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SYNTHESIS AND STRUCTURE OF PHOSPHANYLATED BIS-TRIAZOLES AS POTENTIAL LIGANDS FOR CHIRAL CATALYSTS

A. A. Kirilchuk[1], A. A. Yurchenko[1], Yu. G. Vlasenko[1],
A. N. Kostyuk[1], and A. B. Rozhenko[1,2]*

Potential atropisomeric ligands, diphenylphosphane derivatives of bis-triazoles, were synthesized by direct phosphanylation of the starting bis-triazoles with chlorodiphenylphosphane. Their crystal structure was elucidated by X-ray diffractional analysis. The conformations of these compounds were modeled by DFT calculations.

Keywords: BINAP, 1,2,4-triazole, phosphanes, atropisomerism, DFT, X-ray structural analysis.

Asymmetric catalysis is a new and rapidly developing discipline in the field of organic chemistry. A search of new chiral catalysts has become the key step towards a production of enantiomerically pure drugs, pesticides, etc. Atropisomeric compounds excel among such catalysts and their chirality arises due to the hindered rotation about a single bond allowing separation of individual chiral conformers. Atropisomeric compounds can be used as catalysts in organic synthesis both in pure form [1, 2] and as transition metal complexes.

Substituted biaryls are a classical example of structures with a chiral axis [3]. The first effective atropisomeric catalyst based on 2,2'-bis(diphenylphosphano)-1,1'-binaphthyl (BINAP) was prepared in 1980 [4]. In the last the next years such catalysts have evolved from the laboratory to the industrial usage [5, 6]. Substituting naphthalene groups by heteroaromatic moieties in atropisomeric diphosphanes is interesting from both for varying electronic properties and changing the geometrical and configurational stability of such ligands [7]. Previously, a series of bis(heteroaryl)diphosphane were synthesized as ligands for the catalysts, which demonstrated high activity and enantioselectivity in the model reactions [8, 9]. In these ligands, pyrole, indole, thiophene, and furan rings were used as a the scaffolds. Similar bis(1,2,4-triazol)diphosphanes, also possessing a chiral axis, have not been synthesized previously. Attractively, bis-triazole skeleton is synthetically accessible, and, what is significant, its phosphanylation is highly selective.

The main aim of this study was the synthesis of the atropisomeric bis-triazolediphosphane ligands, examination of their structure in the solid state, study their most favorable conformations by quantum-chemical calculations, and evaluation of the energy barrier to racemization.

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*To whom correspondence should be addressed, e-mail: iamkaant@gmail.com, a_rozhenko@ukr.net.

[1] Institute of Organic Chemistry, National Academy of Sciences of Ukraine, 5 Murmans'ka St., Kyiv 02094, Ukraine.
[2] Bielefeld University, 25 Universitätsstraße, Bielefeld D-33615, Germany.

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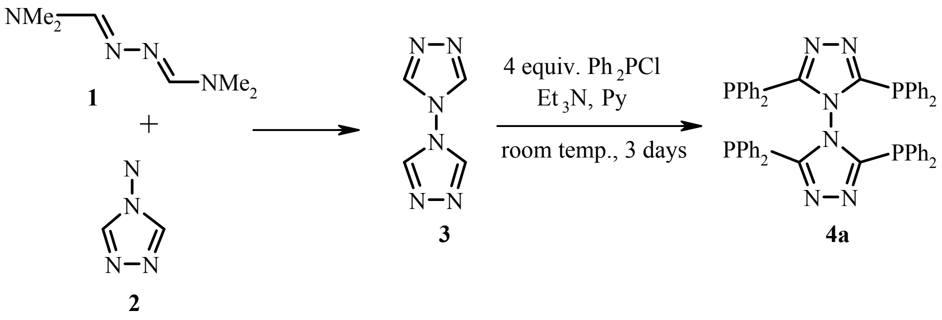
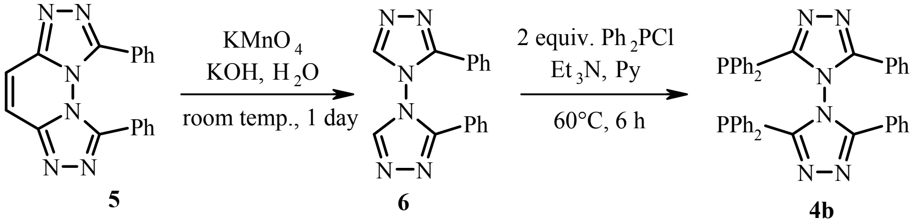
Unsubstituted bis(1,2,4-triazole) **3** was synthesized according to the published procedure [10]. Its 2,2'-diphenyl derivative **6** was prepared by oxidative cleavage of pyridazine ring in the tricyclic compound **5** [11]. Conditions described in literature ($KMnO_4$ in aqueous pyridine) did not allow achieving the expected results. However, we found the reaction to proceed smoothly in aqueous KOH solution. Employing these conditions, diphenylbistriazole **6** was synthesized in 69% yield.





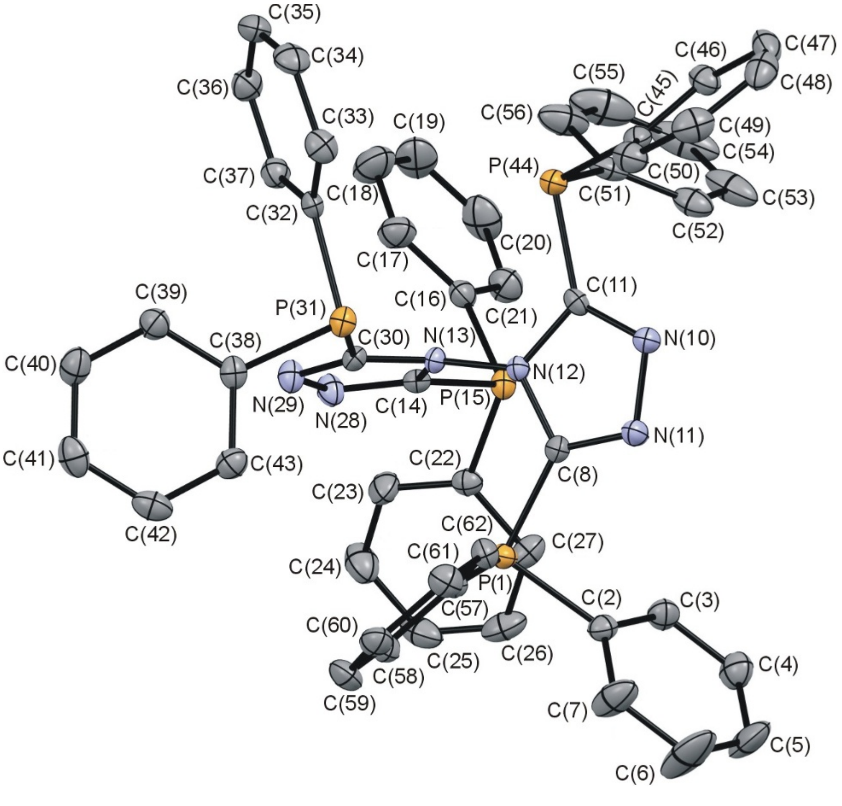


Fig. 1. Molecular structure of compound **4a** represented as thermal vibration ellipsoids with 50% probability (hydrogen atoms not shown).

Phosphanylation of bis-triazoles **3**, **6** with chlorodiphenylphosphane in pyridine in the presence of triethylamine during several days at ambient temperature or 6 h at 60°C according to published procedure [13] afforded high yields of compounds **4a**,**b**. The synthesized products **4a**,**b** are colorless crystals, moisture insensitive, and stable to hydrolysis by refluxing in moist methanol for 1 h. They are also highly stable in regards to oxidizing agents. For instance, compound **4a** did not add sulfur in refluxed benzene. On the other hand, an interaction of compound **4a** with hydrogen peroxide in benzene causes the cleavage of the C–P bond with the formation of Ph_2POH.

Phosphorus signals in ^{31}P NMR spectra of phosphanes **4a**,**b** (-42.6 and -39.4 ppm, respectively) appear upfield in comparison with analogous signals in the known *C*-diphenylphosphanotriazoles (-30 ÷ -33 ppm) [13-15]. In the ^{13}C NMR spectrum a doublet at 155.5-156.0 ppm ($^1J_{C-P} \approx 16$ Hz), corresponding to the C-3 carbon atom, is characteristic.

Monocrystals of compounds **4a**,**b** were grown from toluene and benzene, respectively; the structure of these compounds was determined by X-ray structural analysis (Figs. 1, 2).

In the structure of compound **4a** the lone electron pairs of the phosphorus atoms in all four phosphane groups point to the neighbouring triazole ring. Atoms P(1), P(15), P(31), P(44) have a pyramidal configuration: the sum of the corresponding valence angles ($\Sigma\angle$P) is 298.6(3), 302.3(3), 298.6(3), and 300.4(4)°. The N(12) atom possesses a trigonal-planar configuration ($\Sigma\angle$N = 359.9(3)°). In contrast, the environment of the N(13) atom is slightly out-of-plane ($\Sigma\angle$N = 356.9(6)°). The planes of the two triazole rings are almost orthogonal – the torsion angle between them comprises 83.16°.

The molecular structure of compound **4b** possesses a C_2 symmetry. The triazole rings are planar, the deviations of atoms from the plane C(1)N(1)C(2)N(2)N(3) do not exceed 0.009 Å. The torsion angles between the planes of the central five-membered rings and phenyl groups C(3–8), C(9–14), and C(15–20) are 39.76, 82.86, and 62.50°, respectively. The angle between the planes of the two triazole rings is 75.1°. The atom P(1) possesses a pyramidal configuration, the sum of valence angles on the phosphorus atom $\Sigma\angle$P = 306.9(6)°.

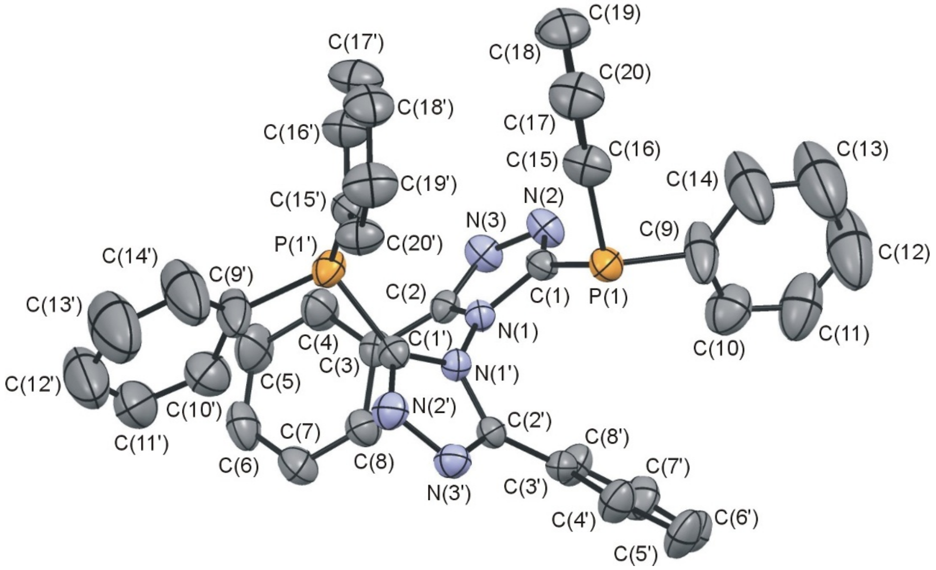


Fig. 2. Molecular structure of diphosphane **4b** represented as thermal vibration ellipsoids with 50% probability (hydrogen atoms not shown).

The conformation of a potential ligand in the gas phase and in solution can differ from its structure in the solid state, which strongly influences its complexation ability. Quantum-chemical calculations for isolated molecules of compounds **4a**,**b** were performed using BP86 [16, 17] and B97-D [18] DFT functionals. The latter functional, which includes empirical corrections for electron dispersion effects, is able to model properly π,π-interactions in the molecules of compounds **4a**,**b**.

As indicated by calculations in the RI-BP86/TZVP approximation, the local minimum in energy for compound **4a** is the C_2 symmetrical conformation. The lone electron pairs of all phosphorus atoms are turned to the side of the N–N bond. Optimization of the geometry of the C_2-symmetrical molecule using Grimme's B97-D functional leads to a conformation where two pairs of phenyl groups are almost parallel to each other, which implies a π,π-stacking interaction between them (Fig. 3*a*). Triazole rings are twisted to each other by 84.7°. Optimization of the experimental structure without restrictions in symmetry leads to an asymmetric structure (C_1) (Fig. 3*b*), where one of the phosphane groups is turned around forming another π,π-stacking interaction between two phenyl groups and triazole ring, as well as an additional CH,π-bonding. The triazole rings in this structure are turned by approximately 80° to each other. Noteworthy, the total energy of this structure is only by 1.3 kcal/mol lower than that calculated for above-mentioned C_2-symmetrical structure. However, the difference of free Gibbs energies (ΔG) calculated under standard conditions (T 298.15 K, p 0.1 MPa) makes the C_2-symmetrical structure slightly more favorable (ΔG -0.2 kcal/mol). Presumably, the large number of substituents taking part in the interaction makes the C_1-structure more rigid, which lowers its entropy, evening the free energy values.

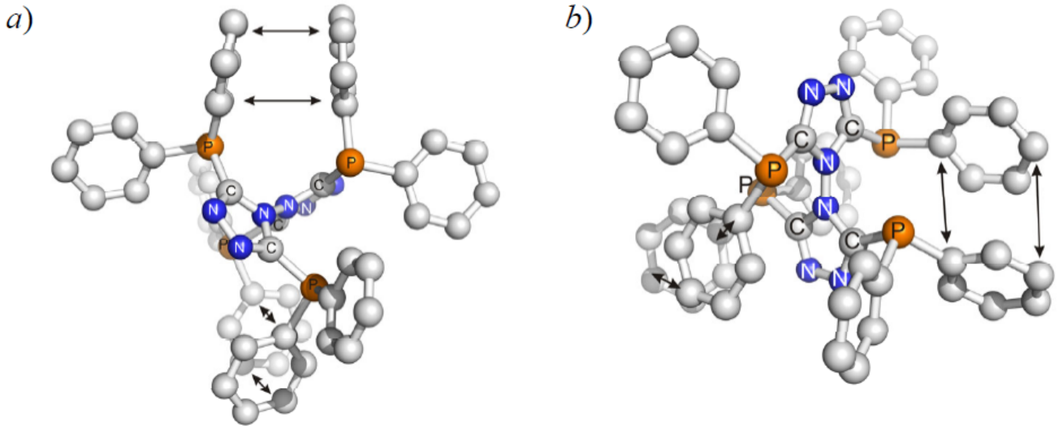


Fig. 3. Structures of compound **4a**, optimized at the B97-D/TZVP level of approximation: *a*) C_2-symmetrical, *b*) asymmetrical (C_1) (hydrogen atoms not shown, presumed π,π-stacking interactions shown by arrows).

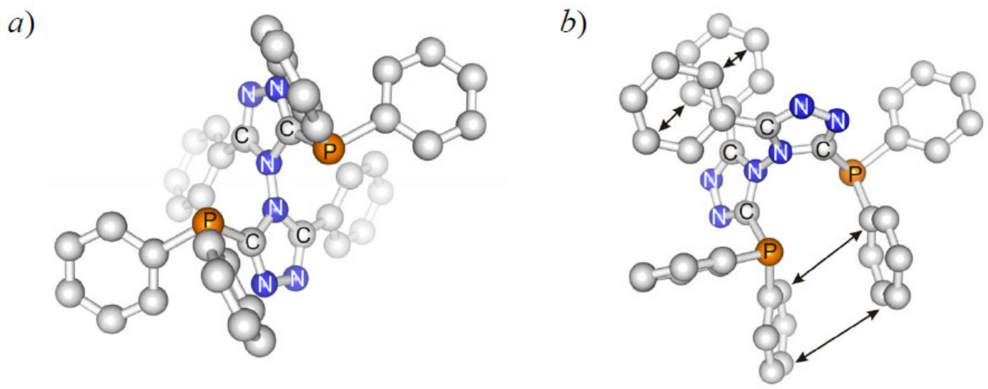


Fig. 4. Structures of compound **4b**, *a*) optimized at the BP86/TZVP approximation and *b*) at the B97-D/TZVP level of approximation (hydrogen atoms not shown, probable π,π-stacking interactions marked by arrows).

The structures of compound **4b**, optimized at the BP86/TZVP and B97-D/TZVP levels of approximations, differ markedly as well. For the former case, optimization yields a C_2-symmetrical structure (Fig. 4*a*). Optimization within the RI-B97-D/TZVP approximation leads to an asymmetrical structure enabling two π,π-interactions between aromatic fragments: between the phenyl groups of the diphenylphosphane groups, and between the phenyl rings connected to the triazole fragments (Fig. 4*b*). Benzene rings in these pairs are at distances of 4.66 and 4.55 Å, slightly displaced to each other, and rotated by 27 and 37°, respectively. In the structure calculated using the BP86 functional the two triazole rings are almost perpendicular (dihedral angle about 87°), while method RI-B97-D provides a value for the dihedral angle of about 70°. Geometry optimization for compound **4b** taking into account dispersional interactions and with fixed C_2-symmetry yields the structure which does not correspond to the true local minimum in energy.

The phenomenon of atropisomerism arises from hindered rotation about the bond connecting two aromatic fragments. In the case of compounds **4a**,**b** the presence of sterically bulky groups accounts for a high barrier for rotation about the N–N bonds. We located the transition state structures for this rotation and determined their energy. The calculated activation energy values ($\Delta G^{\neq}$ 40.5 and 42.5 kcal/mol) preclude racemization under ordinary conditions and allow to predict that phosphanylated bis-triazoles could be used as atropisomeric ligands.

For the characterization of the synthesized structures as potential ligands, we compared the spatial arrangement geometry of the coordination centers, phosphane groups, with that of the above-mentioned BINAP by the X-ray structural data [19]. Similar to structures **4a**,**b**, the lone electron pairs of the phosphorus atoms in BINAP molecule are also aligned almost parallel to the C–C bond between the naphthyl groups towards the second naphthyl group. This peculiar geometry facilitates the efficient interaction of the transition metal atom with both phosphorus atoms. The P···P distance in the BINAP molecule is 4.21 Å, whereas it is 4.10 Å in the C_2-symmetrical structure of compound **4a** (in C_1-symmetrical conformation these distances are about 4.1 and 4.6 Å), while in structure of compound **4b** the corresponding values is 4.76 Å. The found P···P distances in the studied structures in combination with their low deformation energies in symmetrical structures predicts for them a potential ability to form complexes with transition metals. Besides, the nitrogen atoms of the triazole rings can also take part in the complex formation with metal atoms.

Thus, we have for the first time synthesized bistriazolylphosphanes and studied their structure in the solid state by X-ray structural analysis. Comparison of the distances between the coordination centers in the obtained compounds with the distances in the classical diphosphane ligand BINAP shows their similarity, which allows to predict the possibility of using these bis-triazoles as atropisomeric ligands in preparation of novel chiral metal complex catalysts.

EXPERIMENTAL

^{1}H NMR spectra were recorded on Bruker Avance DRX-500 (500 MHz, compound **4a**) and Varian VXR-300 (300 MHz, compound **4b**) spectrometers. ^{13}C NMR spectra were obtained on a Bruker Advance DRX-500 (125 MHz) spectrometer. ^{31}P NMR spectra were recorded on a Varian Gemini-200 (81 MHz) spectrometer. All spectra were obtained in $CDCl_3$ as the solvent; TMS was used as the internal standard for ^{1}H and ^{13}C, while 85% H_3PO_4 was used as the standard for ^{31}P. Melting points were determined on an electrothermal melting point apparatus and are uncorrected. All operations with moisture- and air-sensitive substances were performed under dry argon atmosphere in a flame-dried glass vessel. Solvents were purified and dried according to the standard routines.

3,3',5,5'-Tetrakis(diphenylphosphano)-4,4'-bis(1,2,4-triazole) (4a). A solution of Ph_2PCl (3.40 g, 15.4 mmol), 4,4'-bis(1,2,4-triazole) (**3**) (0.50 g, 3.7 mmol), and Et_3N (2.22 ml, 1.60 g, 15.8 mmol) in pyridine (5 ml) was stirred at room temperature for 3 days, the formed precipitate was filtered off and washed with pyridine. The filtrate was concentrated under reduced pressure, and the residue recrystallized from PhMe. Yield 2.60 g (82%), yellowish crystals, mp >250°C. ^{1}H NMR spectrum, δ, ppm: 7.19-7.32 (40H, m, H Ph). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 128.1; 129.2; 132.1; 133.8 (t, *J* = 11.3); 155.5 (m). ^{31}P NMR spectrum, δ, ppm: -42.6.

3,3'-Bis(diphenylphosphano)-5,5'-diphenyl-4,4'-bis(1,2,4-triazole) (4b). A solution of Ph_2PCl (0.43 g, 2.0 mmol), 3,3'-diphenyl-4,4'-bis(1,2,4-triazole) (**6**) (0.25 g, 0.9 mmol), and Et_3N (0.28 ml, 0.20 g, 2.0 mmol) in pyridine (2 ml) was stirred at 60°C for 6 h, cooled to room temperature, and the precipitate filtered off and washed with pyridine. The filtrate was concentrated, the residue was dissolved in $CHCl_3$ and washed with water. The organic phase was dried over Na_2SO_4 and concentrated. The residue was recrystallized from PhH. Yield 0.44 g (78%), colorless crystals, mp 249-250°C. ^{1}H NMR spectrum, δ, ppm: 7.05-7.40 (30H, m, H Ph). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 124.0; 127.1; 128.6 (m); 129.0; 129.6; 130.1; 130.9; 131.7; 134.1 (dt, *J* = 123.0, *J* = 11.3); 153.2; 156.0 (d, *J* = 16.3). ^{31}P NMR spectrum, δ, ppm: -39.4.

3,3'-Diphenyl-4,4'-bis(1,2,4-triazole) (6). $KMnO_4$ (0.4 g, 2.5 mmol) was added to a suspension of compound **5** (0.5 g, 1.6 mmol) in aqueous KOH (0.5 g in 7 ml H_2O). The mixture was stirred at room temperature for 1 day. EtOH was added to remove the excess of $KMnO_4$, precipitate of MnO_2 was filtered and washed with hot PhH. The aqueous filtrate was concentrated to dryness and extracted with hot PhH. The combined benzene phases were dried over Na_2SO_4, and evaporated to dryness. Yield 0.32 g (69%), colorless crystals, mp 207-208°C (PhH). The NMR spectra of the obtained compound **6** agrees with published data [11].

DFT Calculations. All structures were fully optimized without symmetry constraints (except for specially mentioned cases) using the TURBOMOLE v. 6.2 software package [20, 21]. DFT RI-BP86 [16, 17] and RI-B97-D [18] functionals were used for geometry optimization. The TZVP basis set used by default in TURBOMOLE program is a modification of "triple-zeta" TZV basis functions [22] with added polarization functions. Fine convergence criterion for SCF-calculations (SCFConv = 1.0×10^{-8} Hartree) in combination with the highest integration accuracy (grid = 5) were used for geometry optimization. Vibrational frequencies calculated by a numerical method were used to check if the optimized structures are real energy minima. The PyMOL software [23] was used for graphical representation of the optimized structures.

TABLE 1. Principal Crystallographic Parameters for Compounds **4a**,**b**

Parameter	Compound **4a**	Compound **4b**
Cell parameters *a*, Å	13.1935(4)	12.1072(6)
b, Å	19.2616(5)	25.052(1)
c, Å	17.9868(5)	12.3979(7)
α, deg	90	90
β, deg	104.308(2)	104.823(3)
γ, deg	90	90
V, Å^3	4429.2(2)	3635.2(3)
Z	4	4
$D_{calc.}$, g·cm^{-3}	1.309	1.200
Crystal system	Monoclinic	Monoclinic
Space group	$P2_1/c$	$P2/c$
μ, cm^{-1}	0.215	0.156
F(000)	1816	1368
Miller indices	$16 \geq h \geq -13$, $24 \geq k \geq -18$, $17 \geq l \geq -22$	$15 \geq h \geq -14$, $31 \geq k \geq -31$, $12 \geq l \geq -15$
θ_{max}, deg	26.42	26.56
Reflections:		
collected	32848	17765
independent	9149	3778
in refinement ($I \geq 3\sigma(I)$)	5810	2422
R(int)	0.060	0.044
Number of refined parameters	559	217
$R_1(F)$	0.0428	0.0800
$R_w(F)$	0.0414	0.0847
GOF	1.1379	1.041
$\Delta\rho_{min}$ / $\Delta\rho_{max}$, *e*·cm^{-3}	0.44/-0.34	0.99/-0.60

Scanning of the potential energy surface of the rotational energy around N–N bond was carried out using the GAUSSIAN-03 software [24] at the BP86/6-31G(d) approximation level. Locating the corresponding transition states was performed according to the standard procedure in the BP86/6-311G(d,p) approximation (basis sets used by default in the GAUSSIAN-03 software). To obtain the activation energy values corresponding to local energy minimums, structures **4a**,**b** were reoptimized in an analogous approximation. Vibrational frequencies for all structures were calculated by an analytical method.

X-ray structural analysis of monocrystals of compounds **4a**,**b** were performed at -100°C on a Bruker Smart ApexII (λMo*K*α-beam) diffractometer. Both structures were solved by the direct method and refined by the least-squares technique in the full-matrix anisotropic approximation using SHELXS97 and SHELXL97 software [25, 26]. Chebyshev weight function was used in the refinement. The principal crystallographic data for compounds **4a**,**b** are presented in the Table 1. In both structures all hydrogen atoms were identified from the differential electron density synthesis and are included in the refinement with fixed positional and thermal parameters.

The full set of X-ray structural data for compounds **4a**,**b** was deposited in Cambridge Crystallographic Data Center (deposits CCDC 1003773 and CCDC 1003774, respectively).

The Supplementary materials containing detailed calculations data for isolated molecules of compounds **4a**,**b**, as well as Cartesian coordinates for all optimized structures are available for authorized users.

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