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Polarity and Structure of Diphosphorus-Substituted Isoxazole and 1,2,3-Triazole

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Abstract—Diphosphorus-substituted isoxazole and 1,2,3-triazole were synthesized by a click chemistry method. Their polarity and structure were determined by the dipole moment method and quantum chemical calculations.

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In recent years, an efficient method for the synthesis of heterocycles, Huisgen catalytic 1,3-dipolar cycloaddition of azides to acetylenes, has been applied to phosphorylated substrates to obtain a number of potentially biologically active phosphorus-containing heterocycles [1, 2]. We brought into analogous reactions substrates containing two phosphorus moieties and thus synthesized diphosphorus-substituted heterocycles which, apart from biological activity, could exhibit efficient complexing properties. Scheme 1 illustrates the synthesis of polyfunctionalized isoxazole and 1,2,4-triaxole derivatives **III** and **IV** with phosphorus-containing substituents. We estimated the polarity of molecules **III** and **IV** (Table 1) and examined their structure by the dipole moment method and quantum-chemical calculations [B3PW91/6-31G(*d*), B3PW91/6-311++G(*df,p*)].

The results of theoretical calculations of some conformers of **III** are collected in Table 2. The dipole moments of these conformers, calculated by the vector addition scheme were similar for all rotational isomers and were equal to 4.83 D. In the calculations we used the group dipole moments for isoxazole ring (2.22 D) [3] and dimethoxyphosphoryl group (2.30 D) [4].

As follows from the data in Table 2, the calculated dipole moment of the most energetically favorable conformer **IIIb** is fairly consistent with the experimental value. Conformer **IIIa** is also enegretically favorable, but the theoretical dipole moment of **IIIa** is considerably lower than the experimental dipole moment,

Scheme 1.

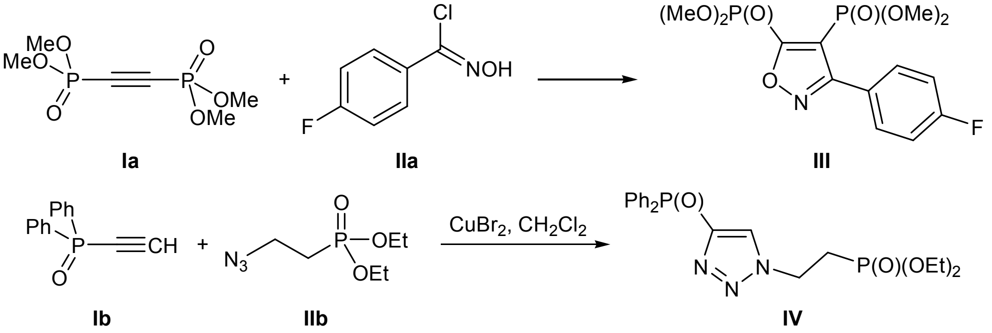


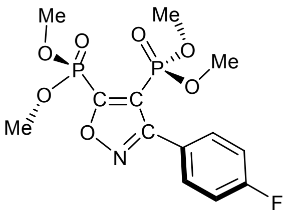
Table 1. Coefficients in the equations for the calculation of dipole moments and the experimental dipole moments of compounds **III** and **IV**

Compound no.	α	γ	P_{or}, cm^3	μ, D
III	6.892	0.000	492.097	4.88
IV	11.669	0.223	933.631	6.72

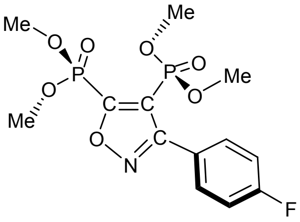
as well as than that calculated by the vector addition scheme. The theoretical dipole moment of conformer **IIIc** coincides with the experimental value, but the energy of **IIIc** is appreciably higher than that of **IIIb**. These findings led us to give preference to conformer **IIIb** where one phosphoryl group (on C^5) is oriented *gauche* with respect to the C^4=C^5 bond (the corresponding dihedral angle is 56°), while the second is oriented *s-trans* with respect to the same bond (125°). It is seen (Table 2) that the calculations performed with the use of extended basis set do not lead to radically different relative energies or dipole moments, but in this case the theoretical dipole moment is better consistent with the experimental value.

The results of calculations for conformers **IVa**–**IVc** differing by the orientation of methyl groups in the phosphoryl moiety are presented in Table 3. The experimental dipole moment of **IV** conforms to neither theoretical dipole moment of the most energetically favorable conformer nor dipole moment calculated by the vector addition scheme (3.78 D); in all cases, the experimental value is appreciably higher. According to the calculations, the triazole ring and the P=O bond in the Ph$_2$P=O group are almost coplanar, and the torsion angle P(O)CCH in all conformers is equal to 0°, the C=C bond in the heteroring and the phosphoryl group

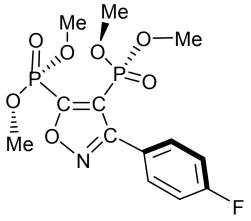
Table 2. Relative energies and theoretical dipole moments of conformers **IIIa**–**IIIc**



IIIa



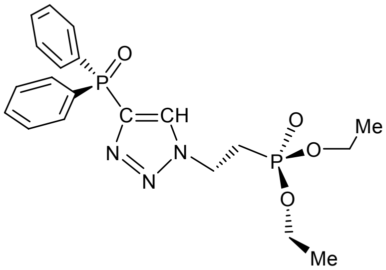
IIIb



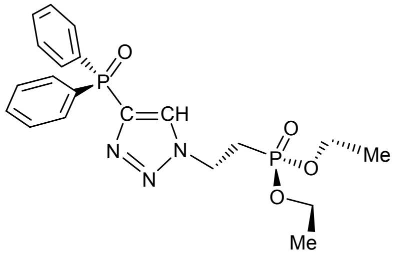
IIIc

Conformer	B3PW91/6-31G(*d*)		B3PW91/6-311++G(*df*,*p*)	
	Δ*E*, kJ/mol	μ_{theor}, D	Δ*E*, kJ/mol	μ_{theor}, D
IIIa	0.06	1.97	0.00	1.72
IIIb	0.00	4.20	0.04	4.52
IIIc	13.69	4.88	13.84	5.15

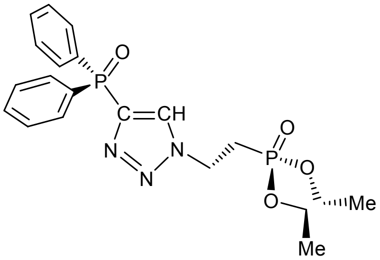
Table 3. Relative energies and theoretical dipole moments of conformers **IVa**–**IVc**



IVa

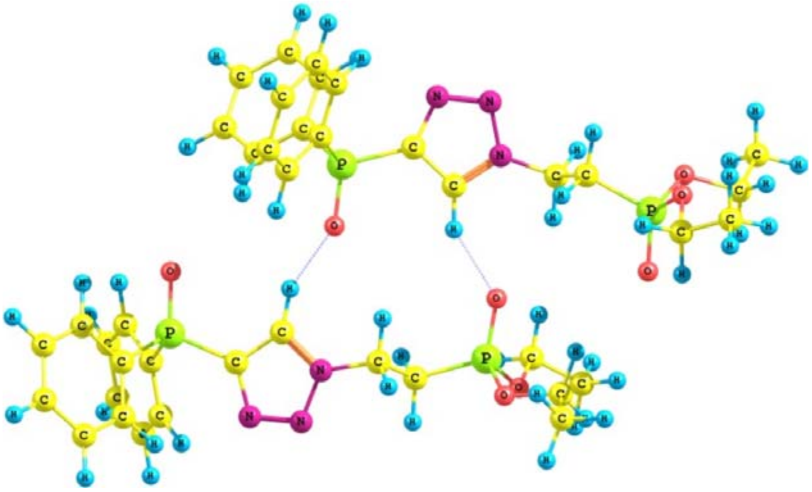


IVb



IVc

Conformer	B3PW91/6-31G(*d*)		B3PW91/6-311++G(*df*,*p*)	
	Δ*E*, kJ/mol	$\mu_{theor.}$, D	Δ*E*, kJ/mol	$\mu_{theor.}$, D
IVa	0.27	3.53	0.26	3.59
IVb	0.00	4.02	0.00	4.21
IVc	8.61	5.32	9.07	5.54



Calculated structure of the head-to-head dimer of diethyl {2-[4-(diphenylphosphoryl)-1*H*-1,2,3-triazol-1-yl]ethyl}phosphonate (**IV**).

being arranged *s-cis*. Such structure allows hydrogen bonding between the P=O oxygen atom and 5-H in the triazole ring. However, it is known that intramolecular hydrogen bonding does not increase dipole moment [5]. By contrast, intermolecular hydrogen bond may increase dipole moment to a considerable extent. We performed quantum-chemical calculations of all possible dimers of **IV** by the B3PW91/6-31G(*d*) method. The results showed that the formation of head-to-head dimer (see figure) provides an energy gain of 51.3 kJ/mol relative to the double energy of single molecule **IV** and that the formation of head-to-tail dimer reduces the energy by 63.1 kJ/mol. The dipole moments of these dimers are 6.98 and 3.56 D, respectively, against 4.02 D for single molecule **IV**. Thus, the higher experimental dipole moment of **IV** as compared to the calculated value may be rationalized by the existence of **IV** in solution as a mixture of two dimers, where the head-to-head dimer considerably prevails (90%).

The calculation results are in a good agreement with the experimental data.

EXPERIMENTAL

The dielectric permittivities of solutions of **III** and **IV** in benzene at 25°C were determined on a BI-870 instrument (Brookhaven Instruments) with an accuracy of ±0.01. The refractive indices of these solutions were measured using an RA-500 refractometer (Kyoto Electronics) with an accuracy of ±0.0001. The experimental dipole moments were calculated by the Debye equation [3]. The orientational polarizations (P_{or}) were calculated by the Guggenheim–Smith formula [3].

In the calculation of dipole moments by the vector addition scheme we used the following geometric parameters (determined by quantum-chemical calculations) and dipole moments of bonds and groups: $m(C_{sp^2}\rightarrow F)$ 0.74 D (calculated from μ_{exp} of C_6H_5F [3]), $m(C_{sp^2}\rightarrow P)$ 0.56 D [4], $m(Me\rightarrow P)$ 0.83 D [4], $m(Me\rightarrow N)$ 0.84 D (calculated from μ_{exp} of Me_3N [3]), $m(Ph\rightarrow P)$ 1.09 D [6], $m(P{=}{>}O)$ 2.95 D [4], $m[P(O)(OMe)_2]$ 2.30 D [4], $m[P(O)(OEt)_2]$ 2.30 D [4], isoxazole ring 2.22 D (group moment calculated from μ_{exp} of isoxazole [3]). Taking into account that the group moments $m(Me\rightarrow O)$ and $m(Et\rightarrow O)$ are equal to each other, the group moment $m[P(O)(OEt)_2]$ was assumed to be equal to $m[P(O)(OMe)_2]$.

Quantum-chemical calculations were performed using GAUSSIAN 09 software package [7]. Stationary points on the potential energy surfaces were identified as energy minima by calculating the second derivatives; in all cases, the Hessian eigenvalues were positive. The calculations were carried out at the Kazan Branch, Joint Supercomputer Center of the Russian Academy of Sciences (*http://wt.knc.ru*).

The ^{1}H, ^{31}P, ^{13}C, and ^{19}F NMR spectra were recorded on Bruker AV-300 and Bruker AV-400 spectrometers from solutions in $CDCl_3$. The IR spectra were obtained on a Nicolet Magna IR750 spectrometer. Initial acetylenes **Ia** and **Ib** [8], *N*-hydroxy imidoyl chloride **IIa**, and azide **IIb** [9, 10] were synthesized by known methods.

Tetramethyl [3-(4-fluorophenyl)isoxazol-4,5-diyl]bis(phosphonate) (III). Potassium hydrogen carbonate, 0.8 g (8 mmol), was added in ~20-mg portions to a solution of 0.48 g (2 mmol) of acetylenic diphosphonate **Ia** and 0.34 g (2 mmol) of 4-fluoro-*N*-hydroxybenzenecarboximidoyl chloride (**IIa**) in 4 ml of *t*-BuOH–H_2O (1:1). The mixture was stirred for 1.5 h at 20°C and evaporated under reduced pressure, the residue was treated with 20 ml of methylene chloride, the extract was washed with water, dried over Na_2SO_4, and evaporated, and the residue was purified by chromatography on silica gel (gradient elution with hexane–acetone, 100:10 to 0:100). Yield 0.61 g (80%), light yellow oily substance. ^{1}H NMR spectrum, δ, ppm: 7.80–7.70 m and 7.20–7.10 m (2H each, C_6H_4F), 3.99 d and 3.71 d (6H each, OCH_3, $^3J_{PH}$ = 12.0 Hz). ^{13}C NMR spectrum, δ_C, ppm: 168.70 d.d (C^5, $^1J_{PC}$ = 217.4, $^2J_{PC}$ = 25.0 Hz), 163.63 d ($C^{4'}$, $^1J_{FC}$ = 250.8 Hz), 162.57 d.d (C^3, $^3J_{PC}$ = $^2J_{PC}$ = 12.6 Hz), 122.88 br.s ($C^{1'}$), 130.90 d ($C^{3'}$, $C^{5'}$, $^3J_{FC}$ = 8.2 Hz), 115.18 d ($C^{2'}$, $C^{6'}$, $^2J_{FC}$ = 21.9 Hz), 113.14 d.d (C^4, $^1J_{PC}$ = 215.8, $^2J_{PC}$ = 25.2 Hz), 54.31 d ($POCH_3$, $^2J_{PC}$ = 6.0 Hz), 52.95 d (OCH_3, $^2J_{PC}$ = 5.5 Hz). ^{31}P NMR spectrum, δ_P, ppm: 9.76 s, 1.28 (intensity ratio 1:1). ^{19}F NMR spectrum: δ_F –109.67 ppm, s. Found, %: C 41.08; H 4.30; F 4.57; N 3.72; P 16.23. $C_{13}H_{16}FNO_7P_2$. Calculated, %: C 41.17; H 4.25; F 5.01; N 3.69; P 16.34.

Diethyl {2-[4-(diphenylphosphoryl)-1*H*-1,2,3-triazol-1-yl]ethyl}phosphonate (IV). Copper(I) bromide, 14.4 mg (5 mol %) was added in small portions under stirring over a period of 10–15 min to a solution of 0.46 g (2 mmol) of diphenylphosphorylacetylene (**Ib**) and 0.41 g (2 mmol) of azide **IIb** in 5 ml of methylene chloride. When the reaction was complete (after ~24 h; TLC, ^{31}P NMR), the mixture was diluted with 20 ml of methylene chloride, washed with 2% aqueous ammonia (3×10 ml) and water (10 ml), and dried over Na_2SO_4, the solvent was removed under reduced pressure, and the residue was purified by chromatography on silica gel (gradient elution with hexane–acetone, 100:10 to 0:100). Yield 0.57 g (66%), mp 129–130°C. IR spectrum (KBr), ν, cm^{-1}: 3096, 2976, 1589, 1438, 1239, 1216, 1181, 1021, 974, 939. ^{1}H NMR spectrum, δ, ppm: 8.21 s (1H, C=CH), 7.93–7.83 m (4H, *m*-H), 7.55–7.50 m (2H, *p*-H), 7.48–7.42 m (4H, *o*-H), 4.67 d.t (2H, NCH_2, $^3J_{HH}$ = 8.0, $^3J_{PH}$ = 12.0 Hz), 4.10–4.00 m (4H, $POCH_2$), 2.42 d.t (2H, PCH_2, $^2J_{PH}$ = 20.0, $^3J_{HH}$ = 8.0 Hz), 1.24 t (6H, $CH_2C\mathbf{H}_3$, $^3J_{HH}$ = 8.0 Hz). ^{13}C NMR spectrum, δ_C, ppm: 141.95 d (C^4, $^1J_{PC}$ = 135.0 Hz), 132.08 d (C^i, $^1J_{PC}$ = 113.5 Hz), 131.19 d (C^5, $^2J_{PC}$ = 26.4 Hz), 132.04 d (C^p, $^4J_{PC}$ = 2.6 Hz), 131.32 d (C^m, $^3J_{PC}$ = 10.3 Hz), 128.40 d (C^o, $^2J_{PC}$ = 12.6 Hz), 62.08 d (OCH_2), $^2J_{PC}$ = 6.6 Hz), 44.72 s (NCH_2), 27.03 d (PCH_2, $^1J_{PC}$ = 141.6 Hz), 16.16 d (CH_3, $^3J_{PC}$ = 6.0 Hz). ^{31}P NMR spectrum, δ_P, ppm: 25.61 s [P(O)$(OEt)_2$], 16.95 s [$Ph_2P(O)$]. Found, %: C 55.14; H 5.81; N 9.81; P 14.32. $C_{20}H_{25}N_3O_4P_2$. Calculated, %: C 55.43; H 5.81; N 9.70; P 14.29.

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