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Synthesis, Molecular, and Crystal Structure of Tris(2-carbamoylmethoxyphenyl)phosphine Oxide

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Abstract—New tripodal ligand, tris(2-carbamoylmethoxyphenyl)phosphine oxide, has been synthesized via the alkylation of tris(2-hydroxyphenyl)phosphine oxide with chloroacetamide. The ligand structure has been studied by means of IR and NMR (^{1}H, ^{31}P) spectroscopy as well as X-ray diffraction.

Keywords: tripodal ligand, tris(2-carbamoylmethoxyphenyl)phosphine oxide, crystal and molecular structure

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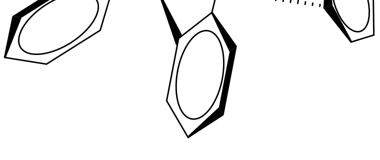
Tripodal ligands form a promising group of organic complex-forming agents, versatile structure of which affords the compounds capable of binding the substrates of different classes. The ligands containing carbamoyl groups can form strong complexes with the salts of *d*- and *f*-elements and can be used as extracting agents for recovery and separation of valuable metals as well as for reprocessing of spent nuclear fuel [1–5]. Tripodal ligands bearing functional proton-donor groups can form complexes with anions [6–9]. Tuning of the tripodal ligands structure has allowed ionophores for ion-selective electrodes and optical sensors for metal ions [10–12]. Tripodal ligands can bind neutral organic molecules, for example carboxylic acids [13] and carbohydrates [14] and act as sensors, receptors, and artificial enzymes.

The so-called propeller ligands based on pyramidal organic compounds with three aryl substituents and functional groups in the side chain form a special type of tripodal ionophores. These ligands include the derivatives of triarylmethane, triarylamine, triarylphosphine, and triarylphosphine oxide. The most stable conformation of such molecules corresponds to the geometry of asymmetric propeller with the *ortho*-substituents in the benzene rings being oriented to the same direction (Scheme 1). Such geometry allows the preparation of ionophores with the coordinating moieties in the side chains being spatially close and hence prone to the formation of multiple bonds with the guest ions and molecules with minor change of the ligand conformation [15–17].

In contrast to the extracting agents used in hydrometallurgy, which should exhibit significant lipophilicity and low solubility in water, sometimes it is desirable to obtain water-soluble ligands and complexes, for example, in industries utilizing water as the cheapest and the most available solvent. Solubility in water is a prerequisite for the ligands and their complexes suitable for application in physiological media (drugs, components of diagnostics systems, contrasting agents, etc.). Moreover, it is desirable that the ligands and complexes applied in biomedicine are neutral and do not significantly affect the solutions pH.

Herein we discuss the synthesis of a novel promising water-soluble tripodal ligand for the binding of cations, anions, and organic molecules in aqueous solutions and biological fluids {tris[2-(carbamoylmethoxy)phenyl]-phosphine oxide $(NH_2COCH_2OC_6H_4)_3PO$ **1**} as well

Scheme 1.



as its structure and properties. Owing to the tripodal structure with concerted orientation of the functional groups, compound **1** can potentially form complexes with cations (via the P=O and C=O groups) as well as with anions and organic molecules (via hydrogen bonding with the NH_2 moiety)

Compound **1** was prepared from tris(2-hydroxyphenyl)phosphine oxide **2** and 2-chloroacetamide (Scheme 2).

Compound **2** is readily formed upon the action of lithium diisopropylamide on triphenyl phosphate **3** [18]. The alkylation of the phosphine oxide **2** with 2-chloroacetamide afforded the tripodal ligand **1** bearing amide functional group in the side chains. The reaction was promoted by KBr. Compound **1** was isolated from the reaction mixture as a trihydrate (as per the elemental analysis data). Compound **1** is noticeably soluble in water, readily soluble in polar organic solvents (EtOH, MeOH, DMF, and DMSO) and insoluble in nonpolar solvents (hexane, ether, CH_2Cl_2, $CHCl_3$).

Composition and structure of compound **1** were confirmed by the data of elemental analysis as well as IR, ^{1}H NMR, and ^{31}P{^{1}H} NMR spectroscopy. The molecular structure was elucidated by X-ray diffraction analysis.

The structure of tris[2-(carbamoylmethoxy)phenyl]phosphine oxide was determined for the trihydrate $(NH_2COCH_2OC_6H_4)_3PO·3H_2O$ which was prepared via crystallization from an aqueous solution. The solvate was crystallized in the *R*-3 space group with 1/3 molecules of compound **1** in the asymmetric unit. The molecules of phosphine oxide **1** adopt the propeller structure (OPCC torsion angles τ = 51.90°), the $OCH_2C(O)NH_2$ groups being turned toward the O^1 atoms of the P=O group (Fig. 1).

Three amide hydrogen atoms formed an intramolecular trifurcate (four-centered) $N^1–H\cdots O^1$ hydrogen bonds, with the $H\cdots O^1$ and $N^1\cdots O^1$ distances being d = 2.398 and 3.251 Å, respectively, and the $N^1–H\cdots O^1$ angle being equal to 171.54°. The $O^2–C^7–C^8–N^1$ torsion angles were –10.768(623)°. The P=O bond (1.502 Å) was longer than that in the analogous triarylphosphine oxides without hydrogen bonds (1.486 Å in $[2\text{-}Bu_2NC(O)·CH_2OC_6H_4]_3PO$ [1]), but approximately equal in length as in the phosphine oxides with the P=O group forming a hydrogen bond {1.502 Å in $Ph_2P(O)CH_2CH_2CH(OH)Me$ [20], 1.503 Å in $[2\text{-}HO(CH_2)_2OC_6H_4]_3PO$ [21], and 1.513 Å in $(HOCH_2CH_2CH_2)_3PO$ [22]}.

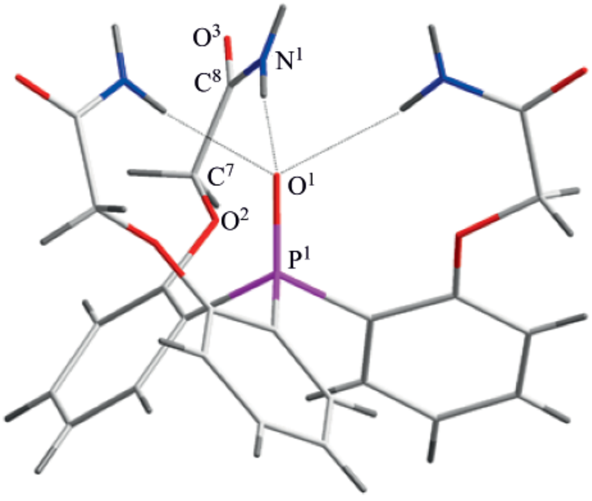
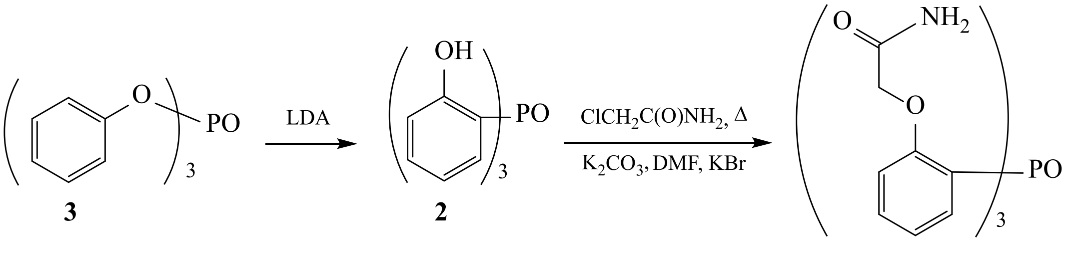


Fig. 1. General view of a molecule of tris[2-(carbamoylmethoxy)phenyl]phosphine oxide **1** in the crystal.

The molecules of compound **1** in the crystal were associated and linked to water molecules via strong $N–H\cdots O$ and $O–H\cdots O$ intermolecular hydrogen bonds, so that each $C(O)NH_2$ group formed a pair of intermolecular $N^1–H\cdots O^3$ hydrogen bonds with an amide group of the neighbor molecule, the $H\cdots O^3$ и $N^1\cdots O^3$ bond lengths in the 8-membered ring being 2.071 and 2.923 Å, respectively. One proton in each group NH_2 formed a $N^1–H\cdots O^1(P)$ hydrogen bond, and another proton was involved in a shorter $N^1–H\cdots O^3(C)$ bond formation. The carbonyl oxygen atom was associated with water molecules via strong intermolecular $O^1(W)–H\cdots O^3$ hydrogen bonds with the $O^1(W)\cdots O^3$ distances being

Scheme 2.



3 **2** **1**

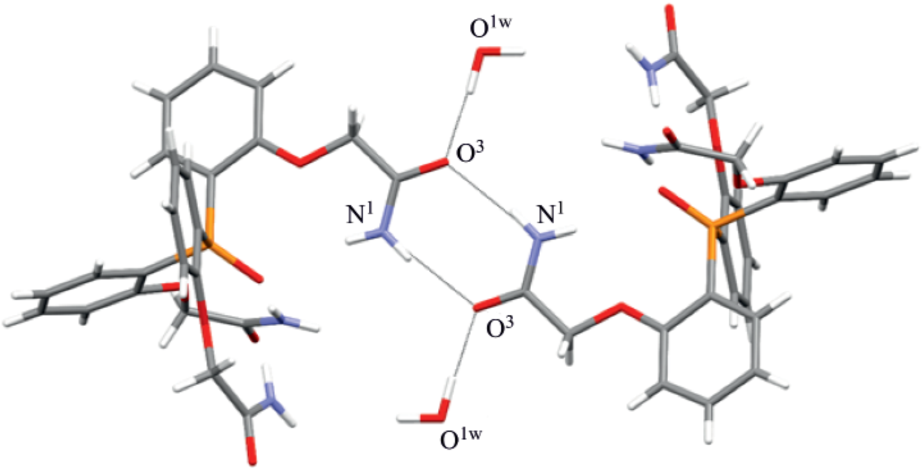


Fig. 2. Intermolecular hydrogen bonds between the molecules of compound **1** and H_2O.

2.780 Å. As a result, a three-dimensional supramolecular network was formed. Figure 2 displays the intermolecular hydrogen bonds between the molecules of compound **1** and H_2O.

IR spectrum of solid compound **1** showed the ν(PO) band at 1117 cm^{-1}, i. e. the wavenumber of the P=O bond vibration was noticeably lower than in the triarylphosphine oxides without hydrogen bonds (1180 cm^{-1} in the spectrum of $[2\text{-}Bu_2NC(O)CH_2OC_6H_4]_3PO$ [1]) but somewhat higher than in the spectrum of tris[2(tetrazol-5-ylmethoxy)phenyl]phosphine oxide (1098 cm^{-1}) with a bifurcate hydrogen bond with two protons of the NH groups [5]. Broad bands of the ν(NH) vibrations showed the maxima at 3343 and 3172 cm^{-1}, which could be assigned to the vibrations of the NH groups associated with phosphoryl and carbonyl groups, respectively. The ν(CO) band appeared at 1685 cm^{-1}. Hence, the IR spectrum of the compound agrees well with its suggested structure.

Dissolution in DMSO usually leads to the disruption of the intermolecular hydrogen bonds, while the intramolecular hydrogen bonds are preserved. However, disruption of the intermolecular C=O···HN groups in compound **1** could lead to the formation of the intramolecular hydrogen groups involving the liberated groups, i. e. rearrangements of the hydrogen bonds system. Comparison of the IR spectrum of the solution of phosphine oxide **1** in DMSO-d_6 with that of the solid sample revealed the absence of the ν(PO) band at 1117 cm^{-1} as well as a band in the region characteristic of the free P=O group. We could not reliably identify the position of the ν(PO) band, possibly due to its overlap with the solvent absorption, which would mean the shift to the low-frequency region {for example, ν(PO) 1090 cm^{-1} in the IR spectrum of $(2\text{-}HOC_6H_4)_3PO$ [18]}. The position of the ν(CO) and ν(NH) bands practically was not changed. It could be suggested that the competing interactions between both proton-accepting groups and the NH_2 moieties occurred in the solution, the possible forms being in equilibrium.

^1H NMR spectrum of a solution of compound **1** in DMSO-d_6 showed a singlet signal of the methylene protons at 4.45 ppm. The region typical of the aromatic protons displayed a triplet of doublets at 7.12 ppm (H^4) and a triplet at 7.66 ppm (H^6). The signals of the H^3 and H^5 protons were overlapping and appeared as a complex multiplet at 7.16–7.29 ppm. The signals of the NH_2 group protons were two strongly separated singlets at 7.31 and 7.85 ppm, likely, due to the hindered rotation of the NH_2 group about the C–N bond [19]. Such difference in the positions of the signals of the NH_2 group protons could be due to the formation of different hydrogen bonds with the PO and CO groups. The $^{31}P\{^1H\}$ NMR spectrum showed a singlet at 30.5 ppm corresponding to the chemical shift of triarylphosphine oxide with a phosphoryl groups involved in strong hydrogen bonding, for example, δ_P 35.9 ppm in the $^{31}P\{^1H\}$ NMR spectrum of $(2\text{-}HOC_6H_4)_3PO$ (DMSO) [18].

The synthesized novel tripodal ligand, tris[2-(carbamoylmethoxy)phenyl]phosphine oxide, can be used in the preparation of various complexes with *d*- and *f*-elements as well as with different organic molecules bearing polar groups. The obtained structural data are applicable in molecular docking of the related compounds.

EXPERIMENTAL

Organic solvents (reagent grade) were dried and purified via conventional methods [23]. The deuterated solvent DMSO-d_6 (Aldrich) was used as received.

IR spectra were recorded using a FTIR Tensor 37 Bruker spectrometer. The spectrum of the crystalline sample (KBr pellets) was recorded over 4000–400 cm^{-1}, and the spectrum of the solution in DMSO-d_6 was obtained over 4000–1090 cm^{-1}. ^{1}H and ^{31}P{^{1}H} NMR spectra of compound **1** were recorded using a Bruker AV-300 instrument operating at 300.13 (^{1}H) and 121.49 (^{31}P{^{1}H}) MHz with residual signals of the deuterated solvent as internal reference for the ^{1}H NMR spectra and 85% H_3PO_4 as external reference for ^{31}P{^{1}H} NMR spectra.

Tris(2-hydroxyphenyl)phosphine oxide **2** was prepared as described elsewhere [18].

Tris[2-(carbamoylmethoxy)phenyl]phosphine oxide (1). A mixture of 0.98 g (0.003 mol) of compound **2**, 20 mL of DMF, 2.50 g (0.18 mol) of potassium carbonate, 1.68 g (0.18 mol) of chloroacetic acid amide, and 0.25 g (0.002 mol) of KBr was stirred during 26 h at 90°C. The solvent was removed under vacuum and 50 mL of water and 50 mL of chloroform were added to the residue. The formed clotted precipitate was filtered off, washed with water and with ether, and triturated in a mixture of ether with methanol (20 : 1). The obtained powder was dried in air. Yield of compound **1** trihydrate 1.51 g (91.2%), mp 191–193°C (methanol–ether). IR spectrum, ν, cm^{-1}: 3343 s. br (NH), 3172 s. br (NH), 1685 s (C=O), 1117 s (P=O). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (J, Hz): 4.45 s (6H, CH_2O), 7.12 t. d (3H, H^4, $^4J_{HH}$ = 2.0, $^3J_{HH}$ = 7.0), 7.16–7.29 m (6H, H^3, H^5), 7.31 s (3H, NH), 7.66 t (3H, H^6, $^3J_{HH}$ = $^3J_{HP}$ = 7.8), 7.85 s (3H, NH). ^{31}P{^{1}H} NMR spectrum (DMSO-d_6): δ_P 30.5 ppm. Found, %: C 52.16; H 5.41; N 7.58. $C_{24}H_{24}N_3O_7P\cdot 3H_2O$. Calculated, %: C 52.27; H 5.48; N 7.62.

X-ray diffraction analysis was performed using a Bruker APEX-II CCD diffractometer (CCD detector; molybdenum anode radiation, λ = 0.71073 Å; graphite monochromator). The absorption was accounted for empirically using SADABS software [24]. The structure was solved using SHELXS97 software [25]; the non-hydrogen atoms were localized in the differential syntheses of the electronic density and refined using SHELXL-2014/7 software [26] under anisotropic approximation. The hydrogen atoms of compound **1** were put in the geometry-derived positions and refined using a *riding* model; hydrogen atoms in H_2O were localized by the differential synthesis and refined under isotropic approximation with limitation on the O–H bond length.

Crystals of compound **1** were trigonal, $C_{24}H_{24}N_3O_7P\cdot 3H_2O$ (M 551.48), space group R-3; unit cell parameters at 296(2) K: a = 13.9869(17), b = 13.9869(17), c = 23.896(3) Å, α = 90.00, β = 90.00, γ = 120.00°, V = 4048.6(11) Å^3, Z = 6, d_{calc} = 1.357 g/cm^3, μ(MoK_α) = 0.161 mm^{-1}; 21932 reflections were measured at 2θ up to 50.8°, 1654 of them being independent (R_{int} = 0.097) and 1034 being observed; R_1(obs) = 0.062, wR_2(all) = 0.177, GOF = 1.058. The crystallographic data were deposited at the Cambridge Crystallographic Data Centre (CCDC 1937005).

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CONFLICT OF INTEREST

No conflict of interest was declared by the authors.

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