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New Phosphorus-Containing Macroheterocyclic Cavitands

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Abstract — Previously unknown phosphorus-containing macroheterocycles were prepared from an accessible symmetrical dipentaerythritol derivative and trivalent phosphorus compounds. The difference in the properties of the phosphocycles containing one and two phosphoric functions was revealed.
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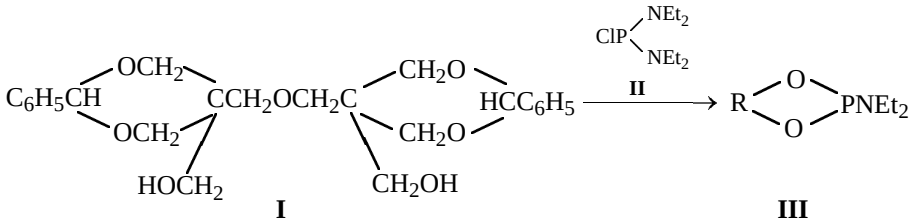
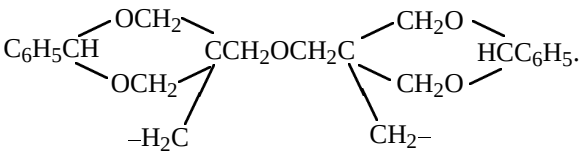
Phosphorus-containing macroheterocycles show promise for the modern supramolecular chemistry. Their significant advantage is the possibility of combining cavities of different configurations with the phosphorus-containing functional groups differing in the phosphorus valence and arrangement of substituents. Unfortunately, the design of such macroheterocycles is developed mainly in the direction of using them as common building blocks, and, therefore, the ranges of the examined molecular cavities remains limited [1–4]. Therefore, our goal was to expand the range of phosphorus-containing macroheterocycles by using as the starting compound dipentaerythritol, which was seldom used previously in fine organic synthesis. A specific structural feature of this compound is the presence of two quarternary carbon atoms. When incorporated in a macroheterocycle, these atoms can "enclose" a part of the space in the cavity.

Recently we showed that dipentaerythritol can be efficiently converted into symmetrical 1,3;1',3'-dibenzylidene derivatives **I** which show promise in the design of novel lipid systems [5]. Here we report on the cyclophosphorylation of this compound. The first part of the study deals with direct binding of two hydroxy groups of diol **I** by the phosphoric function. For such binding, we tested various derivatives of phosphorous acid, among which tetraethylphosphorodiamidous chloride **II** proved to be the most effective. First we studied the reaction of equimolar amounts of diol **I** with compound **II** in dioxane.

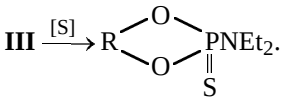


I **III** (1)

Here and hereinafter R = 

We found that the starting compound **I** in the presence of pyridine even at +5°C undergoes deep cyclophosphorylation within 2 h, involving the replacement of the chlorine atom and one diethylamino group at the phosphorus atom by the alkoxy group of diol **I**. In the course of the reaction, we observed in the ^{31}P NMR spectrum of the reaction mixture the disappearance of the signal of phosphorodiamidous

chloride **II** (δ_P 157.3 ppm) and growth of a signal in the range typical of monoamidocyclophosphites (δ_P 147.6 ppm, br.s). We also studied the reaction of **I** with **II** in 1 : 2 molar ratio and found that the expected bisphosphorylation did not occur. Instead, macrocycle **III** was formed, and a half of chloride **II** remained unchanged. This result shows that diol **I** preferentially undergoes cyclophosphorylation. Cycloamidophosphite **III** without isolation was easily converted into the corresponding 10-membered cyclophosphoramidothioate **IV** by treatment with sulfur at room temperature (25°C).



IV (2)

Phosphorothioate **IV** was isolated by chromatography on a column with silica gel. Its overall yield in the two steps was 65%. The product is an oily substance stable in storage at room temperature. Its purity and structure were proved by elemental analysis, TLC, and ^{1}H and ^{31}P NMR spectroscopy. The molecular weight of cyclophosphoramidothioate **IV** was confirmed by the MALDI-TOF mass spectrum.

The ^{31}P NMR spectrum of **IV** contains a broadened signal at δ_P 76.2 ppm. The ^{1}H NMR spectrum, along with the resonance of the *N*-ethyl protons as typical triplet and quartet at δ 1.14 and 3.17 ppm, respectively, contains signals of methylene protons of the molecular core (δ 3.80–4.59 ppm), a broadened singlet of the methine proton of the C*H*C_6H_5 group (δ 5.41 ppm), and also signals of two aromatic rings: two signals at δ 7.27 and 7.29 ppm and a broadened singlet at δ 7.48 ppm (*m*-, *p*-, and *o*-protons).

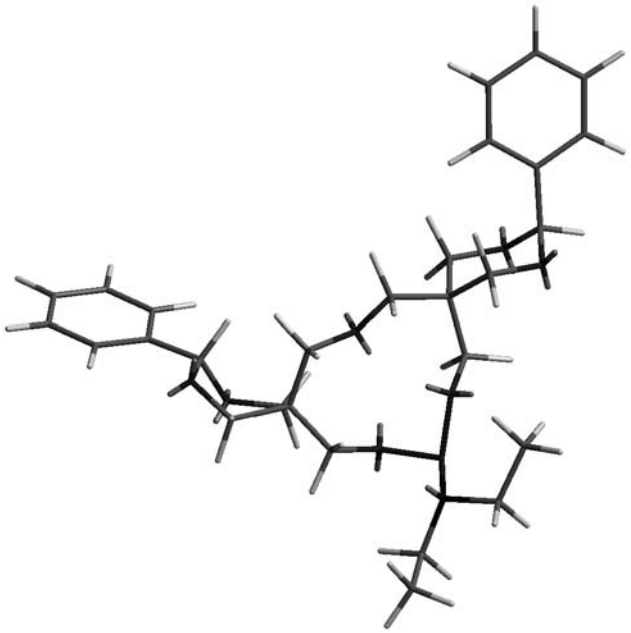
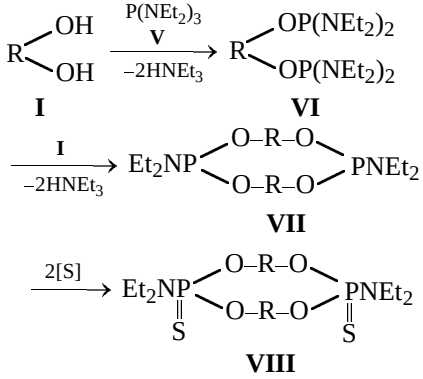


Fig. 1. Optimal conformation of the molecule of **IV**.

Note that the broadening of the signals of the C*H*C_6H_5 methine protons of the two 1,3-dioxane rings of **IV** can be due to their slight magnetic nonequivalence. Molecular modeling performed for the most favorable conformation of compound **IV**[1] showed that one of the 1,3-dioxane rings has a *boat* conformation and hence the *meso* proton of the ring is deshielded and its signal is shifted downfield, whereas the other 1,3-dioxane ring has a *chair* form, the related proton is shielded, and its signal is shifted upfield. This, broadening of these signals in the ^{1}H NMR spectra can be assigned to magnetic anisotropy of the aromatic rings (Fig. 1).

Another novel 20-membered cyclobis(phosphoramidothioate) **VIII** prepared from dibenzylidene pentaerythritol **I** but containing two phosphorothioic residues was synthesized by the method of molecular assembling using a new phosphorylating agent. Dimeric phosphocyclane **VIII** was synthesized in three steps: preparation of bisphosphorylated diol **VI**, cyclophosphorylation of the second molecule of diol **I** with **VI**, and addition of sulfur to the resulting cyclobisphosphite **VII**.



(3)

The reaction of diol **I** and phosphorous triamide **V** was performed at their molar ratio of 1 : 2 in dioxane at room temperature (25°C) without special removal of diethylamine formed in the process. In the course of bisphosphorylation (10 h), the signal of **V** (δ_P 117 ppm) disappears from the ^{31}P NMR spectrum of the reaction mixture, whereas the signal of phosphorodiamidous ester **VI** at δ_P 134.8 ppm (br.s) grows. In this case, the reaction result depends mainly on the

[1] Here and hereinafter, the molecular modeling of the compounds was performed for gas phase by the MM2 procedure in Chem 3D Ultra 7.0 package [6].

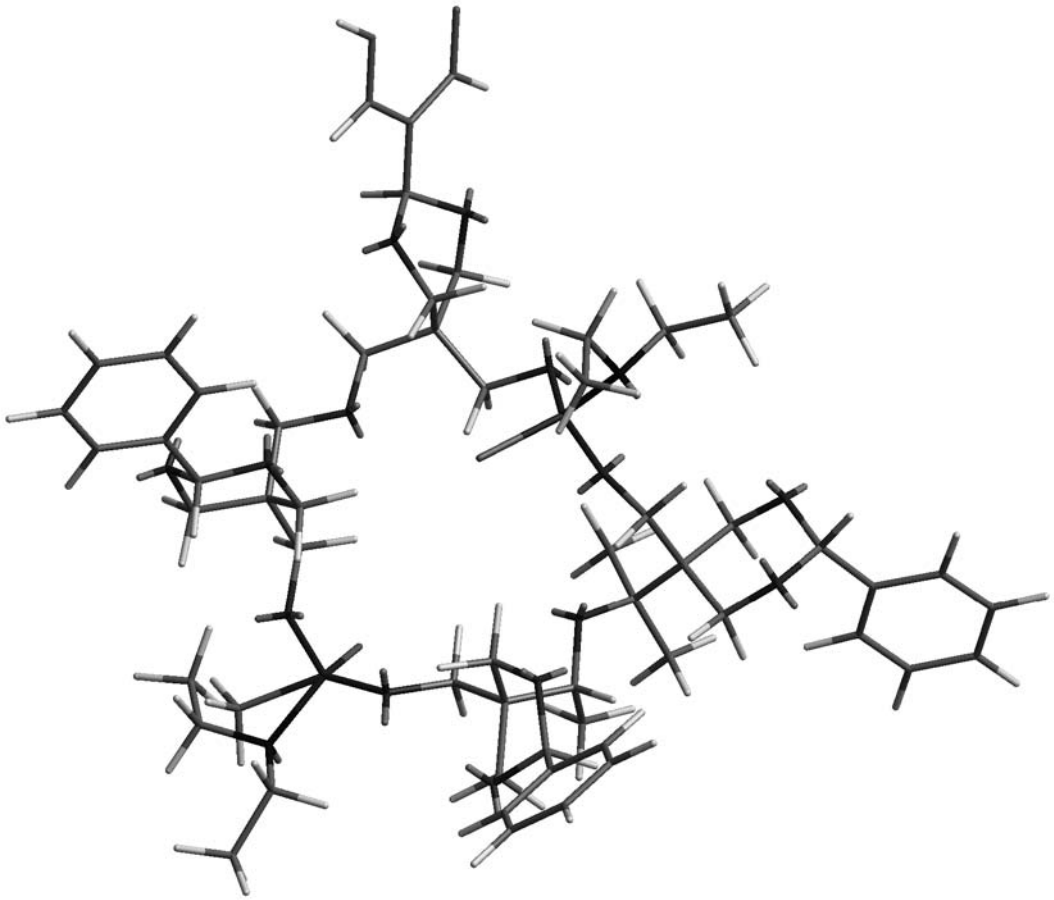


Fig. 2. Optimal conformation of the molecule of **VIII**.

duration of complete bisphosphorylation of diol **I**. The optimal time was elucidated using the results of monitoring the reaction mixture by ^{31}P NMR spectroscopy. After the reaction of **I** with **V** was complete, an additional 1 equiv of diol **I** was added, and the mixture was stirred at 65°C for 50 h. In the ^{31}P NMR spectrum, a broadened signal appeared at δ_P 147.6 ppm. Its chemical shift corresponds to the above-described monophosphocyclic compound **III**.

Phosphorothioate **VIII** was isolated by column chromatography; overall yield in three steps 60%. Compound **VIII** is an oily substance stable in storage. Its purity was confirmed by TLC and MALDI-TOF mass spectrometry. Its structure was proved by elemental analysis and ^{31}P NMR spectroscopy. The ^{31}P NMR spectrum of **VIII** contained a broadened singlet at δ_P 76.5 ppm, and the ^{1}H NMR spectrum contained signals from all proton groups expected for **VIII**. The spectrum of **VIII** closely resembles that of **IV**; the main difference is the existence of a broadened singlet at δ 1.70 ppm in the spectrum of **VIII** with the integral intensity corresponding to protons of one water molecule. We failed to remove water, which is incorporated in the composition of phosphocycle **VIII** in the course of its chromatographic isolation, even by heating for 5 h at 80°C in a vacuum (1 mm Hg).

The possibility of inclusion of a water molecule into **VIII** is confirmed by molecular modeling (Fig. 2). An essential feature of the steric structure of the 10-membered phosphocyclane **IV** and 20-membered diphosphocyclane **VIII** (calculated using van der Waals atomic radii) is the practical absence of a free internal cavity in the molecule of **IV**. The difference in the molecular geometries of **IV** and **VIII** (Figs. 1, 2) can be illustrated by the calculated distances between the atoms taken as the reference [6]. In **IV**, the distance between the quarternary carbon atoms is as short as 4.69 Å, while in the molecule of **VIII** the distance between the opposite phosphorus atoms reaches 7.39 Å, and the inclusion of a water molecule in the cavity of **VIII** is sterically possible.

The steric structure and geometric parameters of the molecules of 20-membered phosphocyclanes **VII**

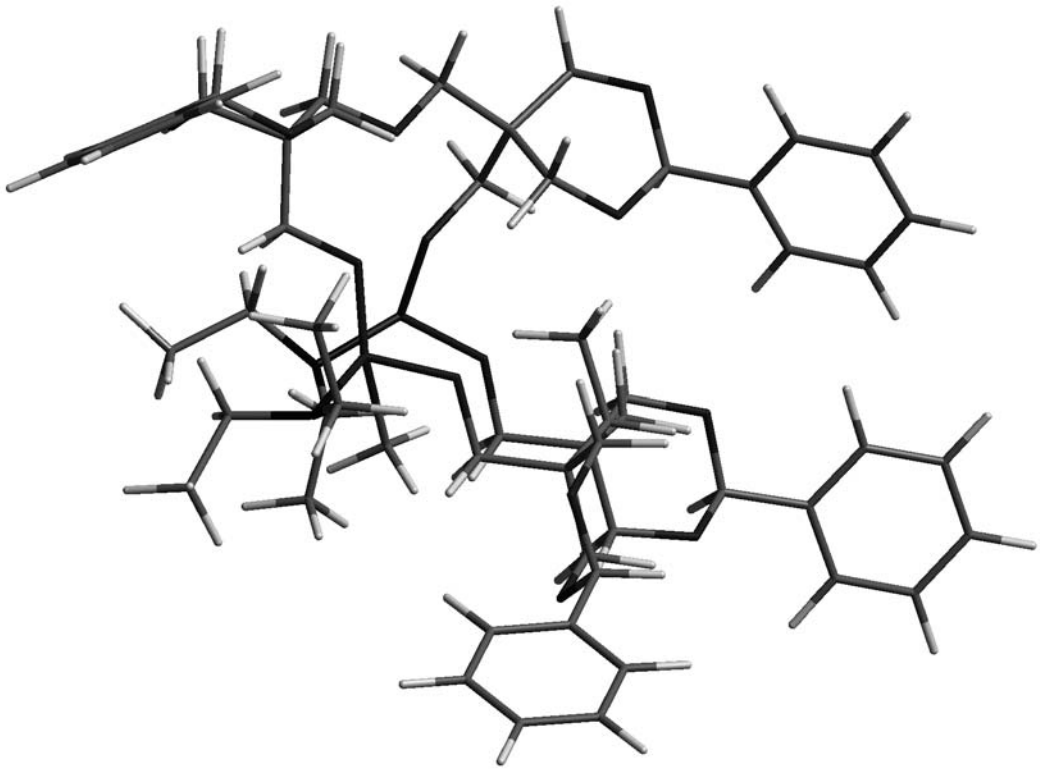


Fig. 3. Optimal conformation of the molecule of **VII**.

and **VIII** containing, respectively, tri- and pentavalent phosphorus atoms were examined in more detail. We compared the bond angles, interatomic distances, and potential energies of these phosphocycles. In **VII**, the OPO angles at the frontal endocyclic phosphorus atoms differ significanly from each other (166.08° and 96.30°). This difference in angles correlates with the difference in the distance between the carbon atoms of CH_2OCH_2 groups at the opposite sides of the cyclic molecules: 7.37 and 6.58 Å. One of the 1,3-dioxane rings is in *chair* conformation, while another has the conformation of a strongly twisted *boat*. These conformations alternate and the whole molecule of **VII** has a folded structure (Fig. 3). On the contrary, the molecule of **VIII**, due to a change in the delocalization of the electron density as compared to **VII**, has a rather regular geometry with alternating *chair–boat* conformations of the 1,3-dioxane rings. The OPO bond angles are close to each other (100.79° and 93.82°), and the distances between the carbon atoms in the CH_2OCH_2 groups at the opposite sides of the molecule differ insignificantly (7.84 and 7.28 Å).

Our experimental results show that phosphocyclanes **VII** and **VIII** are stable under ordinary conditions. However, they differ significantly in the steric energy: –86.6 and –134.92 eV, respectively. This fact apparently originates from the rigidity of P(V) derivative **VIII** compared to P(III) derivative **VII** which is conformationally labile.

To conclude, we demonstrated the possibility of preparing novel macroheterocycles based on dipentaerythritol derivatives. By choosing specific phosphorylating agents and reaction conditions, it is possible to obtain ring systems of different types.

EXPERIMENTAL

The ^1H NMR spectra were recorded on a Bruker WM-250 instrument (250 MHz); the chemical shifts are given relative to internal HNDS; the proton signals were assigned using double magnetic resonance experiments. The $^{31}P–\{^1H\}$ NMR spectra were taken on a Bruker WP-80SY spectrometer, operating frequency 32.4 MHz, external reference 85% phosphoric acid. The monoisotopic (^{12}C) molecular weights were measured on a Bruker UltraFlex (Bruker Daltomics, Germany) instrument. Adsorption chromatography was performed on a colum 15 mm in diameter, packed with silica gel L 100–250 μm. The R_f values were measured on Silufol UV-254 plates in the systems benzene–dioxane, 3:1 (A) and hexane–dioxane, 3:1 (B).

All syntheses involving trivalent phosphorus compounds were performed in an atmosphere of dry argon. Tetraethylphosphorodiamidous chloride **II** and hexaethylphosphorous triamide **V** were prepared as described in [7], and 1,3;1',3'-dibenzylidene pentaerythritol **I**, as in [6]; their constants coincided with the published data.

10-Membered cyclophosphoramidothioate IV. A solution of 0.15 g of acid chloride **II** in 5 ml of anhydrous dioxane was added dropwise with cooling to 5°C and stirring to a solution of 0.2 g of diol **I** and 0.5 g of pyridine in 10 ml of the same solvent. Then the mixture was warmed to 25°C and kept at this temperature for 2 h. The formation of cyclophosphite **III** was monitored by the ^{31}P NMR spectoscopy [δ_P 147.6 ppm, br.s (dioxane)]. Then 0.1 g of sulfur was added, and the reaction mixture was kept at room temperature for 3 h. Excess sulfur was filtered off, and the solvent was removed in a vacuum. Cyclophosphoramidothioate **IV** was purified by chromatography on a column packed with silica gel (5 g) and filled with hexane. Compound **IV** was eluted with 20 ml of a hexane–dioxane (5 : 1) mixture. The solvents were removed in a vacuum, and the residue was kept for 2 h at 80°C (1 mm Hg). Yield 0.17 g (65%), n_D^{20} 1.5663, R_f 0.83 (A), 0.55 (B). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.14 t (6H, NCH_2CH_3, $^3J_{HH}$ 7.01 Hz), 3.17 q (4H, NCH_2CH_3, $^3J_{HP}$ 13.73 Hz), 3.70 s (4H, CH_2OCH_2), 3.80 m (4H$_e$) and 4.55 m (4H$_a$) (CH_2OCH, ^2J(H$_a$H$_e$) 11.82 Hz), 4.18 m (4H, CH_2OP, $^3J_{HP}$ 9.94 Hz), 5.41 br.s (2H, CHC_6H_5), 7.36 br.s (6H, *m*, *p*) and 7.46 br.s (4H, *o*) (C_6H_5). ^{31}P NMR spectrum (dioxane), δ_P, ppm: 76.17 br.s. Found, %: C 59.59; H 6.74; P 5.46. $C_{28}H_{38}NO_7PS$. Calculated, %: C 59.66; H 8.80; P 5.50. *M* 563.65. Found, *M* (^{12}C): 562.90. Calculated, *M* (^{12}C): 563.34.

20-Membered cyclobis(phosphoramidothioate) VIII. A mixture of 0.3 g of diol **I** and 0.3 g of hexaethylphosphorous triamide **V** (molar ratio 1 : 2) in 3 ml of anhydrous dioxane was stirred for 12 h at 25°C. Formation of **VI** was monitored by ^{31}P NMR spectroscopy [δ_P 134.8 ppm, br.s (dioxane)}. Then one more equivalent of diol **I** (0.3 g) was added, and the reaction mixture was heated at 65°C for 50 h. Formation of phosphocycle **VII** was monitored by ^{31}P NMR spectroscopy [δ_P 147.6 ppm, br.s (dioxane)]. Then 0.15 g of sulfur was added at room temperature, and the mixture was heated for 1 h at 50°C. Excess sulfur was filtered off, and dioxane was removed in a vacuum. Compound **VIII** was purified by chromatography on a column packed with silica gell (5 g) and filled with benzene; the product was eluted with 30 ml of benzene. After removing the solvent in a vacuum, the residue was heated for 5 h at 80°C (1 mm Hg). Yield of **VIII** 0.48 g (60%), n_D^{20} 1.5738, R_f 0.75 (A), 0.45 (B). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.16 t and 1.26 t (12H, NCH_2CH_3, $^3J_{HH}$ 6.72 Hz), 1.69 br.s (2H, H_2O), 3.29 q (8H, NCH_2CH_3, $^3J_{HP}$ 11.16 Hz), 3.60 s, 3.70 s, 3.77 s (8H, CH_2OCH_2), 3.90 m (8H$_e$) and 4.60 m (8H$_a$) [CH_2OCH, ^2J(H$_a$H$_e$) 11.70 Hz], 4.14 m (8H, CH_2OP, $^3J_{HP}$ 10.50 Hz), 5.42 s and 5.43 s (4H, CHC_6H_5), 7.36 br.s (12H, *m*, *p*) and 7.47 br.s (8H, *o*) (C_6H_5). ^{31}P NMR spectrum (dioxane), δ_P, ppm: 76.52 br.s. Found, %: C 58.82; H 6.73; P 5.38. $C_{56}H_{76}N_2O_{14}P_2S_2 \cdot H_2O$. Calculated, %: C 58.70; H 6.69; P 5.41. *M* 1145.29. Found, *M* (^{12}C): 1126.38. $C_{56}H_{76}N_2O_{14}P_2S_2$. Calculated, *M* (^{12}C): 1127.67.

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REFERENCES

1. Bauer, I., Khabikher, V.D., Antipin, I.S., and Sinyashin, O.G., *Izv. Ross. Akad. Nauk, Ser. Khim.*, 2004, no. 7, p. 1348.
2. Alfimov, M.V., *Izv. Ross. Akad. Nauk, Ser. Khim.*, 2004, no. 7, p. 1303.
3. Finokkiaro, P., Failla, S., and Consiglio, G., *Izv. Ross. Akad. Nauk, Ser. Khim.*, 2005, no. 6, p. 1313.
4. Nifantyev, E.E., Maslennikova, V.I., and Merkulov, R.V., *Acc. Chem. Res.*, 2005, vol. 38, no. 2, p. 108.
5. Predvoditelev, D.A., Malenkovskaya, M.A., Strebkova, E.V., and Nifant'ev, E.E., *Zh. Obshch. Khim.*, 2006, vol. 76, no. 7, p. 1095.
6. Allinger, H.L., *J. Am. Chem. Soc.*, 1977, vol. 99, p. 8127.
7. Zwierzak, A., *Bull. Acad. Polon. Sci., Ser. Sci. Chim.*, 1965, vol. 13, no. 6, p. 609.