecules **43** and **44**, which takes place in the temperature range 210–290 °C. Polymer chain degradation occurs at temperatures ⩾320 °C (Fig. 6).[72]

In the case of annulated tetrazoles, the azido-tetrazole equilibrium is of constant interest.[44,45] However, the works devoted to the study of the thermal decomposition patterns of annulated tetrazoles and to the determination of the nature of the resulting products are represented by single examples. For example, as shown шт publication,[73] FVP of annulated benzene rings of hexa- and heptamethylenetetrazoles (**45**, **46**) furnishes 9- and 10-membered cyclic carbodiimides **49**, **50** respectively, instead of the expected cyanamides **47**, **48** (Scheme 10).

Scheme 10



To conclude the Section on the thermal decomposition of tetrazoles, it should be noted that the development of this interesting and promising subject would not be possible today without the pioneering studies in the field of the straightforward synthesis and chemical physics of energetic tetrazoles carried out at the end of the last century by scientists and specialists of specialized research institutes, design bureaus and university teams of the USSR, whose references are given in the Introduction. With the development of new methodologies for

decomposition processes such as FVP, where their products can be synthesized and controlled, new results on thermal decomposition studies of both non-annulated and annulated tetrazoles can be expected in the near future.

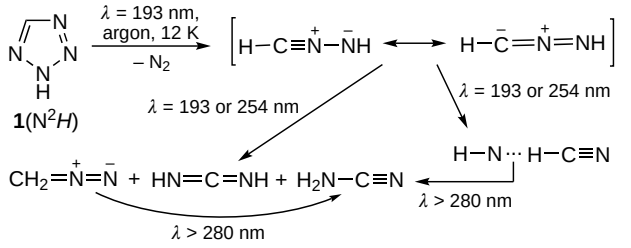
3. Photodegradation of tetrazoles

Tetrazoles are extremely interesting and promising objects of photochemistry. Researchers are attracted by the possibility of inducing controlled degradation of the tetrazole ring under the action of light of a certain wavelength, including coherent radiation generated by lasers.[74,75] The conditions of formation of products of photochemical decomposition of tetrazoles are much milder compared to thermal decomposition, which facilitates analytical control of intermediate and final products. Moreover, these products can be used as reagents in further chemical and biochemical reactions for the synthesis of practically relevant compounds of a given structure. There are several methods of photochemical decomposition currently being developed by leading laboratories around the world, which are briefly described in this Section.

3.1. Photolysis of tetrazoles in cryogenic matrices

The review,[75] with reference to the original publication,[76] presents a scheme of photoinduced decomposition of unsubstituted tetrazole **1**(N^2H) in a cryogenic matrix (deposited in solid argon at 12 K). Photolysis under the action of a 193 nm coherent light source (ArF laser) leads to photodegradation of the tetrazole, accompanied by elimination of the N_2 molecule and formation of a diversity of photochemical transformation products, including nitrile imines, HCN–NH complex, diazomethane, carbodiimide and cyanamide (Scheme 11).

Scheme 11



The structure of nitrile imines generated by photoinduced degradation of 2,5-diaryltetrazoles in cryogenic matrices is reviewed in article.[77]

Spectral methods such as Fourier-transform infrared spectroscopy (FTIR) have been successfully used to monitor the products of chemical transformations occurring during the photoinduced decomposition of tetrazole derivatives in isolated cryogenic matrices. Using this method for tetrazoles **29**, **51a–c**, **52a–c**, it was possible to determine the patterns of photoinduced fragmentation of the tetrazole ring up to the identification of the individual bond cleavage with fixation of the corresponding products in the matrix (Fig. 7).[78,79]

The effect of substituents on the process of photoinduced decomposition of some tetrazoles has been studied in cryogenic matrices, which is a harsh environment of solidified noble gases (argon, xenon) at temperatures of 10 K. Under these conditions, the products are formed and stored in a fixed state, directly in the matrix cell, without being involved in subsequent reactions. This greatly simplifies the sequence of transformations and

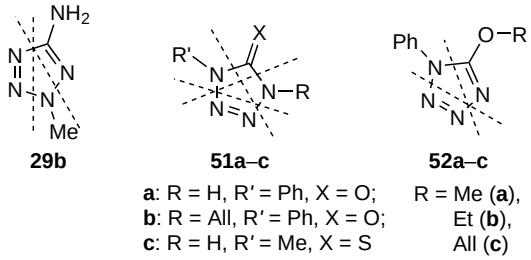
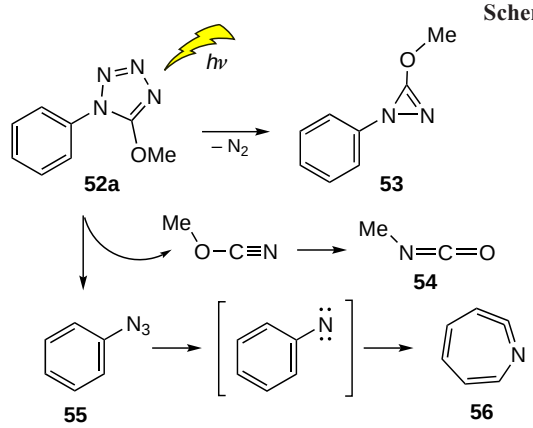


Figure 7. Patterns of heterocyclic covalent bond cleavage (shown by dotted lines) during photoinduced decomposition of 5-amino-2-methyltetrazole (**29**), 1,4-disubstituted 1,4-dihydro-5*H*-tetrazol-5-(thi)ones **51a–c** and 5-alkoxy–1-phenyltetrazoles **52a–c** in cryogenic matrices.

allows to determine the structure of intermediates and some products by FTIR. A useful analytical tool is the ability to compare data from experimental and theoretical spectra calculated for the particle state *in vacuo*.[79] The results of such studies have been demonstrated for a number of 1,5-disubstituted tetrazoles. Schemes 12 and 13 illustrate, as examples, the photoinduced ($\lambda > 235$ nm) decomposition of 5-methoxy-1-phenyl-1H-tetrazole (**52a**) and 1-phenyltetrazolone (**51a**), respectively, in a cryogenic matrix.

As evident from Scheme 12, secondary transformation products of different structures were found in the case of compound **52a**: 3-methoxy-1-phenyl–1*H*-diazirine (**53**), methyl isocyanate (**54**), phenyl azide (**55**) and 1-azacyclohepta-1,2,4,6-tetraene (**56**).

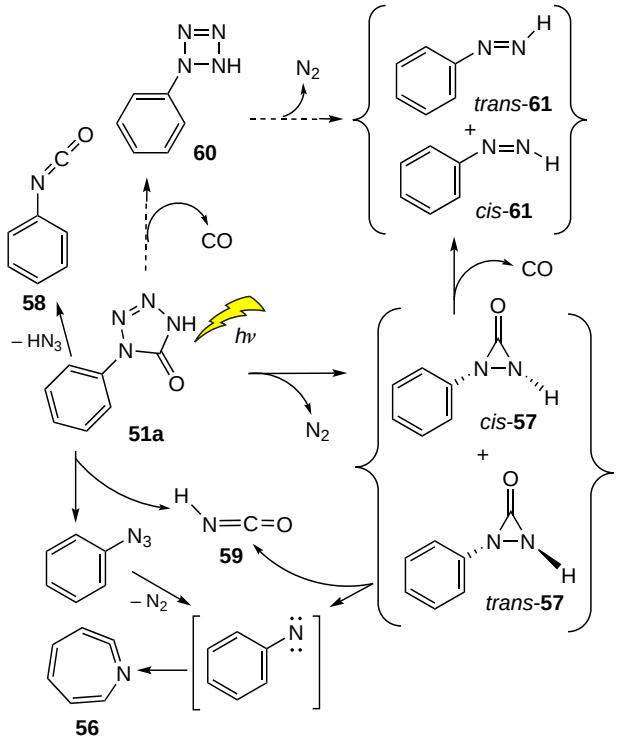
Scheme 12



The result of the photochemical transformation of tetrazolone **51a** includes several unexpected products. The authors of the cited publication[79] reported the formation of two conformers (with *cis* and *trans* configurations) of 1-phenyldiaziridin-3-one (**57**), phenyl isocyanate (**58**), the already mentioned 1-azacyclohepta–1,2,4,6-tetraene (**56**), isocyanic acid (**59**), 3-phenyl-2,3-dihydrotetrazete (**60**), as well as *cis* and *trans* isomers of phenyldiazene **61** (see Scheme 13).

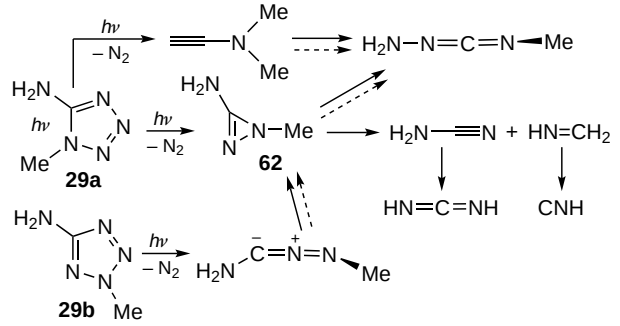
The photoinduced decomposition of tetrazoles in cryogenic matrices is of considerable practical interest as a tool for monitoring the stability of active pharmaceutical ingredients (APIs) of drugs to electromagnetic radiation in the ultraviolet and visible regions of the spectrum. An example of such a method is given in a publication,[80] which is devoted to the study of *N*-methyltetrazolylsaccharinates. Such compounds have attracted attention as catalysts for the oxidation of primary and secondary alcohols and as promising drug candidates with strong cytostatic properties.[80] The authors present the routes of photoinduced decomposition of regioisomeric *N*-methyl-

Scheme 13



tetrazolylsaccharinates exposed to narrowband UV irradiation at different wavelengths. The process was monitored by infrared spectroscopy with *ab initio* quantum chemical calculations used to interpret the data. The present work was preceded by research by the same authors on the photoinduced decomposition of regioisomeric 5-amino–1-methyl- and 5-amino-2-methyl-tetrazoles **29a**,**b** in cryogenic argon matrices at 15 K. Simple arrows indicate photolysis routes of tetrazoles **29a**,**b** upon irradiation with light of wavelength λ = 222 nm and λ = 250 nm, respectively. Dashed arrows indicate photolysis routes upon irradiation with light of wavelength λ = 325 nm (Scheme 14).

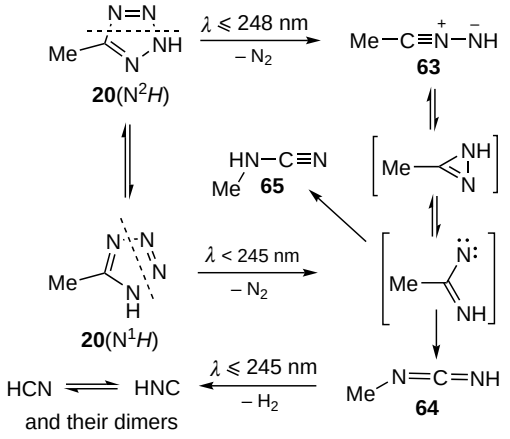
Scheme 14



When comparing the results of the photochemical decomposition of regioisomeric *N*-methyltetrazolylsaccharinates and regioisomeric *N*-methyl-5-aminotetrazoles **29a**,**b** (see Scheme 14), general directions of photoinduced decomposition were identified. For example, the possibility of the formation of 1-methyl–1*H*-diazirin-3-amine (**62**), a common intermediate for isomers **29a**,**b**, has been demonstrated. It was notes that functionalization of the 5-amino group of the tetrazole ring has a significant stabilizing effect.[81] According to the authors, this effect could be useful in the design of model compounds specifically intended to explore the mechanism of tetrazole decomposition in cryogenic matrices.

The photoinitiated degradation of 5-methyltetrazole **20** was studied in a solid cryogenic argon matrix at 10 K. A tunable UV laser system was used to study photodegradation processes at different wavelengths. The reactions were monitored by FTIR spectroscopy. According to the vibrational spectra, the 5-methyltetrazole isomer **20**(N^2H) predominated in the cryogenic matrix. The results were interpreted using kinetic methods and quantum chemical calculations (DFT and its time-dependent variant (TD-DFT)). As a result, three products of the tetrazole ring degradation were successfully identified such as C-methylnitrile imine (**63**), *N*-methylcarbodiimide (**64**) and methyl cyanamide (**65**). In turn, *N*-methylcarbodiimide **64** further decomposes into two molecules of HCN or HNC. The latter are in equilibrium in the matrix cells and further form various dimers through hydrogen bonding (Scheme 15).[82]

Scheme 15



Photolysis of 2-(tetrazol-1-yl)- (**66**), 3-(tetrazol-1-yl)- (**67**) and 2-(tetrazol-5-yl)pyridines (**68**) in cryogenic argon matrices leads to 2-pyridyl- (**69**) or 3-pyridylcarbodiimide (**70**).[83] The formation of a unique product of the rearrangement occurring during photolysis, 1-cyclopenta-2,4-dienylketenimine (**71**), has also been detected by spectral analysis. The formation of ketenimine (**71**) could be explained by using quantum chemical calculation (B3LYP/6-311þþG(2d,2p)) data (Fig. 8).

Despite the unique possibilities and prospects of using cryogenic matrices for the elucidation of structure of tetrazole photolysis products, it should be noted that the isolation of such

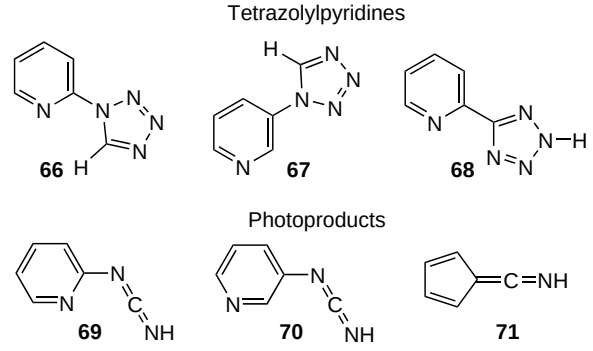


Figure 8. Structures of starting tetrazolylpyridines **66**–**68** and products **69**–**71** of their photoinduces decompositions in cryogenic matrices.

products in pure form, *e.g.* by extraction methods, is a challenging task. This limits the use of photoinduced degradation of tetrazoles as an effective method for the directed synthesis of organic compounds.[75,84]

According to the authors of the above-cited papers, the photodegradation of tetrazoles in organic solvents is a more promising strategy with applications in the synthesis of new or otherwise difficult to obtain compounds.

3.2. Photolysis of tetrazoles in organic solvents

The use of different organic solvents and varying the conditions of the photochemical processes can affect the selectivity and the yield of the target photoproducts.[75] This Section reviews publications dealing with the synthesis of individual compounds by photodegradation of tetrazoles in solution.

Hyatt и Swenton[85] pioneered the photochemical synthesis of 9*H*-pyrimido[4,5-*b*]indoles **72** from annulated 8-(*para*-substituted)tetrazolo[1,5-*c*]pyrimidines in trifluoroacetic acid using a 16 RPR-3000 Å lamp. Quast and Bieber[86] described methods for the synthesis and results of a photolysis study of 1,4-dialkyl–1,4-dihydro-5*H*-tetrazol-5-ones and -5-thiones. Later, Quast and Nahr[87] reported the synthesis of alkenyldiaziridinones **73a–c** by photochemical degradation (λ = 254 nm, 20 °C, degassed sample at 10–5 Torr, 150 W Hg lamp) of the corresponding 1-alkenyl-4-*tert*-butyl–1,4-dihydro-5*H*-tetrazol-5-ones. The same authors[88] showed that 1-allyl-4-alkyltetrazol-5-thiones being irradiated ($\lambda \geqslant$ 254 nm, high pressure Hg lamp, 20 °C) in methylcyclohexane-d_{14} and acetonitrile-d_3 furnish the corresponding carbodiimides **74** in 50–80% yields. The synthesis of benzimidazolones **75** in near quantitative yields by photolysis of 1-phenyl–1,4-dihydro-5*H*-tetrazol-5-ones (λ = 254 nm, 150 W Hg lamp, 20ºC) in methanol, acetonitrile or propan-2-ol was also reported.[88] In a follow-up publication,[89] the preparation of two classes of compounds, hexahydronaphthyridines **76** ($\lambda \geqslant$ 320 nm, high pressure Hg lamp, −60 °C, 1.25 h, 95% yield) and iminoaziridines 77 ($\lambda \geqslant$ 305 or 320 nm, high pressure Hg lamp, 30–50% yield) by photolysis of 5-alkylidene-4,5-dihydro–1*H*-tetrazoles in toluene-d_8 was presented. The successful synthesis of 2-phenylamino–1,3-oxazines **78** by photolysis of 5-allyloxy–1-aryltetrazoles carried out under low pressure mercury lamp irradiation (λ = 254 nm) in methanol, acetonitrile and cyclohexane was published (Fig. 9).[75,90]

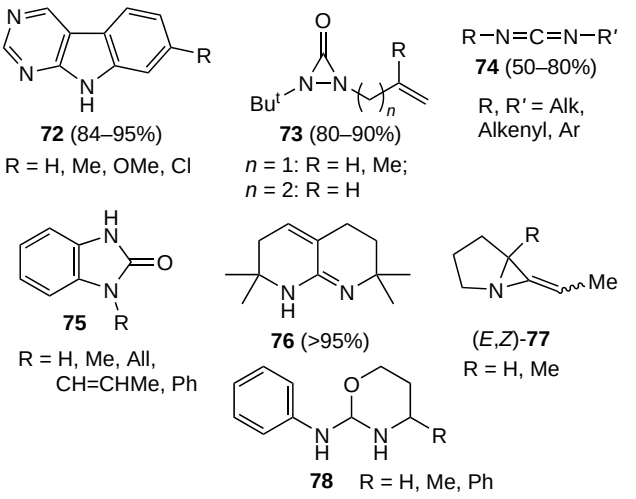
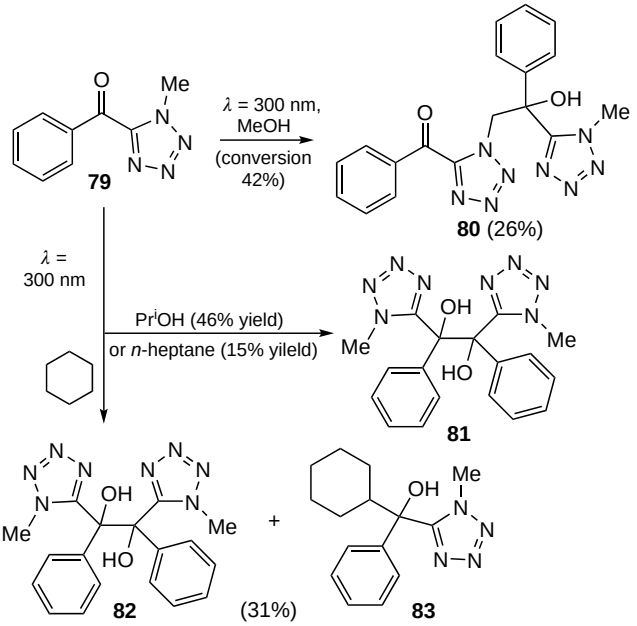


Figure 9. Structures of compounds **72**–**78** obtained by photolysis of appropriate tetrazoles in organic solvents.

According to the authors of the review[75] published in 2010, the photolysis of tetrazoles in organic solvents is one of the most attractive strategies for the synthesis of various products. The selectivity of such photochemical processes can theoretically be controlled and modified towards the formation of desired products by choosing solvents and reaction conditions. At the same time, a common feature of the photochemical degradation of tetrazoles in organic solvents is the release of molecular nitrogen, whereas in cryogenic matrices, many uncontrollable alternative patterns of the tetrazole ring cleavage are realized.

In some cases, the effect of the solvent on photodegradation is particularly pronouced, but it is sometimes difficult to predict the nature of the resulting products. For example, unexpected results were obtained by nanosecond laser photolysis of 5-benzoyl-1-methyltetrazole (**79**). Photolysis in H-donor solvent (propan-2-ol), apolar solvents (heptane, cyclohexane) and finally in aprotic dipolar solvent (acetonitrile) gave various products **80**–**83** (Scheme 16).[91]

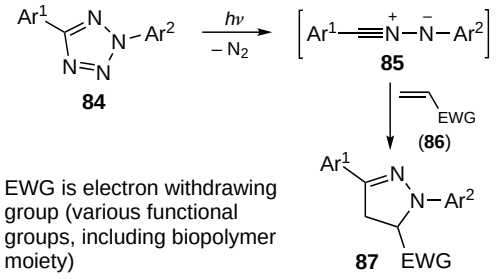
Scheme 16



3.3. ‘Photoclick’ chemistry

The last decade has seen a cardinal revaluation of the role of photodecomposition of tetrazoles as an approach to new or hard-to-reach organic compounds of practical value. New strategies of so-called ‘photoclick’ chemistry are oriented towards the use of active intermediates formed *in situ* during the photoinduced decomposition of the tetrazole ring in reactions with externally introduced compounds, mostly nucleophilic agents. It is worth recalling that pioneering work in this field of tetrazole chemistry was published in the late 1950s by Huisgen *et al.*[47,92,93] (see also anniversary article[41]). The photoclick chemistry strategy has gained prominence in modern science since the award of the 2022 Nobel Prize in Chemistry (see Introduction). The 1,3-dipolar cycloaddition of azides to nitriles leading to the formation of the tetrazole ring, as well as reactions involving active intermediates formed by its decomposition, are among the limited number of transformations that are in line with the concept of bioorthogonal chemistry first formulated by Bertozzi.[94] These transformations include the photo-

Scheme 17



decomposition of 2,5-diaryltetrazoles **84** to give intermediate nitrile imines **85**, dipoles which undergo a cycloaddition with alkenes **86** as dipolarophiles to furnish the corresponding 1,3-diaryl derivatives of 4,5-dihydro–1*H*-pyrazoles **87** (Scheme 17).[95]

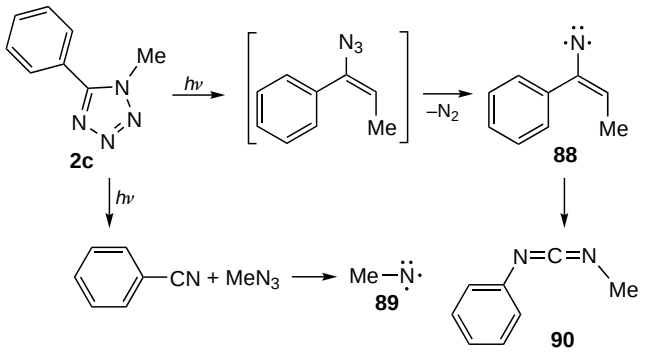
It should be noted that the dynamic development of this concept is directly related to the successes in the elaboration of rational and selective methods for the synthesis of 2,5-diaryl- (**84**) and 2,5-dihetaryltetrazoles as the most promising starting materials required in the 'photoclick' chemistry methodology.[96]

Figure 10 shows examples of 2,5-diaryltetrazoles (**85**–**87**) used in this methodology.[97]

Since 2008, the trend in bioorthogonal chemistry based on photoinduced decomposition of 2,5-diaryltetrazoles and subsequent 1,3-dipolar cycloaddition involving nitrile imines and alkenes has become a priority, along with azide–alkyne and azide–nitrile variants. Noting the advantages and prospects of this strategy of photochemical synthesis, Sinha *et al*.[98] emphasize the need for an in-depth understanding of the mechanisms of chemical, physical and physicochemical processes associated with the photoclick chemistry. For its successful implementation according to the principles of bioorthogonal chemistry, one need information on the chemical structure and reactivity of the above-mentioned active intermediates generated during the photoinduced degradation of the tetrazole ring. The pathways for the formation and further transformation of intermediates such as nitrile imines, imidoyl nitrenes, *etc*. were previously mostly simply postulated,[59] and quantum chemical methods did not always unambiguously determine their most stable form.[99] However, this situation has changed rapidly in the last 15 years. In 2020, a monograph[61] was published on the structure, properties and reactivity of nitrile imines. It systematized and discussed in detail the methods and mechanisms of formation of nitrile imines from 2,5-diaryltetrazoles[84] and cited the works in which the formation of nitrile imines was detected experimentally using spectral methodssuch as UV, IR and NMR spectroscopy.

Wentrup and co-workers[100] experimentally detected the formation of nitrenes **88** and **89** during the photolysis of 1-methyl-5-phenyltetrazole (**2c**) using EPR spectroscopy. In this case, photolysis gave methyl(phenyl)carbodiimide **90** as the final product (Scheme 18).

Scheme 18



The monograph[61] paid considerable attention to the results of the study of the processes of 1,3-dipolar cycloaddition of nitrile imines **9**, generated during the photolysis of 2,5-diaryltetrazoles **84**, to various nucleophilic reagents. Lin and co-workers[101] rationalized the application of photoclick reactions involving inactivated alkenes (dipolarophiles) and nitrile imines (1,3-dipoles), which are products of the photoinduced decomposition of 2,5-diaryltetrazoles **84**, to bioorthogonal chemistry. The 1,3-dipolar cycloaddition of 1,3-dipoles to the corresponding dipolarophiles leads to fluorescent pyrazoline cycloadducts, which can be used to control the process of protein functionalization in cells.[101] For example, a simple alkene tag, homoallylglycine (HAG), was cotranslationally incorporated into the recombinant protein as well as into endogenous, newly synthesized proteins in mammalian cells *via* 1,3-dipolar cycloaddition involving the terminal double bond of HAG and nitrile imines generated by photolysis of 2,5-diaryltetrazoles **84** (Scheme 19).[102]

Based on the findings of the authors of the above-mentioned papers, it can be concluded that tetrazole photochemistry is becoming a useful tool for priority research in modern medicine and biotechnology. For example, such chemical transformations

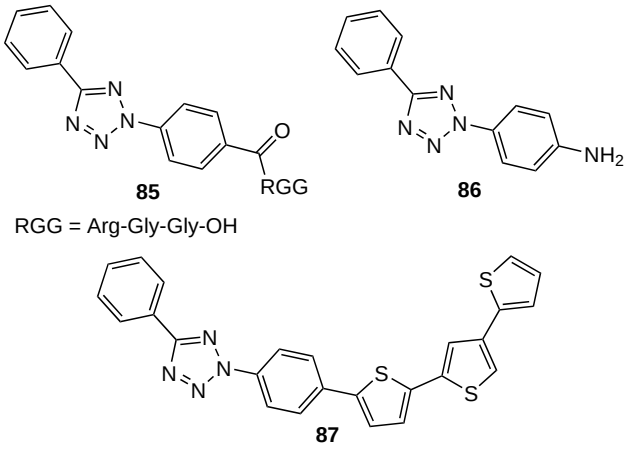
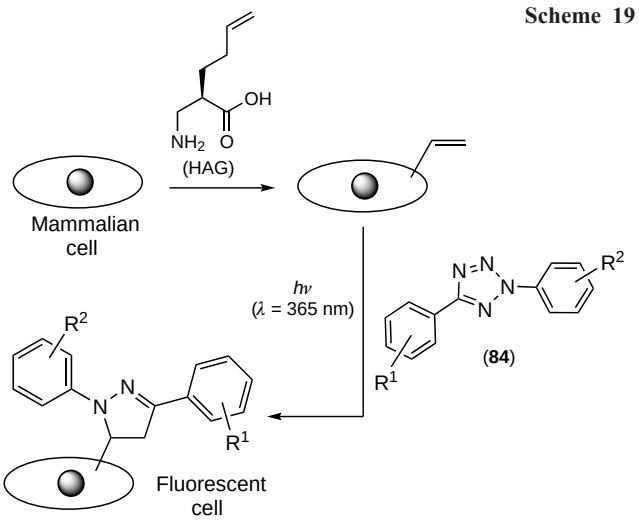
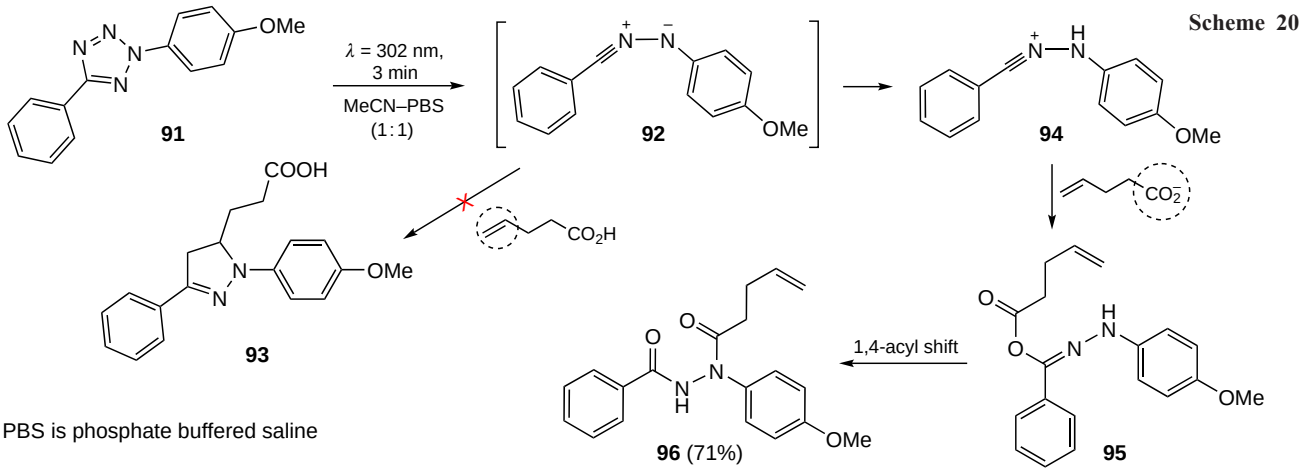


Figure 10. Structures of 2,5-disubstituted tetrazoles **85**–**87** as starting compounds for photodecomposition.

Scheme 19

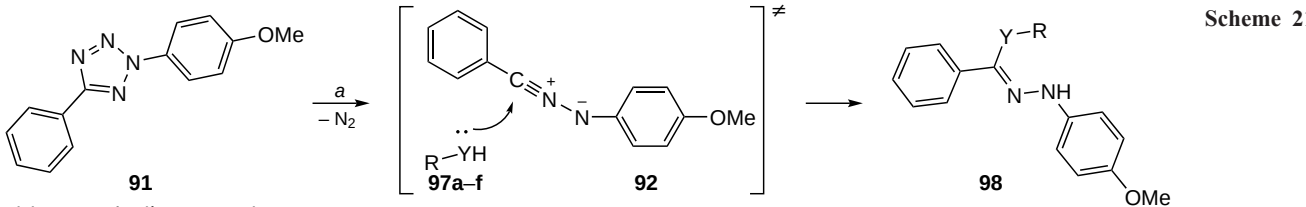


Scheme 20



PBS is phosphate buffered saline

Scheme 21



(*a*) R–YH, *hν* (*λ* = 312 nm), MeCN–H_2O (2:1 (vol.)), rt, 1 h; rt is room temperature

R–YH = (**a**, 34.2%), (**b**, 23.3%),

Bu^nNH_2 (**c**, >15%), glycine (**d**,10%), histidine (**e**, 10%), PhOH (**f**, <5%)

may be in demand for photoradiochemical labelling of monoclonal antibodies (mAbs). The use of photoclick chemistry involving 2,5-diaryltetrazoles **84** in the synthesis of radiopharmaceuticals for positron emission tomography (PET) is reported.[103]

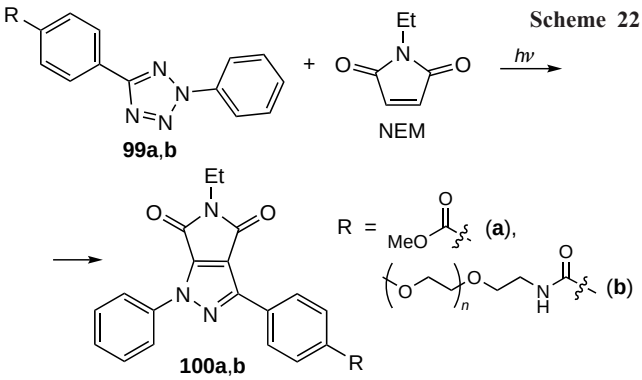
Another interesting area of photoclick chemistry is the possibility of forming self-assembled microlayers (SAMs) in photoinduced microcontact printing.[104]

However, as mentioned above, no universal methodology has yet been developed that would allow these processes to be used with high efficiency in bioorthogonal chemistry. Researchers are sometimes surprised by the structure and dual reactivity of active intermediates, such as nitrile imines **85**.[61] Li *et al.*[105] stated that the photoinduced decomposition of 2,5-diaryltetrazoles **84** in the presence of nucleophilic reagents such as alkenes **86** does not always meet the requirements of bioorthogonal chemistry. For example, the photoinduced decomposition of 2-(4-methoxyphenyl)-5-phenyl-2*H*-tetrazole (**91**) in the presence of pent-4-enoic acid with two reaction centres furnished an unexpected product instead of the cycloaddition product of nitrile imine **92** on the terminal double bond of 3-[1-(4-methoxyphenyl)-3-phenyl-4,5-dihydro-1*H*-pyrazol-5-yl]propanoic acid (**93**). The nucleophilic attack of the carboxylate anion of pent-4-enoic acid on the carbon atom of the nitrile imine moiety of the protonated nitrile imine **94** gives benzhydrazone **95**, which undergoes subsequent rearrangement to afford *N*-(4-methoxyphenyl)-*N*-(pent-4-enoyl)benzhydrazide **96** in 71% yield (Scheme 20).[105]

An important step in the implementation of the photoclick chemistry strategy is a choice of nucleophilic reagents for *in situ* reaction with nitrile imines generated during the photolysis of tetrazoles. In this respect, the publication,[106] which focuses on the reactions of nitrile imine **93**, generated during the photolysis of 2,5-diaryltetrazole **91**, with nucleophiles **97a**–**f** to give hydrazones **98** (Scheme 21), is of particular interest.

A combination of several spectral methods together with quantum chemical calculations is used to identify and determine the structure of nitrile imines. Attempts have also been made to introduce trap compounds into the reaction mixture that are capable of trapping active intermediates.[107] Another very important aspect of the methodology for studying the photoinduced decomposition of tetrazoles, namely, the dependence of the process direction on the wavelength of the excitation radiation, is outlined. The authors draw attention to the need for a quantitative study of the reactivity and mechanism of photoinduced decomposition of tetrazoles. Using a complex wavelength-tunable laser system to initiate photochemical processes, they managed to determine a number of quantitative patterns. This study was exemplified by the photoinduced decomposition in the presence of *N*-ethylmaleimide (NEM) of methyl 4-(2-phenyl-2*H*-tetrazol-5-yl)benzoate (**99a**) and polyethylene glycol (PEG)-based macromolecule **99b** bearing a terminal 2,5-diphenyltetrazole moiety in the chain. As a result,

Scheme 22

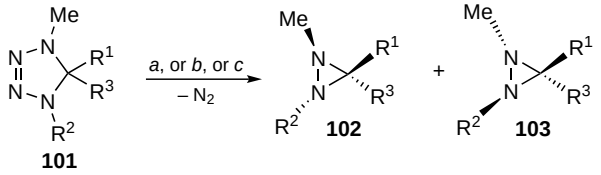


derivatives of 5-ethyldihydropyrrolo[3,4-*c*]pyrazol-4,6(1*H*,5*H*)-dione **100a**,**b** were obtained (Scheme 22).[107,108]

3.4. Photolysis of 4,5-dihydro-1*H*-tetrazole derivatives

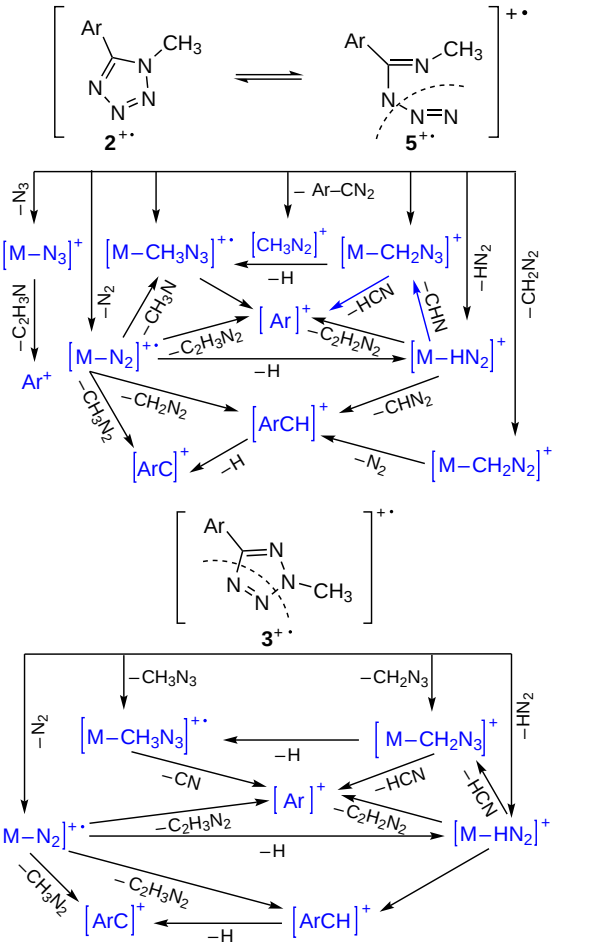
2,5-Diaryltetrazoles **84**, the molecules of which have a π-electron system with a high aromaticity index, are mainly used as models to study the photoinduced decomposition of tetrazoles. As discussed above (see Scheme 17), the photolysis of 2,5-diaryltetrazoles **84** involves the losee of the N_2 molecule to give reactive nitrile imines.[61,98,109] When the aromaticity of the cycle is disturbed, for example in the case of 4,5-dihydro-1*H*-tetrazoles, the transformation pathways can be very different. In the review,[110] concerning the chemistry of 5-alkyl(aryl)- and 5-alkylidene-substituted 4,5-dihydro-1*H*-tetrazoles, attention is drawn to the study[111,112] on the photolysis of such compounds. Based on these data, it can be confidently stated that both photolysis in an organic solvent (CH_2Cl_2) or cryogenic matrix and thermolysis of 1-methyl-4,5-dihydro-1*H*-tetrazoles **101** lead to the elimination of the nitrogen molecule and the formation of two enantiomeric diaziridines **102** and **103**, the ratio of which is governed by the process conditions and the nature of the substituents R^1, R^2 and R^3 (Scheme 23).

Scheme 23



(*a*) *hν*, CH_2Cl_2, rt; (*b*) *hν*, PhH, –155 °C (matrix); (*c*) 100 °C, PhMe, 3 h

Scheme 24



4. Fragmentation of tetrazoles under mass spectrometric conditions

Studies of tetrazoles by mass spectrometry began in the 1960s.[113,114] The relationship between fragmentation products and the structure of molecular ions derived from regioisomeric 1-methyl- (**2**) and 2-methyl-5-aryltetrazoles (**3**) as a result of 'hard' electron impact ionization (70 eV) has been found.[115] Under electron impact, 1-methyl-5-aryltetrazoles 2 generates a molecular ion, which can exist in both cyclic (tetrazole) and open (azidoazomethine) forms due to the ring chain equilibrium.[115] It is the molecular ion $\mathbf{5}^{+\bullet}$ in the form of azidoazomethine, which in this case is the main source of the products formed in the subsequent stages of fragmentation (Scheme 24).

The molecular ion produced through electron impact from 2,5-disubstituted tetrazoles **3** undergoes synchronous cleavage of the N(2)–N(3) and N(4)–C(5) bonds. This process determines both the effects common to the regioisomeric molecular ion $\mathbf{2}^{+\bullet}$, such as the loss of the N_2 molecule, and the peculiarities of its further fragmentation. The recordred mass spectra show a preferential elimination of N_2, HN_3 and HCN species.[115] Both the cited experimental study[115] and the subsequent review article[116] compare and summarize the results of independent studies of thermal decomposition (see Scheme 1) and mass spectrometric fragmentation of regioisomeric tetrazoles (see Scheme 24). The authors of both papers point out certain analogies in the decomposition patterns of tetrazoles initiated by different energy sources.

A characteristic trend in modern mass spectrometric studies of tetrazoles is the use of 'soft' ionization methods (*e.g.* electrospray). This is used, for example, to study the properties of the active pharmaceutical ingredients of modern tetrazole-containing drugs. These are usually multi-atomic systems with bulky substituents in the tetrazole ring. For example, soft ionization mass spectrometry is used to monitor the degradation pathways of the molecules of the active ingredients of sartans — modern drugs for the treatment of arterial hypertension.[117–121] In recent years, the use of these methods has become an essential requirement for the manufacture and storage of medicines under GMP regulations.[119]

In addition to applied studies, soft ionization methods have recently been used to determine the individual molecular ion features of previously inaccessible tetrazole-containing compounds, *e.g.* for NH-unsubstituted 5-vinyltetrazole (**104**) (Fig. 11).[118,120–123] Mass spectra often show molecular peaks of adducts with sodium or potassium, ions which are always present in trace amounts in the mobile phase.[121,123] In the full mass range scan mode in the spectrum of tetrazole compounds, fragment ions generated *via* soft ionization are also detected. For example, the maximum intensity in the spectrum of 3-(5-phenyl-2*H*-tetrazol-2-yl)pyridine **105** in this mode is observed for the ion corresponding to the $[M+H-N_2]^+$ fragment, while the intensity of the protonated molecular ion is only 10%.[96] When recording fragment spectra of tetrazole-containing compounds, a characteristic elimination of the N_2 molecule is observed.[118,120] Other typical fragmentation pathways for relatively small molecules of tetrazole-containing compounds are also observed,

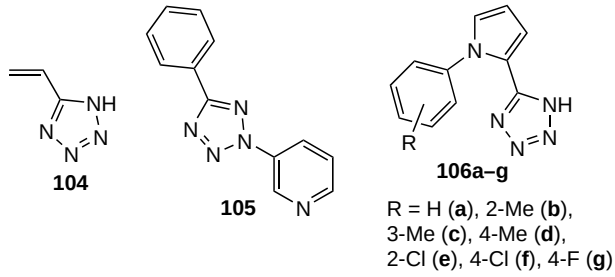


Figure 11. Structures of tetrazoles **104**–**106** studied by electrospray ionization mass spectrometry.

with release of HCN and HN_3 fragments. For example, such a result was observed when studying the fragmentation of 5-(1-aryl-1*H*-pyrrol-2-yl)-1*H*-tetrazoles **106a**–**g** in positive and negative ion modes (see Fig. 11).[118,123]

To conclude this Section, it should be noted that both hard (see Scheme 24) and soft ionization methods show that fragmentation follows the specific patterns related to the structure of tetrazoles. Indirectly, this points to the major contribution of the nitrogen-rich tetrazole ring as a conservative factor determining the degradation pathways and the nature of the resulting species to the mechanism of mass spectral fragmentation during degradation.

5. Radiation destruction of tetrazoles

Studies of the effects of radioactive radiation on tetrazole-containing organic compounds are important not only from a scientific point of view, but also for solving practical problems. One such task is to determine the conditions for the storage and use of tetrazole-containing vital drugs and energetic compositions under increased radiation background in emergency situations and in space, as well as in the treatment and diagnosis of diseases using radiopharmaceuticals. For a number of compounds, it is the tetrazole ring, as the most energetic unit, that is capable of activating destructive processes. Some tetrazole derivatives can be considered as effective radioprotectors, trapping ionizing radiation and protecting more complex biological molecules from its impact.[124]

The published data are mostly devoted to the evaluation of the effect of γ-radiation on the tetrazole ring. It should be noted that the classical systematic works in this field were carried out in the last century and have not been fundamentally revised. Berk and Gisser[125] pioneered the study of the γ-radiolysis of unsubstituted tetrazole **1** in 1973. It was shown that irradiation of tetrazole with doses ranging from 1.1×10^{20} to 4.7×10^{22} eV g^{-1} at 100 °C produced a large number of gaseous products (97% of the total), with this gas mixture consisting of 99% nitrogen. Destruction of the tetrazole ring was also observed at low irradiation dose (1.0×10^{18} eV g^{-1}) and lower temperature with generation of radical species, as confirmed by EPR. The decomposition of the energetic 5-aminotetrazole (**25**) and its derivatives **107**–**111** on exposure to γ-irradiation has been discussed in several publications (Fig. 12).[125–128]

Moorthy and co-workers[126] reported the results of experiments on the radiolysis of tetrazole **25** in aqueous solutions by high-energy electron pulses (7 MeV with pulse durations of 2 μs and 50 ns) obtained using a linear accelerator. The irradiation dose to the samples was 15–25 Gy/pulse. Experiments were carried out at pH 4.5 and 7.5, where 5-aminotetrazole is present in the neutral **25**(N^1*H*) and anionic

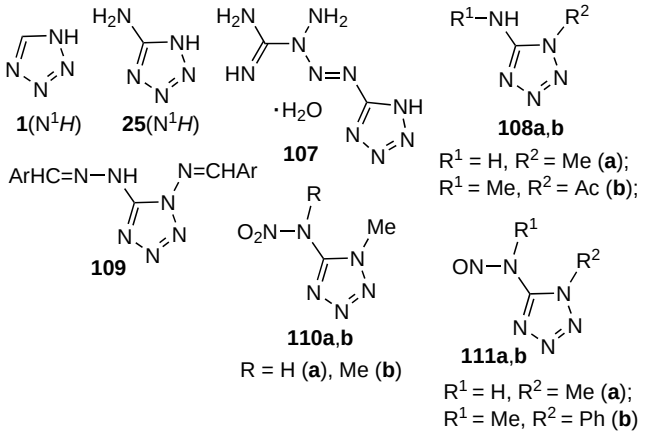
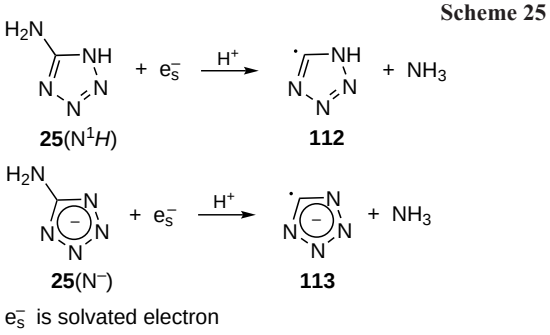


Figure 12. Structures used in radiation degradation studies: tetrazole **1**(N^1*H*), 5-aminotetrazole **25**(N^1*H*), tetrazene **107**, *N*-substituted aminotetrazoles **108a**,**b** and **109**, 1-methyl-5-nitroaminotetrazole **110a**,**b**, 5-nitrosoaminotetrazoles **111a**,**b**.

25(N$^-$) forms. The secondary processes occurring in these solutions were also studied. These findings show that both forms eliminated ammonia to generate radicals **112** and **113**, respectively. It should be noted that the corresponding tetrazolate anion (tetrazolide) was more resistant to irradiation (Scheme 25).

Scheme 25



In the 1970s, Butler and co-workers[127,128] used electron spin resonance to study the γ-irradiation-induced degradation of three series of 5-aminotetrazole derivatives: 1*H*-tetrazol-5-ylamines **25**, *N*-(1-methyl-1*H*-tetrazol-5-yl)nitramines **110** and *N*-(1-methyl-1*H*-tetrazol-5-yl)nitrosamines **111**. Methyl-substituted compounds **110** decompose to give radicals of the $XCH_2^{\bullet}$ и $CH_3^{\bullet}$ types according to Scheme 26. The degradation of nitramines **110** proceeds with the cleavage of the exocyclic N–N bond and the formation of the NO_2 radical (see Scheme 26). The degradation of nitrozoamines **111** is even more complicated.

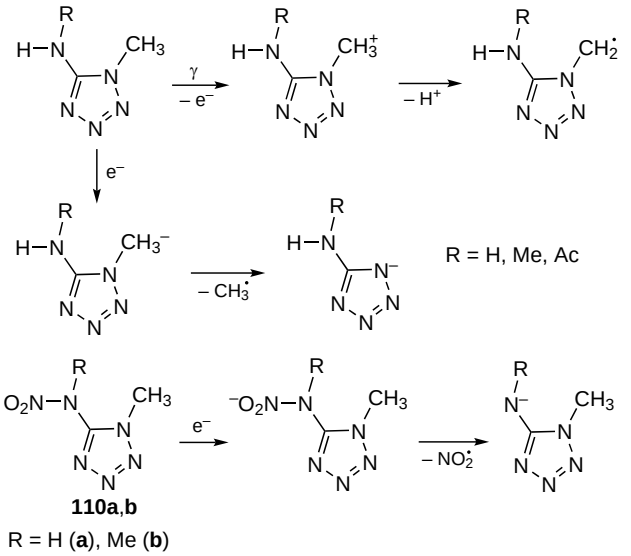
Ryabykh and Kholodkovskaya[129] showed that the radiation chemical yield (*G*) dependence for tetrazene **107** under γ-radiolysis conditions is described by an empirical formula:

$$G = \alpha T^{1.53}$$

where α is a coefficient, *T* is temperature.

The authors of a study[130] also investigated the effect of ionizing radiation (radiation doses of 20–80 kGy,) obtained using a linear electron accelerator, on the physicochemical properties of poly(*N*-methylallyl-5-vinyltetrazole) and compositions based theron. It has been shown that the thermal decomposition character of the polymer exposed to high doses of radiation (up to 80 kGy) changes significantly compared to the non-irradiated sample, which may be related to the

Scheme 26

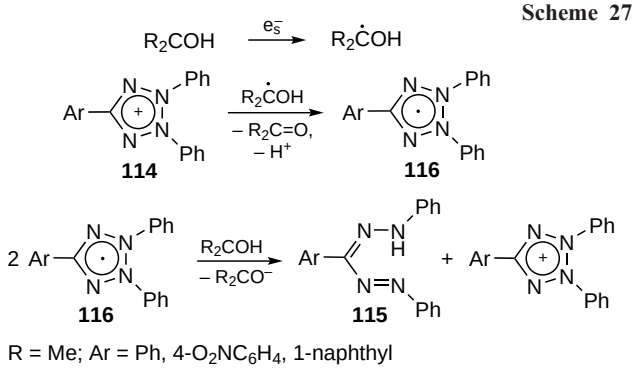


degradation of the copolymer components. The use of ionizing radiation can significantly reduce the curing time of such polymer compositions.

A large number of publication are devoted to the radiolysis of triaryltetrazolium salts **114** in various media (alcoholic, aqueous, aqueous-alcoholic solutions, solid matrices), which is of practical value. Pikaev and Kriminskaya[131] have made a significant contribution to this field of chemistry; their results are summarized in the review. The γ-radiolysis of triaryltetrazolium salts **114** proceeds with high radiochemical yields to furnish coloured formazanes **115**. Such radiolysis is a two-electron process, but the *G* value often exceeds half the number of solvated electrons, indicating that other radicals formed in the reaction medium are also involved in the transformation. For example, according to a plausible scheme confirmed by EPR, in the presence of propan-2-ol, a tetrazolium radical **116** is formed in a first step, which is further converted to formazan **115** *via* disproportionation (Scheme 27).

These processes can be used in the development of promising dosimetric systems, as the coloured products can be easily

Scheme 27



detected by the naked eye or quantified spectrophotometrically.[132,133] The presence of oxidizing and reducing agents has a noticeable effect on this reaction.[134,135]

As mentioned above, an important characteristic of drugs is their resistance to ionizing radiation. This property determines the possibility of using the drug at high radiation levels or methods of sterilizing it using X-rays or β-radiation. Considering that the tetrazole heterocycle is highly sensitive to radiolysis, such studies seem quite relevant. For example, Sarcan *et al*.[136] showed that the active ingredient of the antihypertensive drug losartan (**117**) is resistant to X-ray radiation. The mechanism of degradation of compound **117** in aqueous solutions under γ-radiolysis (doses of 0.5–4 kGy) was explored.[137] The degradation products of the starting compound, including the unsubstituted tetrazole **1**(N^1*H*), were determined by liquid chromatography-mass spectrometry. It was also found that the process is initially induced by the hydroxyl radical generated from water (Scheme 28).

Several papers (see *e.g.*,[138]) are devoted to the evaluation of the stability of the active ingredient of the semisynthetic antibiotic cefazolin (Kefzol, **118**) in aqueous solutions and in the solid phase (Fig. 13). The degradation of compound **118** under electron pulse radiolysis conditions (average doses of 3–5 Gy per 2–3 ns pulse) in aqueous medium is also activated by hydroxyl radical. However, the composition of the degradation products of this compound could not be determined.

The sodium salt **118** in the solid phase has proven to be very resistant to the action of γ-radiation.[139] Under irradiation using a linear electron accelerator up to doses of 25 kGy, no significant degradation of this compound in the solid phase was observed either, making it safe to sterilize this drug by irradiation.[140]

6. Conclusion

The processes of tetrazole decomposition initiated by thermal heating, electromagnetic or radiation irradiation and ionization under mass spectrometric conditions have now become the focus of attention of a wide range of researchers. The chemical energy stored in the tetrazole ring is released and gaseous products, mainly molecular nitrogen, are eliminated. This gives rise to highly reactive intermediates, such as the nitrile imines

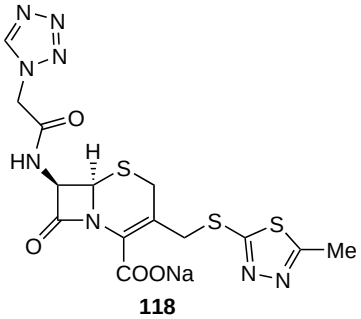
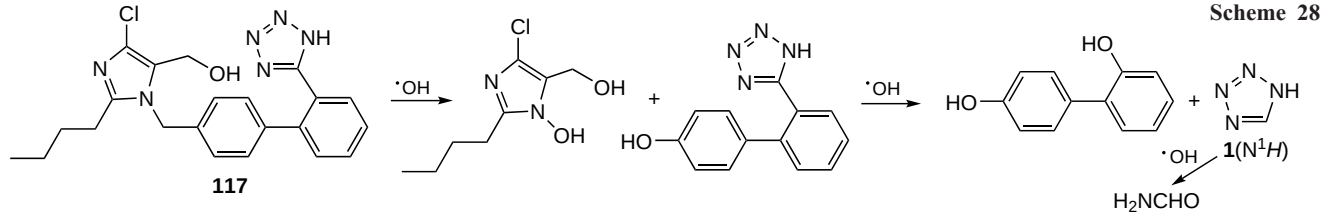


Figure 13. Structure of cefazolin (Kefsol).

Scheme 28



discovered by R.Huisgen, which can react rapidly and selectively with dipolarophiles *via* the 1,3-dipolar cycloaddition pathway, and also react with nucleophiles. The intensive development of this field of research is associated with the emergence of new techniques, including equipment for flash vacuum pyrolysis. Due to the pulsed temperature (up to 500–900 °C) and the use of vacuum technology, FVP makes it possible to control the formation of tetrazole decomposition products using spectral methods. The decomposition of tetrazoles is one of the components of the scientific concept of click chemistry and bioorthogonal reactions, the authors of which were awarded the Nobel Prize in Chemistry in 2022. This proves the relevance of the topic in relation to the formation of various tetrazole-derived products and their further transformations. At the same time, its development will largely depend on progress in the development of methods for the preparative isolation of target compounds, as well as for the performance and control of bioorthogonal reactions occurring in the cell.

The authors of this review hope that it will be of interest to a wide scientific audience.

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7. List of abbreviations and designations

API — active pharmaceutical ingredient,
BTATz — 3,6-bis(1*H*–1,2,3,4-tetrazol-5-ylimino)–1,2,4,5-tetrazine,
DFT — density functional theory,
DSC — differential scanning calorimetry,
e_s — solvated electron,
EWG — electron-withdrawing group,
FTIR — Fourier-transform infrared spectroscopy,
FVP — flash vacuum pyrolysis,
G — radiation chemical yield,
ΔH_f^o — enthalpy of formation,
HAG — homoallylglycine,
mAbs — monoclonal antibodies,
MW — microwave activation,
NEM — *N*-ethylmaleimide,
PBS — phosphate buffered saline,
PEG — polyethylene glycol,
PET — positron emission tomography,
rt — room temperature,
SAM — self-assembled microlayers,
SMD — solvation model,
TCB — trichlorobenzene,
TGA — thermogravimetric analysis.

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