X-RAY STRUCTURES AND MOLECULAR ORBITAL CALCULATIONS OF 6-PHOSPHAPENTACYCLO-$[6.3.1.0^{2,4}.0^{3,7}.0^{5,10}]$DODECANE 6-OXIDES

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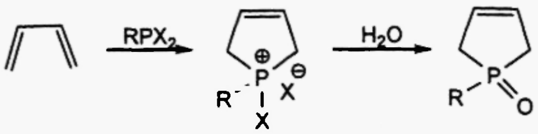
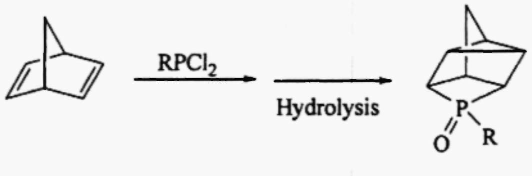
Abstract: The X-ray analyses of a novel type of the P-caged compounds, 6-ethyl and 6-chloro-6-phosphapentacyclo-$[6.3.1.0^{2,4}.0^{3,7}.0^{5,10}]$dodecane 6-oxide 4b, 4c established the same *cis*-stereochemistry around the phosphorus atom as that of the previously reported 4a. The results of molecular orbital calculations of 4 and their *trans*-isomers at semiempirical, *ab initio*, and DFT (DGauss) levels were in agreement with the more thermodynamically stable 4 than the non-obseved *trans*-isomer.

Introduction

Among the large numbers of heterocyclic compounds, a relatively few caged heteropolycycles have been investigated. Although a few bridged aza- (1)、 oxa- (2) and phosphacycles (3) have been reported, to the best of our knowledge, only a few caged heteropolycycles have been known. Among them, aza- (1a) and oxaiceanes (called 3-oxawurtzitane by Swiss group) (2a,b) are classically notable examples. A more recent example is a caged polynitrosamine (1e). One of the simplest strategies for construction of such caged compounds would be the homo-Diels-Alder reaction with bicycle[2.2.1]heptadiene (norbornadiene) (1f) and thus the first caged phosphocycle, e.g. 4-methyl-4-phophatetracyclo$[3.3.0^{2,8}0^{3,6}]$ 4-oxide 1, was synthesized by analogous cheletropic tactics (McCormack reaction; Scheme-1, 2) (3a-d, 4). Previously, we have briefly reported, employing McCormack reaction, a facile synthesis of 6-phosphapentacyclo$[6.3.1.0^{2,4}.0^{3,7}.0^{5\ 10}]$dodecane 6-oxides 4. Structure 4a was unambiguously established by an X-ray analysis (5) (Scheme-3). We now describe X-ray structures of 4b and 4c as well as the results of computational calculations of 4a-c.

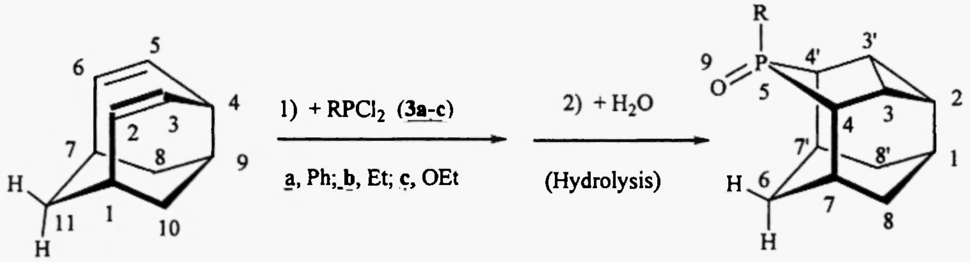


Scheme 1. McCormack cycloaddition reaction



R=Me; 1

Scheme 2. Formation of phosphatetracyclo$[3.3.0.0^{2,8}.0^{3,8}]$octane 4-oxides



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4a-c

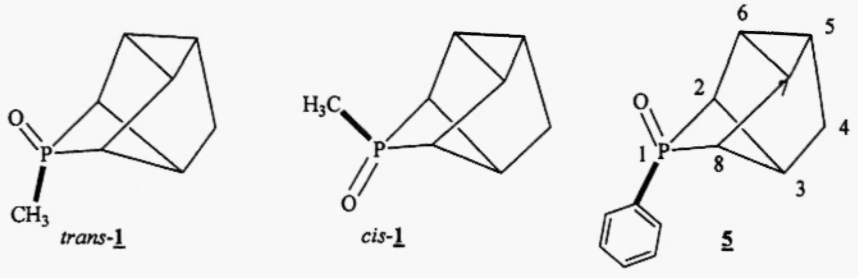
4a: R=Ph 85 %
4b: R=Et 40 %
4c: R=Cl 19 %

Scheme 3. Reaction of tricyclo[5.3.1.$0^{4,9}$]undeca-2,5-diene 2 with dichlorophosphines 3

Results and Discussion

Preparation, reactions, and stereochemistry of 4-methyl-4-phosphatetracyclo[3.3.$0^{2,8}$.$0^{3,6}$] 4-oxide 1 and its derivatives have been intensively investigated by Cremer *et al.* in connection with phosphetanes which received extensive review (6). In contrast to the earlier reports (3a), they obtained a mixture of *trans*-1 and *cis*-1. The former was thermodynamically stable (7). Whereas employment of dibromophenylphosphine with norbornadiene at rt for 2 weeks after hydrolysis gave only *trans*-4-phenyl-4-phosphatetracyclo[3.3.$0^{2,8}$.$0^{3,6}$] 4-oxide 5 in 13 % yield. Peculiarly enough no reproducibility was observed. Stereochemical assignments for *trans*-1 and *cis*-1 were based upon NMR lanthanide shift experiments (3d,8), while the structure of 5 was later established by an X-ray analysis along with those of the more stable sulfur analogs of 1 (8). Recently, we reported a comparative study of X-ray structures and molecular orbital calculations of 4a and 5 (9). In the solid state, 5 is much more strained and asymmetric, whereas 4a is less strained and highly symmetric. The results of molecular orbital calculations were in complete agreement with the more thermodynamic stability of 4a compared with *trans*-6-phenyl-6-phosphapentacyclo-[6.3.1.$0^{2,4}$.$0^{3,7}$.$0^{5,10}$]dodecane 6-oxide (7). Whereas this was not the case for 5 and its isomer *cis*-4-phenyl-4-phospha-tetracyclo[3.3.$0^{2,8}$.$0^{3,6}$] 4-oxide.

In contrast with norbornadiene, tricyclo[5.3.1.$0^{4,9}$]undeca-2,5-diene 2 (10) possessing the same 1,4-pentadiene moiety underwent a smooth cheletropic reaction with dichlorophosphine 3a to produce 4a in 85 % isolated yield even at rt for 21 h. Analogous reactions of 2 with dichloroethylphosphine 3b and dichloroethoxyphosphine 3c gave the corresponding 6-ethyl-6-oxide 4b and 6-chloro-6-oxide 4c albeit in much lower yields, e.g. in 40 and 19 % isolated yields. X-ray analyses of 4b and 4c established *cis* stereochemistry (7) of ethyl and chloro group around phosphorus atom. The ORTEP drawings of 4b and 4c are shown in Figure-1 (11). In the latter case, the elimination of ethoxide ion rather than chloride ion took place upon hydrolysis of the initial adduct.



trans-1 *cis*-1 5

Scheme 4. 4-Phophatetracyclo[3.3.$0^{2,8}$.$0^{3,6}$]octane 4-oxides

In Table 1, the bond lengths and bond angles of 4 are summarized. An inspection of the Table reveals 4a is completely symmetric, whereas 4b and 4c are slightly but less asymmetric than 5 in the solid state (8). This asymmetric character is generally attributed to "forces" in solid state (8). It was noted that 4b and 4c are completely symmetric in solution as confirmed by ^1H and ^{13}C NMR studies (12).

Although both the transition state structure of an initial McCormack reaction and the mechanism of hydrolysis of the initial adducts are unknown, it is believed that thermodynamically more stable phosphine oxides form predominantly in McCormack reaction regardless of the stereochemistry of an initial cheletropic adduct because of intervention of subsequent hydrolysis process (3d, 4).

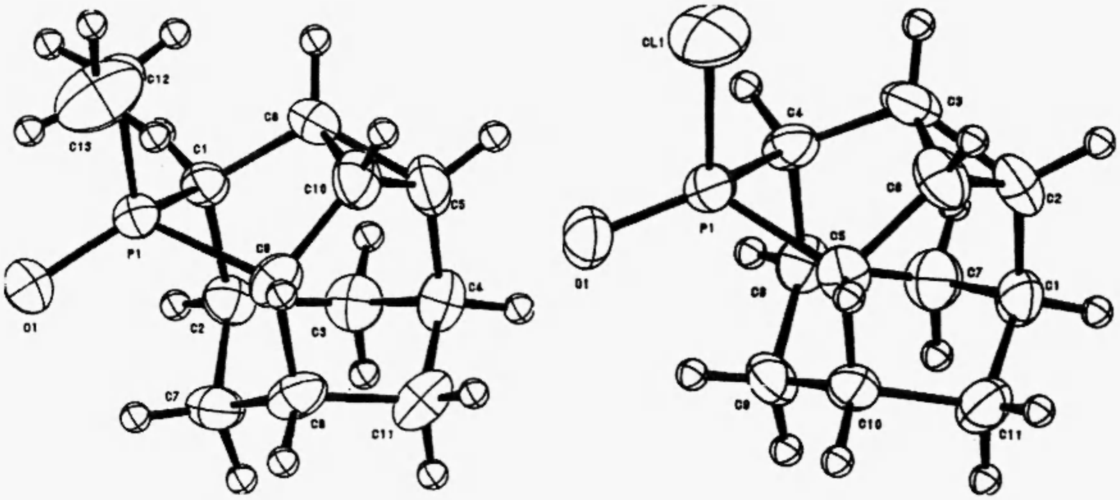


Figure-1 : ORTEP Drawings of 4b and 4c

Table-1 : Selected bond lengths (Å) and bond angles (°) for 4a-c

Atoms	4a	4b	4c	Atoms	4a	4b	4c
C1-C2	1.515 (3)	1.517(3)	1.510(6)	C4 P5 C4'	89.1(1)	87.98(9)	89.6(1)
C4-C7	1.568(2)	1.574(3)	1.572(5)	P5 C4 C7	110.1(1)	109.1(1)	107.0(2)
C4'-C7'	1.568(2)	1.570(3)	1.566(5)	P5 C4' C7'	110.1(1)	110.4(1)	107.5(2)
C2-C3	1.502 (3)	1.496(3)	1.487(6)	C2 C3 C3'	59.4(1)	59.5(2)	59.1(3)
C2-C3'	1.502 (3)	1.504(3)	1.484(6)	C2 C3' C3	59.4(1)	59.0(1)	59.3(3)
C3-C3'	1.528 (3)	1.533(3)	1.521(6)	C3 C2 C3'	61.1(1)	61.5(1)	61.6(3)
C4-P5	1.883 (2)	1.835(3)	1.827(3)	C3 C4 C7	114.8(1)	114.7(2)	114.4(3)
C4'-P5	1.883 (2)	1.841(3)	1.835(3)	C3' C4' C7'	114.8(1)	114.3(2)	114.0(3)
CR-P5	1.809 (2)	1.814(2)	2.045(1)	C4 C3 C2	120.0(1)	119.7(2)	119.9(3)
C3-C4	1.522(2)	1.525(3)	1.529(5)	C4' C3' C2	120.0(1)	119.8(2)	120.2(3)
C3'-C4'	1.522(2)	1.520(3)	1.526(5)	C4' C3' C3	110.0(1)	109.5(2)	110.2(3)
C1-C8	1.526(2)	1.528(3)	1.530(5)	C4 C3 C3'	110.1(1)	109.6(2)	110.4(3)
C1-C8'	1.526(2)	1.531(3)	1.529(5)	C3 C2 C1	119.6(1)	120.1(2)	120.1(3)
C6-C7	1.531(2)	1.530(3)	1.523(5)	C3' C2 C1	119.6(1)	119.7(2)	120.1(3)
C6-C7'	1.531(2)	1.535(3)	1.536(5)				
C7-C8	1.530(2)	1.532(3)	1.531(5)				
C7'-C8'	1.530(2)	1.532(3)	1.533(5)				

Table 2. Calculated energies and heats of formation for 4 and non-observed products.[a)]

Method	4a			4b			4c		
	(Obsrvd)	(Not obsrvd)	Δ E[b)]	(Obsrvd)	(Not obsrvd)	Δ E[b)]	(Obsrvd)	(Not obsrvd)	Δ E[b)]
MM3	51.78	50.47	-1.31	58.07	61.74	3.67	49.07	49.42	0.35
AM1	-11.86	-4.34	7.52	-52.47	-40.85	11.62	-59.42	-49.11	10.31
PM5	-41.02	-38.97	3.05	-75.12	-71.15	3.97	-97.19	-94.09	3.10
6-31G**	-1070.43336	-1070.42525	5.09	-918.96222	-918.95081	7.10	-1299.80805	-1299.79945	5.40
B88-PW91	-1075.82677	-1075.82021	4.12	-923.40388	-923.39308	6.78	-1304.37254	-1304.36594	4.14
B88-LYP	-1075.55527	-1075.54817	4.46	-923.16372	-923.15387	5.55	-1304.15186	-1304.15186	3.92
D-VWP	-1068.15319	-1068.14526	4.98	-917.07233	-917.06016	7.64	-1297.29828	-1297.29046	4.91

a) Not obsrvd means *trans*-isomer of 4 which were not obtained. For calculation methods, see experimental. The units of MM3, AM1, and PM5, methods are shown in kcal/mol, while *ab initio* and DFT methods are shown in au.

b) Energy differences in kcal/mol with respect to the observed product.

In order to help clarify the thermodynamic stability of 4 and the non-observed *trans*-isomers of 4, molecular orbital calculations of 4 at semiempirical, *ab initio*, and DFT(DGauss) levels were performed. The results are shown Table 2. Geometrical optimiza 4b and 4c also led to an exactly symmetric structure (C1) probably due to the effect of packing on structure was not under consideration in the present work. The results indicate that **4** is much more thermodynamically stable than the non-observed *trans*-isomers of **4,** which is in agreement with the experimental results.

Experimental

4b and 4c were prepared exactly in a similar fashion as reported previously (9). Molecular mechanics, semiempirical, and DFT(DGauss) calculations were performed using a CAChe V7 package (Fujitsu : MM3, AM1, PM5, B88-PW91, B88-LYP and D-VWP). *Ab initio* calaculations were carried out using a Spartan '04 Windows software package (Wavefunction, Inc.: 6-31G**). Geometry optimizations were carried out until convergence was attained.

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References and Notes

1. a) R. O. Klaus and C. Ganter, *Helv. Chim. Acta.*, **63**, 2559 (1980); b) R. Furstoss, R. Tadayoni and B. Waegell, *J. Org. Chem.*, **42**, 2844 (1977); c) A. T. Nielsen, S. L. Christian and D. W. Moors, *J. Org. Chem.*, **52**, 1656 (1987); d) J. Lacrampe, A. Heumann, R. Furstoss and B. Waegell, *J. Chem. Res. Synopses*, 334 (1978); e) A. T. Nielsen, T. Arnold, A. P. Chafin, S. L. Christian, D. W. Moore, M. P. Nadler, R. A. Nissan, D. J. Vanderah, R. D. Gilardi, C. F. George, F. Clifford and J. L. Flippen-Anderson, *Tetrahedron*, **54**, 11793 (1998); f) E. M. Burrage, R. C. Cookson, S. S. Gupte and I. D. R. Stevens, *J. Chem. Soc. Perkin Trans 2*, 1325 (1975).
2. a) R. O. Klaus, H. Tobler and C. Ganter, *Helv. Chim. Acta.*, **57**, 2517 (1974); b) D. P. G Hamon, G F. Taylor and R. N. Young, *Aus. J. Chem.*, **30**, 589 (1977); c) J. L. Jessen, C. Wolff and W. Tochtermann, *Chem. Ber.*, **119**, 297 (1986); d) M. Sander and E. V. Dehmlow, *Org. Prep. Proc. Int.*, **32**, 189 (2000); e) S. Muthusamy, S. A. Babu, C. Gunanathan, E. Suresh, P. Dastidar and R. V. Jasra, *Tetrahedron*, **57**, 7009 (2001).
3. a) M. Green, *Proc. Chem. Soc.*, 177 (1963); *J. Chem. Soc.*, 541 (1965); b) S. E. Cremer, F. R. Farr, P. W. Kremer, H.-O. Hwang, G. A. Gray and M. G. Newton, *J. Chem. Soc. Chem. Commun.*, 374 (1975); c) R. M. Mazhar-ul-Haque and S. E. Cremer, *J. Chem. Soc. Perkin Trans.* **2**, 1115 (1978); d) S. E. Cremer, J. M. Cowles, F. R. Farr, H.-O. Hwang, P. W. Kremer, A. C. Peterson and G. A. Gray, *J. Org. Chem.*, **57**, 511 (1992).
4. L. D. Quin, 'The Heterocylic Chemistry of Phosphorous' Wiley-Interscience, New York, 1981, Chap.2.
5. M. Toda, I. Miyahara, K. Hirotsu, R. Yamaguchi, S. Kojima and K. Matsumoto, *Chem. Lett.*, 1677 (1991).
6. L. D. Quin, 'The Heterocylic Chemistry of Phosphorous' Wiley-Interscience, New York, 1981, Chap.4 and references cited therein.
7. For convenience, stereochemical nomenclature was used according to Cremer *et al.* (3d).
8. T. M. Lane, A. C. Peterson, S. E. Cremer, D. W. Bennett and P. E. Fanwick, *Main Group Chemistry*, **2**, 43 (1997).
9. K. Matsumoto, M. Toda, H. Iida and H. Hamana, *Heterocycles*, **70**, 627 (2006).
10. T. Katsushima, R. Yamaguchi and M. Kawanishi, *J. Chem. Soc. Chem. Commun.*, 692 (1975); *Bull. Chem. Soc. Jpn.*, **55**, 3245 (1982); T. Katsushima, K. Maki, R. Yamaguchi and M. Kawanishi, *Bull. Chem. Soc. Jpn.*, **53**, 2031 (1980).
11. Crystal data:4b: $C_{13}H_{19}OP$, M=222.27, monoclinic, space group P21/c, a=9.964 (3), b=8.924 (2), c=12.758 (2)Å , β=92.77 (2)°, *U*=1130.0 (4) Å ^{3}, Z=4, Dc=1.303gcm^{-1}, μ=2.07 cm^{-1}. 2926 Reflections with 2θ<55.0 were recorded on a four circle diffractometer (Rigaku AFC5S) with graphite-monocromated Mo-Kα radiation. The structure was solved by direct method and refined by full-matrix least-squares method to R=0.045 (R_w=0.052) for 2096 reflections with I>2σ(I). 4c:, $C_{11}H_{14}OPCl$, M=228.86, orthorhombic, space group Pca2_1, a=10.721 (1), b=9.213 (1), c=10.463 (1)Å , *U*=1033.3 (4)Å ^{3}, Z=4, Dc=1.470 gcm^{-1}, μ=4.83 cm^{-1}. 1393 Reflections with 2θ<54.9; R=0.032 (R_w=0.037) for 1125 reflections with I>2σ(I)
12. Detailed aspects of spectroscopic data as well as transition state structures will be reported elsewhere in due oourse.

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