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SYNTHESIS AND STRUCTURE OF TRIS(5-PHENYLTETRAZOL-1-YL)METHANE

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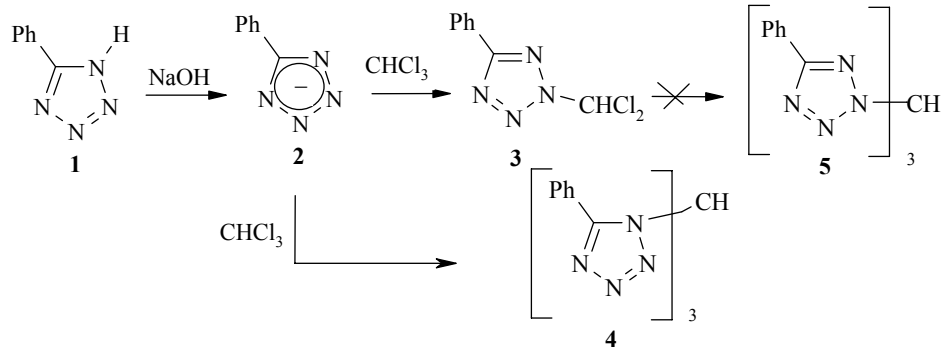
*The interaction of 5-phenyltetrazolate anion with chloroform in strongly alkaline medium leads to the formation of tris(5-phenyltetrazol-1-yl)methane and 2-dichloromethyl-5-phenyltetrazole. The structures of tris(5-phenyltetrazol-1-yl)-methane and of its isomer tris(5-phenyltetrazol-2-yl)methane have been investigated by X-ray structural analysis and theoretical calculations carried out on the B3LYP/6-31G** basis.*

Keywords: polynuclear heterocycles, tetrazole, X-ray structural analysis, theoretical calculations by the DFT method.

Polynuclear tetrazoles are considered as efficient ligands for binding metal ions [1, 2], and also as potentially biologically active substances [3]. Information on polytetrazolylmethanes is limited in comparison with other poly-N-azolylalkanes. We previously reported the synthesis of one such compound [4]. In the present work we have investigated the reaction of 5-phenyltetrazolate anion with chloroform under various conditions (aqueous NaOH solutions of various concentration, in the presence or absence of a phase-transfer catalyst) and also the structures of the compounds obtained.



In alkaline medium 5-phenyltetrazole **1** dissociates with the formation of the corresponding anion **2**, the reaction of which with chloroform leads to 2-dichloromethyl-5phenyltetrazole (**3**) and tris(5-phenyltetrazol-1-yl)methane (**4**). The presence of tris(5-phenyltetrazol-2-yl)methane (**5**) in the reaction products was not

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observed. Probably in the first step anion **2** reacts with dichlorocarbene, generated from chloroform in strongly alkaline medium, with the formation of a mixture of two regioisomers, 1- and 2-dichloromethyl-5-phenyltetrazoles. 1-Dichloromethyl-5-phenyltetrazole is then converted into polynuclear tetrazole **4** by means of a series of sequential reactions, in the course of which all the chlorine atoms are replaced by tetrazolyl fragments. The corresponding 2-isomer **3** proved to be less reactive under analogous conditions. Apart from the above-mentioned, the absence of tristetrazol-2-ylmethane **5** may also be explained by its low stability.

The structures of compounds **3** and **4** were confirmed by data of ^{13}C and ^{1}H NMR spectroscopy and also by mass spectra. The structure of tris(5-phenyltetrazol-1-yl)methane **4** was investigated by X-ray structural analysis and with the aid of quantum chemical-calculations.

Previously in [4] we mistakenly assumed that the interaction of anion **2** with chloroform in a chloroform–aqueous sodium hydroxide solution system leads to the formation of compounds **5** and **3**. The results obtained in the present investigation indicate that in [4] the structure of the polynuclear tetrazole was established incorrectly. Compound **4**, formed in this reaction, is the product of the sequential substitution of three chlorine atoms in the chloroform molecule by tetrazole fragments.

To increase the yield of polynuclear compound **4** by changing the reaction conditions for this process was unsuccessful. Increasing the sodium hydroxide concentration to 40% increases the yield of 2-dichloro-methyltetrazole **5** somewhat (up to 10%), while the formation of tristetrazole **4** was not recorded at all. A similar situation is also observed on adding the phase transfer catalyst, tetrabutyl ammonium bromide, to the reaction medium. In the latter case only compound **3** is also formed in 15% yield. The results enumerated above may be explained both by interphase effects and by hydrolysis processes of the intermediate and final compounds **3**, **4** to the initial tetrazolate anion **2**. In the latter case it is assumed that under these reaction conditions the stability of the polynuclear 1H-substrates is greater than the stability of the 2H- isomers.

According to X-ray structural analysis data compound **4** in the condensed phase has a molecular structure corresponding to the symmetry group C_3, in which all three phenyltetrazole fragments are identical (Fig. 1, Table 1). The phenyl substituents are oriented in one direction which enables the separating out of two spatially distinct portions, polar and nonpolar, for this molecule. The hydrogen atom of the methine group is disposed in a cavity surrounded by benzene rings. It may be expected that on retaining the molecular structure the reactivity of this hydrogen atom will be small.

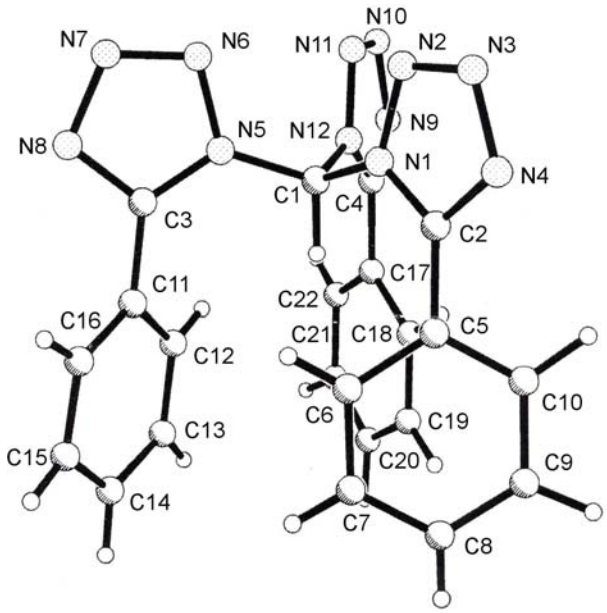

Fig. 1. Geometry of compound **4** determined by X-ray structural analysis.

TABLE 1. Sample Bond Lengths (*d*), Valence and Dihedral Angles (ω) for Compound **4**, Determined by X-ray Structural Analysis

Bond	*d*, Å	Angle	ω, deg.	Angle	ω, deg.
$C_{(1)}$–$N_{(1)}$	1.450(5)	$C_{(1)}$–$N_{(1)}$–$N_{(2)}$	120.9(4)	$H_{(1)}$–$C_{(1)}$–$N_{(1)}$–$N_{(2)}$	177.1
$C_{(1)}$–$N_{(5)}$	1.438(5)	$C_{(1)}$–$N_{(5)}$–$N_{(6)}$	121.3(4)	$H_{(1)}$–$C_{(1)}$–$N_{(5)}$–$N_{(6)}$	170.4
$C_{(1)}$–$N_{(12)}$	1.437(5)	$C_{(1)}$–$N_{(12)}$–$N_{(11)}$	120.5(4)	$H_{(1)}$–$C_{(1)}$–$N_{(12)}$–$N_{(11)}$	178.9
$N_{(1)}$–$N_{(2)}$	1.370(5)	$C_{(1)}$–$N_{(12)}$–$N_{(11)}$–$N_{(10)}$	-176.5	$H_{(1)}$–$C_{(1)}$–$N_{(1)}$–$C_{(2)}$	4.3
$N_{(5)}$–$N_{(6)}$	1.372(5)	$C_{(1)}$–$N_{(1)}$–$C_{(2)}$–$N_{(4)}$	174.0	$H_{(1)}$–$C_{(1)}$–$N_{(5)}$–$C_{(3)}$	-3.8
$N_{(12)}$–$N_{(11)}$	1.362(5)	$C_{(1)}$–$N_{(5)}$–$C_{(3)}$–$N_{(8)}$	174.7	$H_{(1)}$–$C_{(1)}$–$N_{(12)}$–$C_{(4)}$	3.9
$N_{(1)}$–$C_{(2)}$	1.356(5)	$C_{(1)}$–$N_{(12)}$–$C_{(4)}$–$N_{(9)}$	175.9	$C_{(1)}$–$N_{(1)}$–$N_{(2)}$–$N_{(3)}$	-174.7
$N_{(5)}$–$C_{(3)}$	1.354(5)			$C_{(1)}$–$N_{(5)}$–$N_{(6)}$–$N_{(7)}$	-75.8
$N_{(12)}$–$C_{(4)}$	1.357(6)				

The geometry, dipole moments, and total energy of compound **4** and its isomer, the hypothetical tristetrazol-2-ylmethane **5** in the gas phase were calculated using the DFT quantum-chemical method with full optimization on the basis B3LYP//6-31G** (Table 2). As may be noted from Fig. 2 and Table 2 the structure of compound **4**, optimized theoretically, is not in poor agreement with X-ray structural analysis data. Both in the crystalline state and in the gas phase the geometry of this molecule is close to symmetry group C_3. For this compound significant differences between the theoretically optimized and experimentally determined geometries are displayed only in the values of the torsion angles between the planes of the tetrazole rings and the axis passing through the C-H bond of the methine fragment. According to the data of theoretical calculations these angles are ~45°, while according to X-ray structural analysis data they are ~0°.

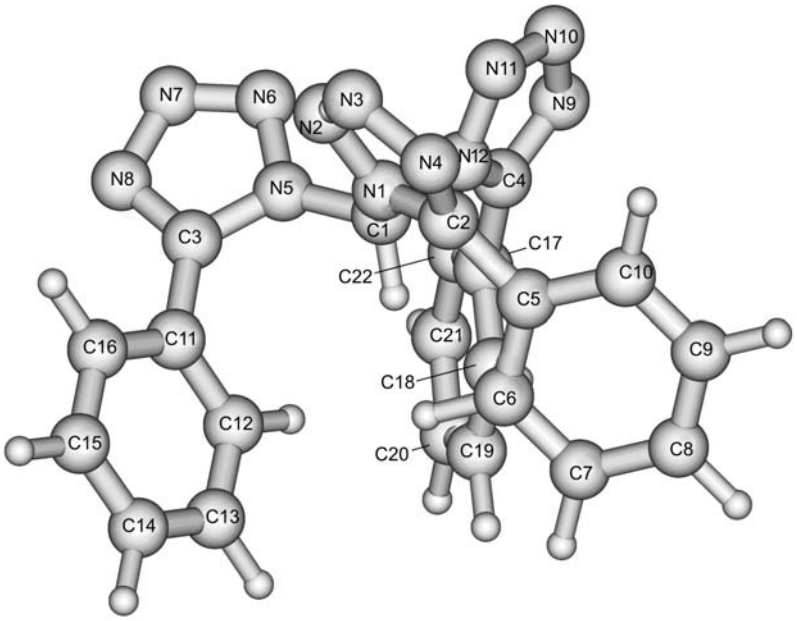

Fig. 2. Geometry of compound **4** optimized on the B3LYP/6-31G** basis.

The difference may be caused by the effects of molecular packing in the crystal. The optimized geometry of compound **5** differs in principle from the geometry of compound **4** (Fig. 3). The absence of symmetry is a characteristic of the molecular structure of compound **5**. In this compound the hydrogen atom of the methine group is spatially available. The tetrazole fragments are significantly removed from one another. At

Table 2. Results of Calculations by the B3LYP/6-31G** Method for Compounds **4** and **5***

Bond	*l*, Å		Angle	ω, deg	
	4	**5**		**4**	**5**
$C_{(1)}$–H	1.087	1.090	H–$C_{(1)}$–$N_{(5)}$	108.3	108.3
$C_{(1)}$–$N_{(5)}$	1.453	1.453	H–$C_{(1)}$–$N_{(1)}$	—	106.7
$C_{(1)}$–$N_{(12)}$	1.453	1.447	H–$C_{(1)}$–$N_{(12)}$	—	106.8
$C_{(1)}$–$N_{(1)}$	1.453	1.444	H–$C_{(1)}$–$N_{(5)}$–$C_{(3)}$	46.0	—
$N_{(1)}$–$N_{(2)}$	—	1.344	$N_{(5)}$–$C_{(3)}$–$C_{(11)}$–$C_{(16)}$	132.0	—
$N_{(2)}$–$N_{(3)}$	—	1.296	$C_{(18)}$–$C_{(17)}$–$C_{(4)}$–$N_{(9)}$	—	0
$N_{(3)}$–$C_{(2)}$	—	1.373			
$N_{(4)}$–$N_{(1)}$	—	1.331			
$N_{(5)}$–$N_{(6)}$	1.365	—			
$N_{(6)}$–$N_{(7)}$	1.283	—			
$N_{(7)}$–$N_{(8)}$	1.364	—			
$N_{(8)}$–$C_{(3)}$	1.319	—			
$C_{(2)}$–$N_{(4)}$	—	1.331			
$C_{(3)}$–$N_{(5)}$	1.366	–			

*For numbering of atoms see Figs. 2 and 3; total energy, *E*, a.u.: -1504.81202 (compound **4**), 1504.84669 (compound **5**); μ, D: 12.6 (compound **4**), 2.8 (compound **5**).

the same time for compound **4**, according to the theoretical and experimental data, the phenyltetrazole groups have a nonplanar structure, in the case of tristetrazol-2-ylmethane **5** the torsion angle between the planes of the benzene and tetrazole rings is ~0°.

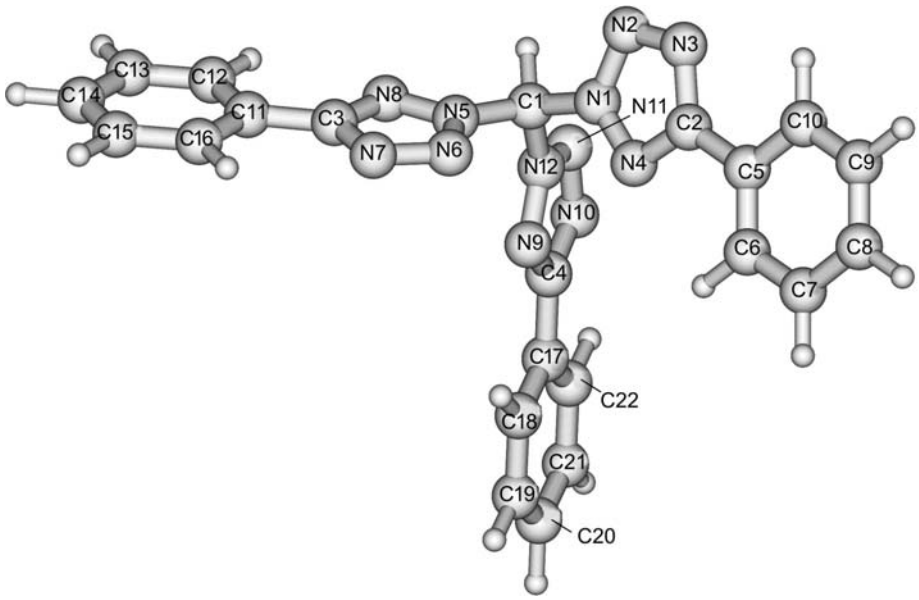

Fig. 3. Geometry of compound **5** optimized on the B3LYP/6-31G** basis.

We note that the reactivity of the methine fragment hydrogen atom must play a definite role in the majority of chemical conversions involving tristetrazolylmethanes. In the case of compound **4** the availability of this hydrogen atom is limited by spatial factors (Figs. 1, 2). It might be expected that just this circumstance determines the high stability of compound **4** in comparison with heterocycle **5,** the isolation of which in the free state was unsuccessful.

According to the data of the theoretical calculations (Table 2), tristetrazol-1-ylmethane **4** is thermodynamically less preferred by 21.76 kcal/mol in comparison with the isomeric tristetrazol-2-ylmethane **5**. However the anomalously high value of μ for the 1-isomer **4** enables its significant stabilization in the condensed phase to be expected due to intermolecular interactions.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX 300 spectrometer (300 and 75 MHz respectively) in DMSO, internal standard was the solvent signal. The IR spectra were recorded on a Shimadzu FTIR 8400 instrument in KBr disks. Elemental analysis was carried out on a Hewlett-Packard 185B C,H,N analyzer. Mass spectra were recorded on a Varian MAT 311 instrument, ionization was at 70 eV. Melting points were determined on a PTP type instrument with a heating rate of 1°C/min in the melting range.

X-ray Structural Investigation of Compound 4. The intensities of 1850 independent reflections were measured on a CAD 4 diffractometer (MoKα radiation with β-filter, θ/2θ scanning). Crystals of compound **4**, obtained from the system DMF–ethanol were triclinic, belonging to the space group $P\bar{1}$, a = 9.204(2), b = 13.096(3), c = 14.886(3) Å, α = 102.85(3), β = 93.99(3), γ = 95.21(3)°, V = 1734.7(6) Å^3, Z = 2 [$C_{22}H_{16}N_{12}.3C_3H_7NO$ (DMF), one molecule of DMF is disordered], d_{calc} = 1.278 g/cm^3; M = 448.45. In the refinement 1699 independent reflections with $I>2\sigma(I)$ were used. The structure was solved by the direct method in an anisotropic appoximation for the non-hydrogen atoms. The coordinates of the hydrogen atoms were established from an electron density difference map and were refined isotropically. The final value of the R factor, calculated on 1699 reflections, was 0.033. All calculations were carried out using the program SHELX 97 [5].

Theoretical Investigation of Compounds 4, 5. Theoretical calculations by the DFT method on the B3LYP//6-31G** basis (full optimization of the structure on the basis indicated) were carried out using the Molcas 6.2 program [6].

Compounds 3, 4 (General Procedure). Chloroform (25 ml) was added in portions with vigorous stirring during 1 h at 45°C to a solution of 5-phenyltetrazole (5 g, 34 mmol) in 25% NaOH solution (75 ml). The reaction mixture was maintained at the same temperature for a further 6 h, cooled, and poured into ice-water (200 ml). The obtained mixture was treated with ether (100 ml). The solid precipitated at the phase separation boundary was filtered off, washed with water, and with ether, and dried. Compound **4** (1.2 g, 23% calculated on the initial 5-phenyltetrazole **1**) was obtained, and was then purified by recrystallization from DMF–ethanol. The ether extract was washed with water, dried, and evaporated. The residue was decolorized on a column of silica gel, using chloroform as eluent. Compound **3** (0.3 g, 4%) was obtained, and was purified further by recrystallization from aqueous ethanol.

2-Dichloromethyl-5-phenyltetrazole (3). Cream-colored crystals, mp 93°C (from aqueous ethanol). IR spectrum, ν, cm^{-1}: 2950, 2890 (CH), 1704, 1616, 1544, 1472, 1422, 1355, 1260, 1200, 1145, 1130, 1025, 920 (tetrazole). ^{1}H NMR spectrum, δ, ppm: 9.52 (1H, s, CH); 8.13, 7.65 (5H, m, C_6H_5). ^{13}C NMR spectrum, δ, ppm: 76.45 (CH); 125.53, 126.94, 129.56, 131.68 (C_6H_5); 165.64 (tetrazole). Mass spectrum, *m/z* (*I*, %): 230, 228 (7) $[M]^+$,202, 200 (19); 167, 165 (100); 140, 138 (69); 104, 103 (93); 89 (7); 77 (60); 63 (17); 51 (15). Found, %: C 42.3; H 2.5; N 24.9. $C_8H_6Cl_2N_4$. Calculated, %: C 42.1; H 2.6; N 24.6.

Tris(5-phenyltetrazol-1-yl)methane (4). Colorless crystals, mp 155°C (decomp., from DMF–ethanol). IR spectrum, ν, cm^{-1}: 2960 (CH); 1605, 1535, 1470, 1448, 1425, 1360, 1260, 1170, 1095, 1075, 1030, 1000, 925 (tetrazole). ^1H NMR spectrum, δ, ppm: 9.28 (1H, s, CH); 7.62, 7.38 (15H, m, C_6H_5). ^{13}C NMR spectrum, δ, ppm: 72.96 (CH); 121.64, 129.14, 129.29, 132.13 (C_6H_5); 155.04 (tetrazole). Mass spectrum, *m/z* (*I*, %): 448 (1) $[M]^+$; 364, 363 (11); 349 (4); 337 (3); 288 (3); 273 (6); 246, 245 (100); 221 (5); 146 (7); 129 (8); 118 (50); 103 (32). Found, %: C 59.1; H 3.8; N 37.8. $C_{22}H_{16}N_{12}$. Calculated, %: C 58.9; H 3.6; N 37.5.

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