Unexpected Conformational Behaviour of a Diphosphate Derived from a Spherand-Type Calixarene

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The spherand-type calixarene **2a**, which consists of three diphenol units linked by methylene bridges, was treated with phosphorus pentachloride and then with water. A C_1-symmetrical conformation was found for the resulting bisphosphate **7** in the crystalline state by X-ray analysis, with an *anti* orientation of the phosphoryl groups. MM3 calculations lead to a nearly identical conformation for the most stable isomer (*RRS*-twist), while a slightly higher energy was found for an *RRS*-crown isomer with a *syn* orientation of the phosporyl groups. Surprisingly, all NMR studies (^{1}H, ^{13}C and ^{31}P) of **7** are in agreement with a dynamic C_2 symmetry in solution.

Introduction

Calixarenes such as compounds **1** are usually prepared by base-catalyzed condensation of 4-*tert*-butylphenol with formaldehyde.[1] Macrocyclic compounds consisting of three or four methylene-linked bisphenol units **2** can be obtained by analogous condensation reactions.[2,3] Structurally, they represent intermediates between spherands (where all phenolic units are directly linked) and calixarenes (where the phenolic units are linked by methylene bridges), which explains the name "spherand-type calixarenes".

Reactions of calixarenes with phosphorus pentachloride usually lead to the connection of three neighbouring hydroxy groups. Thus, a cyclic bisphosphate **3** has been isolated from *tert*-butylcalix[6]arene (**1b**) after hydrolysis of the primary reaction products with water.[4] The same bisphosphate was obtained by acylation with $ClP(O)(OEt)_2$ and subsequent heating.[5] More-complex reaction products have been found for calix[4]- and calix[8]arenes **1a** and **1c**, where the number of hydroxy groups is not a multiple of three, while for calix[9]arenes a triphosphate with *trans*-cavity bridging was isolated.[6] We have recently analyzed the very complicated stereochemical behaviour of the spherand-type calixarene **2a**,[7] and we became interested in studying its reaction with phosphorus pentachloride in comparison with the well known calix[6]arene. In addition to the stereochemical aspects, such phosphorus-containing macrocycles are of interest for the complexation of cations, especially the cations of the f-block elements.[8]

Results and Discussion

Treatment of the spherand-type calixarene **2a** with phosphorus pentachloride in the molar ratio 1:4 led to a reaction product for which the structure of the bis-phosphonium salt **4** is likely. The ^{31}P NMR spectrum of the reaction mixture displays three intense signals at δ = 25.9, 20.8 and –299.0 ppm. The positive chemical shifts suggest the formation of chlorotrioxyphosphonium cations, while the negative one corresponds to a hexachlorophosphate anion. This interpretation was confirmed by the addition of $SbCl_5$ to the reaction mixture, which did not change the signals with positive chemical shift while the signal with negative value was replaced by a new signal at δ = 86.0 ppm. This is in agreement with the formation of the hexachloroantimonates **5** and **6**.

As observed for the corresponding derivative of the calix[6]arene **1b**,[4b,4c] the two chlorophosphonium atoms are magnetically non-equivalent, which means that their environment is not identical. Considering the dication alone, this would mean that it contains neither a symmetry plane, which is unlikely for steric reasons, nor a twofold axis. Within ion pairs the difference could be due, at least in principle, to the situation of the anion(s), which would explain why only one phosphorus signal is found for **7**.

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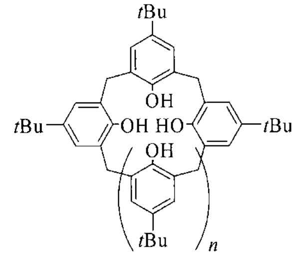
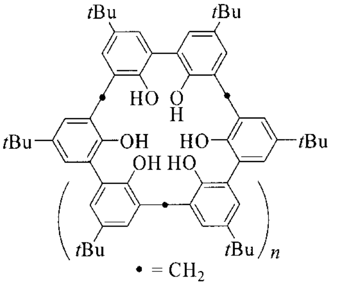
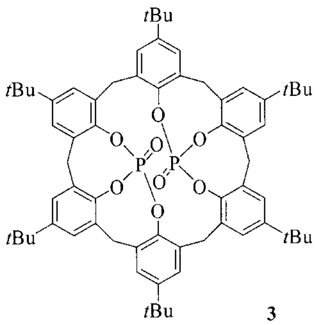


1a: $n = 1$
1b: $n = 3$
1c: $n = 5$



2a: $n = 1$
2b: $n = 2$



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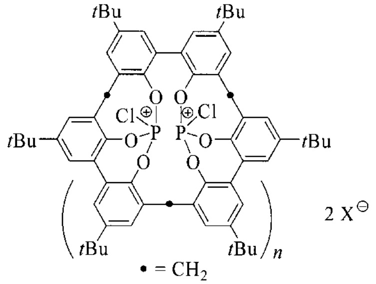
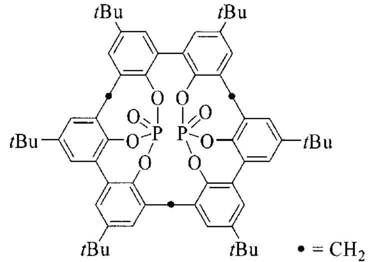
The salt **4** is extremely sensitive to hydrolysis and thus only its hydrolysis product, the bisphosphate **7**, was isolated and purified in 42% yield. Its ^{31}P NMR spectrum displays a single signal at δ = –7.14 ppm, which indicates an identical environment for both phosphorus atoms. Addition of (*S*)-1-(9-anthryl)-2,2,2-trifluoroethanol leads to the splitting of this signal (δ = –7.11, –7.17 ppm), thereby indicating the presence of two enantiotopic phosphorus atoms. Their presence in one molecule with C_S symmetry is sterically highly unlikely. A symmetry plane would require, for instance, that one of the bisphenol subunits adopts a planar conformation. Thus, a mixture of enantiomers **7A** and **7B** with two identical enantiotopic phosphorus atoms remains the most likely explanation. This means the molecules must have (dynamic) C_2 symmetry. No further splitting of the signals by freezing in a C_1-symmetrical conformation (see X-ray discussion) was observed in the ^1H or ^{31}P NMR spectrum upon cooling to –55 °C.



4: X = PCl_6 **6**: $PCl_4^{\oplus}$ $SbCl_6^{\ominus}$
5: X = $SbCl_6$



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We also tried the analogous reaction with PCl_5 followed by hydrolysis with the larger spherand calixarene **2b**, but without a definite result. The ^{31}P NMR spectrum (two signals at δ = –4.9 and –10.7 ppm) and the mass spectrum (m/z = 1489 and 1561) of the solid reaction product can be interpreted as being due to a mixture of a cyclic tetrachlorophosphate and a cyclic tetraphosphoric acid with -P(O)Cl- and -P(O)OH- bridges connecting the oxygens of the diphenylmethane subunits, respectively.

Reaction of **2a** with $POCl_3$ in the presence of *N*-methylmorpholine led to a bis(chlorophosphate) (according to elemental analysis and mass spectrum), for which three regioisomers exist if bridging occurs only between adjacent oxygens. Two signals at δ = 11.7 and –4.8 ppm in the ^{31}P NMR spectrum suggest a compound in which a biphenyl and a diphenylmethane subunit are bridged by -P(O)Cl-, although additional stereoisomers exist for these bridges.

Recrystallization of **7** from acetonitrile gave single crystals suitable for X-ray analysis. Figure 1 shows the conformation of **7** and the numbering scheme. The X-ray data confirm the structural properties discussed so far. The molecule contains two bicyclic phosphate subunits in which three adjacent phenolic oxygen atoms are involved in the formation of a seven- and an eight-membered ring. Both rings are connected by a phosphorus atom as bridgehead. Such a double bicyclic system has not yet been described to the best of our knowledge. The phosphoryl groups are found on different sides of the plane defined by the methylene carbon atoms, which means that they adopt an *anti* arrangement. This is in contrast to the analogous bisphosphates **3** obtained from *tert*-butylcalix[6]arene, where the phosphoryl groups are found in a *syn* position.[9] In contrast to the time-averaged C_2 symmetry found in solution, in the crystal the molecule assumes a conformation without any symmetry element (C_1 symmetry).

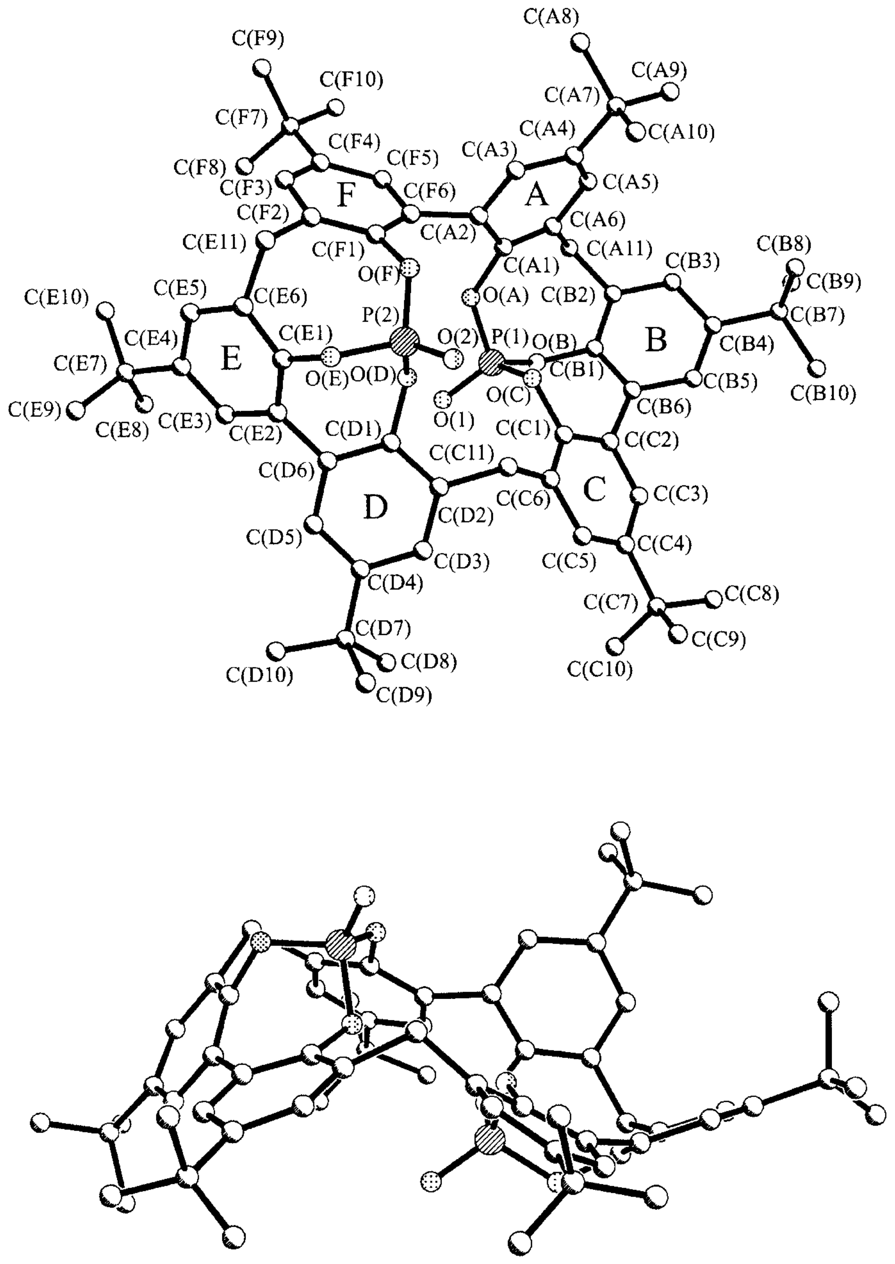

Figure 1. Crystal structure of **7** seen from two directions, including the numbering scheme used.

For the description of the stereochemistry of spherand-type calixarenes **2** it is reasonable to establish first the configuration of the bisphenol units (*R* or *S*). Two diastereomeric pairs of enantiomers exist with *RRR*/*SSS* and *RRS*/*SSR* configurations and dynamic D_3 and C_3 symmetry. These conformations have been discussed by analogy to the cyclotriveratrylenes by the mutual orientation of the methylene protons.[7] Two conformations can be distinguished for the *RRR*/*SSS* enantiomeric pair – a crown (the three axial methylene protons point in one direction) and a twist conformation (one of the axial methylene protons points in the opposite direction) with idealized C_3 and C_2 symmetries – and three conformations must be considered for the *RRS*/*SSR* enantiomeric pair, namely the crown and two twist conformations (with idealized C_2 and C_1 symmetries, respectively). For the diphosphates discussed here it seems more appropriate to look primarily to the situation of the two phosphoryl groups, which may be *syn* or *anti* with respect to the macrocycle (or its mean plane, defined by the methylene carbons). The *syn* orientation requires opposite configurations of the two phosphorus atoms while they are identical in the *anti* orientation. According to this description compound **7** is present in the crystal in the *anti* *RRS*-twist form.

Molecular mechanics calculations have been performed in order to estimate the relative energies for the different configurational or conformational isomers of **7**. The results of the calculations are summarized in Table 1. In agreement with the crystal structure, the *anti RRS*-twist isomer has the lowest energy. Only a slightly higher energy is predicted for

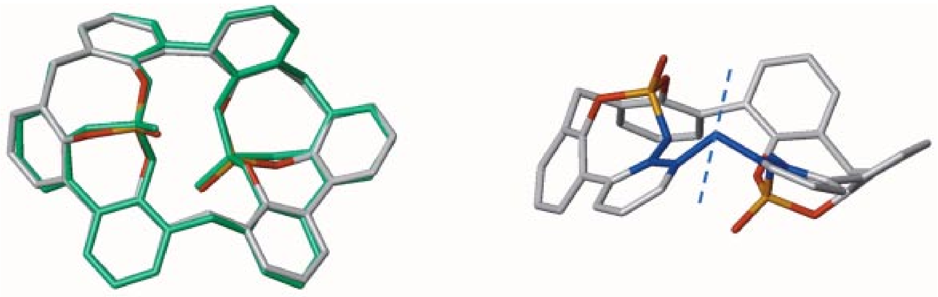

Figure 2. (a) Superposition of the molecule found in the crystalline state (carbon atoms in grey) with the calculated most-stable *RRS*-twist isomer of **7** (carbon atoms in green). (b) Illustration of the twofold axis suggested by the NMR results. The atoms indicated in blue [O(C), C(C1), C(C6), C(C11), C(D2), C(D1) and O(D)] show the most pronounced deviation from this axis and must be coplanar in the time-averaged conformation.

the *syn RRS*-crown isomer, which, however, was obviously not formed or isolated. Further isomers are distinctly higher in energy. As shown in Figure 2, the most stable isomer closely resembles the structure found in the crystal. The root mean square (rms) deviation of all heavy atoms, excluding the *tert*-butyl groups, is 0.26 Å. Table 2 compares the torsion angles around the aryl–aryl and aryl–CH_2 bonds and the bond angles for the two phosphorus atoms.

Table 1. MM3(96) calculated energies (kcal mol^{-1}) for the low energy isomers of b **7**.[a]

	FSE[b]	ΔE	ΣE_{bond}[b]	ΣE_{nonb}[b]
anti RRS-twist	107.0	0.0	39.2	67.8
syn RRS-crown	108.0	1.0	34.2	73.8
anti RRR-twist	111.8	4.8	35.6	76.2
syn RRR-crown	115.6	8.6	34.2	81.4

[a] A diphosphate of type **7** cannot adopt the *RRS*-twist (C_2) conformation for steric reasons. [b] FSE denotes the final steric energy, and ΣE_{bond} and ΣE_{nonb} denote the sum of the energies associated with bonding and nonbonding interactions, respectively.

Table 2. Comparison of the geometrical parameters of the X-ray structure and the isomer with the lowest energy obtained from MM3 calculations. Torsion angles around the π-bonds are also given to characterize the steric strain.

Torsion angles	X-ray structure	MM3
C(F1)–C(F6)–C(A2)–C(A1)	120.7	107.8
C(A1)–C(A6)–C(A11)–C(B2)	–95.6	–95.2
C(A6)–C(A11)–C(B2)–C(B1)	79.5	76.1
C(B1)–C(B6)–C(C2)–C(C1)	–41.9	–48.0
C(C1)–C(C6)–C(C11)–C(D2)	97.3	95.5
C(C6)–C(C11)–C(D2)–C(D1)	–121.7	–108.6
C(D1)–C(D6)–C(E2)–C(E1)	–37.5	–44.1
C(E1)–C(E6)–C(E11)–C(F2)	81.0	81.8
C(E6)–C(E11)–C(F2)–C(F1)	–83.9	–83.3
Bond angles		
O(A)–P(1)–O(B)	106.8	101.3
O(B)–P(1)–O(C)	102.4	103.9
O(C)–P(1)–O(1)	118.4	114.8
O(1)–P(1)–O(A)	109.9	113.6
O(F)–P(2)–O(E)	108.5	105.5
O(*E*)–P(2)–O(D)	101.4	103.9
O(D)–P(2)–O(2)	118.5	114.8
O(2)–P(2)–O(F)	111.1	114.0
Torsion angles around π-bonds		
O(C)–C(C1)–C(C6)–C(C11)	–7.2	–6.2
C(C4)–C(C5)–C(C6)–C(C11)	–171.8	–173.9
O(D)–C(D1)–C(D2)–C(C11)	14.3	3.6
C(D4)–C(D3)–C(D2)–C(C11)	172.7	177.5

In summary, single-crystal X-ray analysis and MM3 calculations show a molecular structure of C_1 symmetry, and both are in excellent agreement. On the other hand, the NMR spectroscopic data suggest a C_2-symmetrical molecule, as shown, for instance, by the presence of three singlets for the six *tert*-butyl groups in the ^{1}H NMR spectrum and a single signal for the two phosphorus atoms in the ^{31}P NMR spectrum. The twofold axis intersects the aryl–aryl C(F6)–C(A2) bond and the opposite methylene carbon C(C11). The two methylene protons appear as a singlet while the other two methylene groups [C(A11) and C(E11)] give rise to a doublet and a doublet of doublets. For this discrepancy only two tentative explanations can be offered: either there is an accidental isochrony for all the nuclei involved in a more or less rigid molecule with C_1 symmetry or there is a dynamic C_2 symmetry, which requires an exchange between involved atoms or groups that is rapid on the NMR timescale(s). Arguments against the first explanation are the quite different geometrical factors. For instance, the distance between C(C11) and P(1) and P(2) differs by 0.46 Å in the crystal structure and 0.36 Å in the calculated structure. The two methylene protons at C(C11) have calculated distances to the phosphorus atoms of 3.09/3.92 Å and 4.37/5.34 Å, and their distances to the adjacent aromatic protons at C(C5) and C(D3) are 2.55 and 3.70 Å, respectively. These differences are hardly compatible with exactly identical magnetic environments. A dynamic C_2 symmetry would require a time-averaged structure (transition state) in which the atoms O(C), C(C1), C(C6), C(C11), C(D2), C(D1) and O(D) are more or less in one plane. Considering the steric strain, which is expressed by those torsion angles collected in Table 2 and which in unstrained systems should be 0° or 180°, such a rapid equilibrium might be likely. MD simulations showed that such a conformational change is possible, although it occurs rarely even under rather drastic conditions (1000 K, corresponding to a high kinetic energy to overcome higher rotational barriers). Thus, we cannot draw a definite conclusion from the different experiments and the calculations at moment. It is, however, interesting to note that, as with the parent spherand-type calixarenes **2a**, the conformation with the highest symmetry does not correspond to the energy minimum.

Experimental Section

General Remarks: Melting points are uncorrected. The ^{31}P NMR spectra were recorded on a Varian Mercury 200 spectrometer, whereas the ^{1}H and ^{13}C NMR spectra were recorded on a Varian Inova 600 spectrometer equipped with a 5 mm inverse detection probe with a z-gradient coil. Unless otherwise stated $CDCl_3$ was used as solvent at room temperature. The assignment of the ^{1}H and ^{13}C resonances was achieved by measuring 2D spectra (COSY, HSQC and HMBC) and by selective 1D NOE spectra. All 2D and selective 1D spectra were obtained using pulse sequences from the Varian pulse-sequence library. The mass spectra were recorded on a Micromass Autospec instrument. The C and H analyses were performed with a CE Instruments Analyzer (Carlo Erba) and the P analysis on an ICP instrument Optima 3000VL (Perkin–Elmer).

Bisphosphate 7: A solution of **2a** (0.465 g, 0.5 mmol) and phosphorus pentachloride (0.208 g, 1.0 mmol) in dry dichloromethane (20 mL) was refluxed for 30 min. A sample of the solution showed three main signals in the ^{31}P NMR spectrum (δ = 25.9, 20.8, –299 ppm). The solution was then evaporated under reduced pressure and the residue dissolved in 5 mL of dioxane. Conc. HCl (20 mL) was added and the mixture refluxed for 1 h. After cooling a solid was separated by filtration, washed with water, dried and extracted with 10 mL of boiling hexane. The residue was purified by chromatography (silica gel, acetone/hexane, 1:3). Final recrystallization from chloroform/diethyl ether gave pure **7** (0.216 g, 42%), m.p. 464–466 °C. $C_{63}H_{72}O_8P_2$ (1019.2): calcd. C 74.24, H 7.14; found C 73.94, H 6.98. MS (FAB): m/z = 1019 [MH$^+$]. MS (MALDI-TOF): m/z = 1042 [MH + Na]$^+$. ^{1}H NMR: δ = 1.18 (s, 18 H, *t*Bu{F,A}), 1.37 (s, 18 H, *t*Bu{B,E}), 1.38 (s, 18 H, *t*Bu{C,D}), 3.62 (d, ^2J = 13.2 Hz, 2 H, CH_2 $\{A_{11},E_{11}\}$), 4.15 (s, 2 H, $CH_2\{C_{11}\}$), 4.84 (dd, ^2J = 13.2, ^4J = 2.5 Hz, 2 H, $CH_2\{A_{11},E_{11}\}$), 6.59 (br. s due to ^4J = 2.5 Hz and ^4J = 2 Hz, 2 H, ArH$\{F_3,A_5\}$), 7.10 (d, ^4J = 2 Hz, 2 H, ArH$\{F_5,A_3\}$), 7.20 (d, ^4J = 2 Hz, 2 H, ArH$\{B_5,E_3\}$), 7.42 (d, ^4J = 2 Hz, 2 H, ArH$\{B_3,E_3\}$), 7.52 (d, ^4J = 2 Hz, 2 H, ArH$\{C_3,D_5\}$), 7.67 ppm (d, ^4J = 2 Hz, 2 H, ArH $\{D_5,C_3\}$). ^{13}C NMR: δ = 29.58 (s, 1 C, C_{11}), 31.14 (s, 6 C, F_{8-10},A_{8-10}), 31.37 (s, 6 C, B_{8-10},E_{8-10}), 31.41 (s, 6 C, C_{8-10},D_{8-10}), 34.17 (s, 2 C, F_7,A_7), 34.51 (s, 2 C, C_7,D_7), 34.68 s (2 C, B_7,E_7), 34.83 (s, 2 C, A_{11},E_{11}), 123.13 (s, 2 C, C_3,D_5), 124.02 (s, 2 C, B_3,E_5), 125.59 (s, 2 C, B_5,E_3), 127.58 s (2 C, F_3,A_5), 128.08 (s, 2 C, C_5,D_3), 128.51 (d, $^3J_{P,C}$ = 2.4 Hz, 2 C, B_6,E_2), 128.90 (s, 2 C, C_6,D_2), 129.42 s (2 C, F_5,A_3), 132.27 (d, $^3J_{P,C}$ = 2.4 Hz, 2 C, C_2,D_6),132.45 (d, $^3J_{P,C}$ = 5.8 Hz, 2 C, F_6,A_2), 133.49 (d, $^3J_{P,C}$ = 1.9 Hz, 2 C, F_2,A_6), 133.62 (d, $^3J_{P,C}$ = 5.8 Hz, 2 C, B_2,E_6), 142.49 (d, $^2J_{P,C}$ = 10.9 Hz, 2 C, F_1,A_1), 143.00 (d, $^2J_{PC}$ = 12.0 Hz, 2 C, B_1,E_1), 144.45 (d, $^2J_{P,C}$ = 9.2 Hz, 2 C, C_1,D_1), 147.85 (s, 2 C, F_4,A_4), 149.38 (s, 2 C, B_4,E_4), 149.81 ppm (s, 2 C, D_4,C_4).

X-ray Structure Analysis: Colourless crystals with dimensions 0.1 × 0.15 × 0.15 mm, monoclinic space group $P2_1/n$, a = 16.911(3), b = 17.563(4), c = 22.428(4) Å, β = 98.96(3)°, V = 6580.01 Å^3, Z = 4, T = 293 K. Data were collected with an Enraf–Nonius CAD-4 diffractometer in $\omega/2\theta$ scan mode with Mo-K_α radiation, collected reflections 12267, independent reflections 3953. The structure was solved by direct methods,[10] and structure refinement with a full-matrix least-squares procedure on F^2; R_1 (on F) = 0.135, wR_2 (on F^2) = 0.343, GoF = 1.014.

CCDC-258871 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Computational Studies: The conformational analysis of **7** was carried out with the stochastic search routine of MM3(96) using the default conditions, except for the number of cycles, which was set to 10000. Missing parameters for the C_{Ar}–O–P=O torsion angles were taken from the MM3 parameter estimator and used without further modification. A molecular dynamics simulation in vacuo was performed starting from the lowest energy *RRS*-twist isomer for 1 ns at 500 K followed by 2 ns at 1000 K using the Tripos force field.[11] The analysis and visualization of the calculated structures was performed with the SYBYL program package.[12]

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