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Highly electophilic, *gem*- and *spiro*-activated trichloromethylnitrocyclopropanes: synthesis and structure

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Abstract

New highly electrophilic gem- and spiroactivated trichloromethylnitrocyclopropanes were obtained by the Michael Initiated Ring Closure (MIRC) reaction of 1-bromo-1-nitro-3,3,3-trichloropropene with linear and cyclic CH-acids catalyzed by bases.

Conditions for obtaining the target cyclopropanes were optimized. The process is characterized by high diastereoselectivity and allows obtaining cyclopropanes with the trans-configuration of NO_2 and CCl_3 groups. Monocyclic (based on malonic acid dinitrile, methyl cyanoacetate, ethyl cyanoacetate, benzoylacetonitrile), spirocarbo- (based on 1,3-indanedione) and spiroheterocyclic (based on Meldrum's acid, 3-methyl-1-phenyl-5-pyrazolone, dimethylbarbituric acid) cyclopropane structures were isolated and characterized.

Keywords

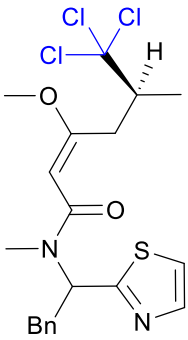
Cyclopropanes; nitrocyclopropanes; bromonitropropene; trichloromethyl group; CH-acids; X-ray

Introduction

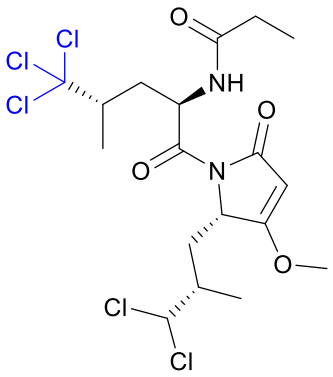
Trichloromethyl-containing compounds are widely used in the organic synthesis of practically significant substances [1, 2]. Based on them, methods have been developed for the synthesis of inaccessible 5-aminoisoxazoles [3], α- and γ-heterosubstituted unsaturated carboxylic acids [4]. The trichloromethyl group is a convenient precursor of the carboxylic function, which determines their use in synthesis of α-aminoacids [5]. A number of natural trichloromethyl-containing compounds are metabolites of symbionts of marine sponges – cyanobacteria [6-8] – and have biologically active properties. Thus, barbamide exhibits molluscicidal activity [7], and syntocamide A is active against prostate cancers [8].

Derivatives of strained and unique in structure and properties [9, 10] cyclopropane are of interest for entering into various transformations along the path of ring opening or

expanding [11-13]. Thus, known trichloromethyl-containing cyclopropanes can serve as precursors for inaccessible halogenated β,γ- and γ,δ-unsaturated esters [14, 15].



Barbamide



Syntocamide A

Nitrocyclopropanes are known as highly electrophilic substrates can form a carbanion stabilized by a nitro group upon breaking the C–C bond [16, 17]. Substituted nitrocyclopropanes in reactions with various nucleophiles form linear precursors for the synthesis of γ-substituted α-aminobutyric acids [18, 19], cyclic nitropyrrolines [20] and isoxazoline N-oxides [18]. Nitrocyclopropane fragment is a part of the hormaomycin antibiotic [21], and also acts as a precursor for the synthesis of aminocyclopropane [22] moiety, which is a component of some drugs, such as ciprofloxacin [23] and belactosin A [24]. Thus, the construction of cyclopropanes containing vicinal nitro- and trichloromethyl groups seems attractive for both theoretical chemistry and synthesis of 2-aminocyclopropanecarboxylic acids, which representatives have biologically active properties against kynurenine-3-monooxygenase [25] and GABA receptors [26].

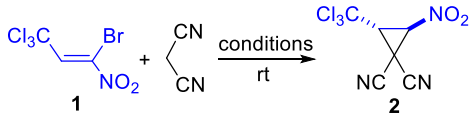
It is worth noting that vicinal trichloromethylnitrocyclopropanes have not been described before. And their analogues, *vic*-trifluoromethylnitrocyclopropanes, were obtained by treating 2-nitrocyclopropanecarboxylic acid with sulfur tetrafluoride [27, 28], Kori-Tchaikovsky reaction with nitroalkenes [29], as well as through the tandem reaction of trifluoromethyl-containing alkenes with derivatives of nitro- [30] and bromonitromethane [31, 32].

At the same time, one of the methods of synthesis of vicinally substituted nitrocyclopropanes is the Michael Initiated Ring Closure (MIRC) reaction of *gem*-halonitroalkenes and CH-acids [33, 34]. Thus, 2-nitrocyclopropanecarboxylates were obtained based on the tandem reactions of cyclic CH-acids with alkyl-3-bromo-3-nitroacrylates [35]. Despite the structural proximity and high activity of 1-bromo-1-nitro-3,3,3-trichloropropene **1** [36] in reactions with nucleophiles, including those following the formation of cyclic products in tandem transformations [37-40], methods for obtaining cyclopropane structures based on it are not known. In this way, it seemed desirable to synthesize vicinal trichloromethylnitrocyclopropanes based on the well-known 1-bromo-1-nitro-3,3,3-trichloropropene **1** [33].

Results and Discussion

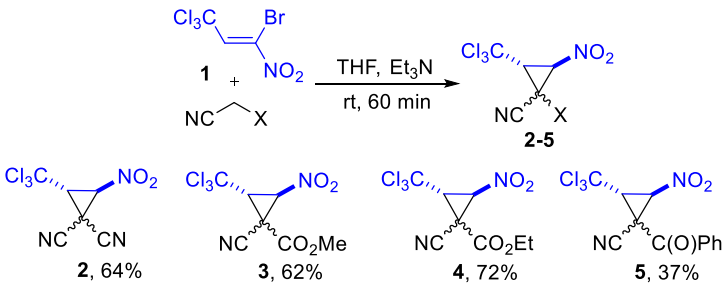
It turned out that the synthesis of the target trichloromethylnitrocyclopropane **2** based on the reaction of 1-bromo-1-nitro-3,3,3-trichloropropene **1** with malononitrile under conditions similar to those described earlier [35] results in its formation in 18% of yield (Table 1, method A). Optimization of the process by using various bases and solvents showed that the best yield of cyclopropane **2** (64%) was obtained in a tetrahydrofuran (THF) solution in the presence of triethylamine (Table 1, method E).

Table 1: Reaction of compound **1** with malononitrile leading to cyclopropane **2** under various conditions.



Method	Reaction conditions			Yield of **2**, %
	Solvent	Base	Time, min	
A	MeOH	AcOK	15	18
B	MeOH	MeONa	10	oligomers
C	THF	AcOK	120	20
D	THF	DBU	60	oligomers
E	THF	Et_3N	60	64

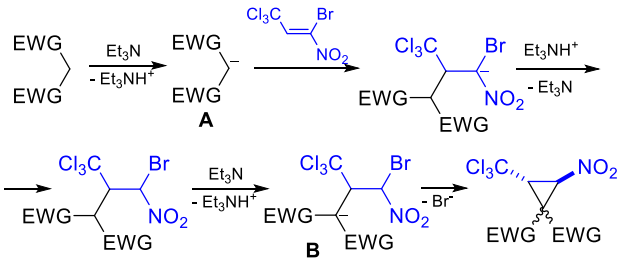
The use of method E in the reaction of 1-bromo-1-nitro-3,3,3-trichloropropene **1** with methyl cyanoacetate, ethyl cyanoacetate or benzoylacetonitrile makes it possible to obtain cyclopropane **3**-**5** in the yields up to 72% (Scheme 1).



Scheme 1: The synthesis of monocyclic trichloromethylnitrocyclopropanes **2**-**5**.

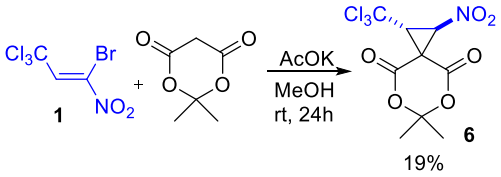
The proposed mechanism for this transformation is depicted in Scheme 2. The Michael addition of the CH-acid anion to the bromonitroalkene afford the intermediate anion **A**, followed by tautomerization and formation of the anion **B**, which undergoes

intramolecular nucleophilic substitution of the bromide along the C-alkylation pathway [33-35] (Scheme 2).



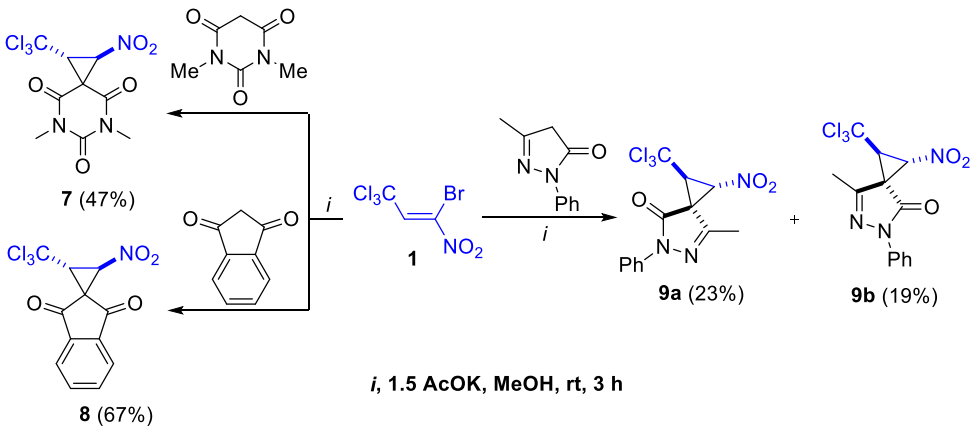
Scheme 2: The proposed mechanism of trichloromethylnitrocyclopropanes formation.

The synthesis of spiro-fused trichloromethylnitrocyclopropane **6** based on the reaction of *gem*-bromonitroalkene **1** and Meldrum's acid under the conditions of method D is completed by tarring the reaction mixture. At the same time, using the conditions of method A (bromonitroalkene : CH-acid : base = 1 : 1 : 1.5 ratio) for 24 hours makes it possible to isolate the target cyclopropane **6** with a yield of 19% (Scheme 3).



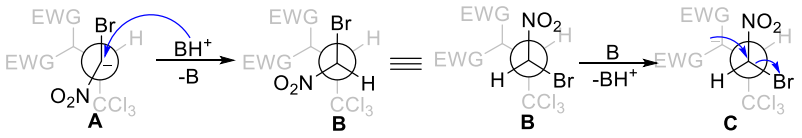
Scheme 3: The synthesis of spiro-fused trichloromethylnitrocyclopropane **6**.

Application of method A and the 1 : 1 : 1.5 ratio (bromonitroalkene : CH-acid : base) according to the literature method [34] for the synthesis of spiro-fused *vic*-trichloromethylnitrocyclopropanes **7**-**9** based on other cyclic CH-acids (dimethylbarbituric acid, 1,3-indandione, 3-methyl-1-phenyl-5-pyrazolone) in this reaction turned out to be more successful (yields 42-67%, Scheme 4).



Scheme 4: The synthesis of spiro-fused trichloromethylnitrocyclopropanes **7**-**9**.

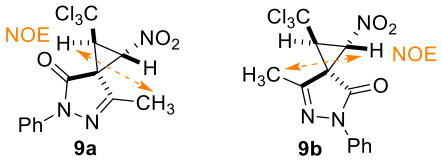
Cyclopropanes **2**-**8** are formed as single diastereomers. Compound **9** is mixtures of diastereomers (1.3 : 1 dr), according to the ^{1}H NMR spectrum. The vicinal spin-spin coupling constants of C^{1}H-C^{2}H protons of the cyclopropane ring ($^{3}J_{H(1)H(2)}$ = 5.7-7.5 Hz) indicate their transoid arrangement, which agrees with the literature data for structurally similar compounds [34, 35, 41]. This makes it possible to assign *rel*-1*S*,2*R* configurations to stereocenters.



Scheme 5: Proposed mechanism of transformation of intermediate **A** into intermediate **C** in Newman projections.

The pyrazolone-conjugated trichloromethyl-containing nitrocyclopropane **9** is formed as a mixture of two diastereomers **9a** and **9b** due to the axial chirality of this molecule. The mixture was easily separated by silica gel column chromatography. Each of the isomers is also characterized by the *trans*-configuration of the nitro- and trichloromethyl groups in the cyclopropane ring ($^{3}J_{H(1)H(2)}$ = 6.6-6.8 Hz). According to ^{1}H-^{1}H NOESY

spectroscopy data, NOE correlation of C^1H (δ_H = 4.44 ppm) / CH_3 (pyrazolone) (δ_H = 2.15 ppm) protons is observed in major diastereomer **9a**, and C^2H (δ_H = 5.54 ppm) / CH_3 (pyrazolone) (δ_H = 2.15 ppm) in the minor isomer **9b** (scheme 6). Thus, the relative configurations of the stereocenters in these molecules can be defined as *rel*-1*S*,2*R*,3*S* (**9a**) and *rel*-1*S*,2*R*,3*R* (**9b**).



Scheme 6: The main NOE correlations in **9a**, **9b**.

X-ray diffraction analysis data for compounds **2**, **3**, **9a**, **9b** convincingly confirm the accepted structures, the position of cyclopropane protons, and the relative configurations of asymmetric atoms (Figure 1-4). It should be noted that the lengths of the C^1-C^2 (1.470(2)-1.491(4) Å) and C^2-NO_2 (1.472(4)-1.486(2) Å) bonds according to X-ray diffraction analysis in the molecules of nitrocyclopropanes **2**, **3**, **9a**, **9b** turn out to be close to those in the molecules of nitrospirocyclopropancarboxylates (C^1-C^2 (1.464(1)-1.474(2) Å), C^2-NO_2 (1.482(1)-1.485(1) Å) [35] and fused nitrocyclopropane (C^1-C^2 1.4903(19) Å and C^2-NO_2 1.4811(17) Å) [42].

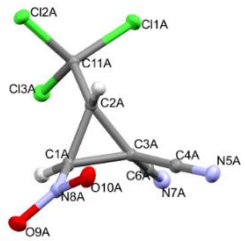


Figure 1: Geometry of molecules **2** in crystal.

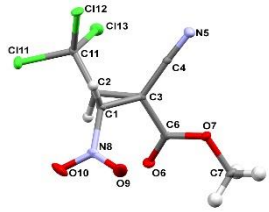


Figure 2: Geometry of molecules **3** in crystal.

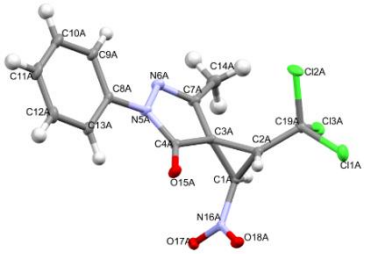


Figure 3: Geometry of molecules **9a** in crystal.

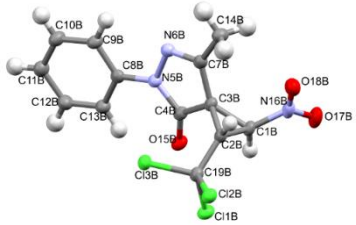


Figure 4: Geometry of molecules **9b** in crystal.

In crystal 2, the polar non-centrosymmetric space group contains two independent molecules with the same configuration of atoms C^1 – *S*, C^2 – *R*. That is, compound **2** is obtained as a racemic diastereomeric pair *rel*(*S*,*R*). Centrosymmetric crystals **9a** and **9b** are diastereomers and crystallize as a true racemate. The configuration of the chiral atoms C^1 and C^2 in the molecules is the same as in molecules **2**, and the difference is the configuration of atom C^3. In crystal **9a**, the enatiomeric pair *S,R,S*/*R,S,R* is realized, and in crystal **9b** – *S,R,R*/*R,S,S*.

The main geometric parameters (bond lengths and valence angles) and the conformation of independent molecules in crystals **2**, **3**, **9a** and **9b** coincide within the experimental errors, so Figures 1-4 show the geometry of one of the independent

molecules. Note that crystals **2**, **3**, **9a** and **9b** have a relatively high density (d_{calc}/g cm^{-3} 1.739, 1.748, 1.595 and 1.567) for crystals that do not contain heavy atoms.

In the absence of hydrogen bonds in the crystals **2**, **3**, **9a** and **9b**, multiple specific interactions of the types such as lone (electron) pair – the π-system of the nitro group, and bonds of the Cl…O, Cl…N, C-H…X (X = Cl, O, N) are realized, which are shown in Figures S47-S57. The energy of such interactions can be comparable with the energy of “classical” hydrogen bonds [43].

Conclusion

In summary, we have proposed a diastereoselective method for the synthesis of new *rel*-1*S*,2*R* *vic*-trichloromethylnitrocyclopropanes by reacting of 1-bromo-1-nitro-3,3,3-trichloropropene with a number of linear (malononitrile, benzoylacetonitrile), carbocyclic (1,3-indandione) and heterocyclic (Meldrum’s acid, 3-methyl-1-phenyl-5-pyrazolone, dimethylbarbituric acid) CH-acids in mild conditions. The reaction is carried out either in tetrahydrofuran in the presence of triethylamine, or in a methanol solution in the presence of fused potassium acetate. The structures of the isolated individual products were characterized by ^{1}H, ^{13}C NMR, IR spectroscopy, mass spectrometry and confirmed by the results of single crystal X-ray diffraction analysis.

Experimental

Physicochemical studies were performed using the equipment of the Center for Collective Use "Physicochemical methods for the study of nitro compounds, coordination, biologically active substances and nanostructured materials" of the Interdisciplinary Resource Center for collective use "Modern physicochemical methods

for the formation and study of materials for the needs of industry, science and education" Herzen State Pedagogical University of Russia.

Some spectral studies were performed at the Center for Magnetic Resonance, the Center for Chemical Analysis and Materials Research, and the Research Center for X-ray Diffraction Studies of Saint Petersburg State University, Saint Petersburg, Russia. The X-ray diffraction study was performed at the Department of X-ray Diffraction Research of the Multiple-Access Center on the basis of the Laboratory of Diffraction Research Methods of the A. E. Arbuzov Institute of Organic and Physical Chemistry, the Kazan Scientific Center of the Russian Academy of Sciences.

The ^{1}H, $^{13}C\{^{1}H\}$, $^{1}H–^{1}H$ dqfCOSY, $^{1}H–^{1}H$ NOESY, $^{1}H–^{13}C$ HMQC, $^{1}H–^{13}C$ HMBC NMR spectra were recorded on a Jeol ECX400A spectrometer operating at 399.78 MHz (^{1}H), 100.53 MHz (^{13}C) in $CDCl_3$ using residual signals of the nondeuterated solvent (δH 7.26, δC 77.16) as the references. The vibrational spectra were measured on a Shimadzu IR-Prestige-21 Fourier-transform IR spectrometer in $CHCl_3$ solutions (c = 20 mg/mL) and KBr pellets over 400–4000 cm^{-1} range (resolution was 2 cm^{-1}). Mass spectra were obtained using a MaXis mass spectrometer (Bruker Daltonik GmbH) equipped with an electrospray ionization source (4.5 eV) and a quadrupole time-of-flight analyzer (ESI-QTOF) in the positive ions detection mode, with methanol (0.1% FA [formic acid]) as solvent.

Isolation of individual diastereomers was carried out by column chromatography on silica gel MN Kieselgel 60 Mecherey-Negel 140-270, eluent was a mixture of solvents hexane–EtOAc, 3:1. The reaction progress and purity of the obtained compounds were controlled by TLC on Silufol UV-254 plates with 3:1 hexane–EtOAc mobile phase. Visualization under UV light (λ 254 nm).

Reagents were obtained from commercial supplier and used without further purification unless otherwise noted.

X-Ray Crystallography. X-ray diffraction analysis of the structure **2**, **3**, **9a**, **9b** was performed on a Rigaku 'SuperNova, Single source at offset/far, HyPix3000' automatic four-circle diffractometer with a Hybrid Pixel Array two-dimensional detector and a micro-focus sealed X-ray tube (λ [Cu Kα] = 1.54184 Å) at cooling conditions (100 K). Data collection and processing of diffraction data were performed using an CrysAlisPro 1.171.41.103a (Rigaku OD, 2021) software package. All of the structures were solved by the direct method using the SHELXT program [44] and refined by the full-matrix least squares method over F^2 using the SHELXL program [45]. All of the calculations were performed in the WinGX software package [45], the calculation of the geometry of the molecules and the intermolecular interactions in the crystals was carried out using the PLATON program [46] and the drawings of the molecules were performed using the MERCURY [47] programs. The non-hydrogen atoms were refined in the anisotropic approximation. The hydrogen atoms were placed in geometrically calculated positions and included in the refinement in the “riding” model.

Crystal **2**, $C_6H_2Cl_3N_3O_2$, M = 254.46, monoclinic, space group $P2_1$, at 100.4(5) K: a = 11.6233(2), b = 6.39530(10), c = 13.1586(2) Å, β = 96.5730(10), V = 971.71(3) $Å^3$, Z = 4 (two independent molecules), D_{calc} = 1.739 $g \cdot cm^{-3}$, μ(MoKα) 8.393 mm^{-1}, F(000) = 504, 9545 reflections measured (6.762° ≤ 2Θ ≤ 139.896°), 3676 unique (R_{int}° = 0.0391, R_{sigma}° = 0.0425) which were used in all calculations. Flack parameter 0.299(14), crystal is a racemic twin, and final refinement of this structure was completed as racemic twin. The final R_1 was 0.0260 (I > 2σ(I)) and wR_2 was 0.0655 (all data).

Crystal **3**, $C_7H_5Cl_3N_2O_4$, M = 287.48, monoclinic, space group $P2_1/n$, at 100.00(10) K: a = 8.3468(3), b = 6.1819(2), c = 21.2056(6) Å, α = 90, β = 93.234(3), γ = 90°, V = 1092.45(6) $Å^3$, Z = 4, D_{calc} = 1.748 $g \cdot cm^{-3}$, μ(MoKα) 7.658 mm^{-1}, F(000) = 576.0, 3763 reflections measured (8.352° ≤ 2Θ ≤ 139.956°), 2056 unique (R_{int} = 0.0223, R_{sigma} =

0.0260) which were used in all calculations. The final R_1 was 0.0321 ($I > 2\sigma(I)$) and wR_2 was 0.0844 (all data).

Crystal **9a**, $C_{13}H_{10}Cl_3N_3O_3$, M = 362.60, monoclinic, space group *P2₁/n*, at 100(2) K: a = 11.4834(6), b = 11.0564(5), c = 23.7834(10) Å, α = 90, β = 91.057(4), γ = 90°, V = 3019.1(2) Å^3, Z = 8 (two independent molecules), D_{calc} = 1.595 g·cm^{-3}, μ(MoKα) 5.651 mm^{-1}, F(000) = 1485.2, 21310 reflections measured (7.44° ≤ 2Θ ≤ 139.94°), 5708 unique (R_{int}° = 0.0984, R_{sigma}° = 0.0556) which were used in all calculations. The final R_1 was 0.0696 (I>=2u(I)) and wR_2 was 0.2072 (all data).

Crystal **9b**, $C_{13}H_{10}Cl_3N_3O_3$, M = 362.59, monoclinic, space group *P2₁/n*, at 100(2) K: a = 16.6097(2), b = 9.76570(10), c = 19.4325(2) Å, α = 90, β = 102.7570(10), γ = 90°, V = 3074.25(6) Å^3, Z = 8 (two independent molecules), D_{calc} = 1.567 g·cm^{-3}, μ(MoKα) 5.550 mm^{-1}, F(000) = 1472.0, 25819 reflections measured (6.346° ≤ 2Θ ≤ 140°), 5821 unique (R_{int}° = 0.0567, R_{sigma}° = 0.0359) which were used in all calculations. The final R_1 was 0.0378 ($I > 2\sigma(I)$) and wR_2 was 0.0979 (all data).

1-Bromo-1-nitro-3,3,3-trichloropropene **1** was obtained by the literature method [36].

The crystallographic data of the structure are deposited in the Cambridge Crystal Structure Data Bank (CCDC **2**: 2237758; CCDC **3**: 2481941; CCDC **9a**: 2450586; CCDC 9b: 2450587). Statistics on the collection of X-ray diffraction data and refinement of the structure are shown in Table S1 in Supporting Information File 1.

Supporting Information

Supporting Information File 1 General synthetic procedures, characterization data and copies of IR spectra, ^{1}H, ^{13}C{^{1}H}, ^{1}H–^{1}H dqfCOSY, ^{1}H–^{1}H NOESY, ^{1}H–^{13}C HMQC, ^{1}H–

^{13}C HMBC NMR spectra of all synthesized compounds, and the crystallographic data for compounds **2**, **3**, **9a**, and **9b**.

Acknowledgements

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The study was carried out at the Center for Magnetic Resonance, Center for Chemical Analysis and Materials Research, and Research Center for X-ray Diffraction Studies of the Science Park of Saint Petersburg State University (Saint Petersburg, Russia) within the framework of project 125021702335-5

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