HETEROCYCLES, Vol. 70, 2006, pp. 627 - 633. © The Japan Institute of Heterocyclic Chemistry
Received, 10th October, 2006, Accepted, 15th November, 2005, Published online, 17th November, 2006. COM-06-S(W)57

COMPARATIVE STUDY OF X-RAY STRUCTURES AND MOLECULAR ORBITAL CALCULATIONS OF 6-PHENYL-6-PHOSPHAPENTACYCLO[6.3.1.0^{2,4}.0^{3,7}.0^{5,10}]DODECANE 6-OXIDE WITH 4-PHENYL-4-PHOSPHATETRACYCLO-[3.3.0^{2,8}.0^{3,6}]OCTANE 4-OXIDE

Kiyoshi Matsumoto, *[1] Mitsuo Toda,[2] Hirokazu Iida,[1] and Hiroshi Hamana[1]

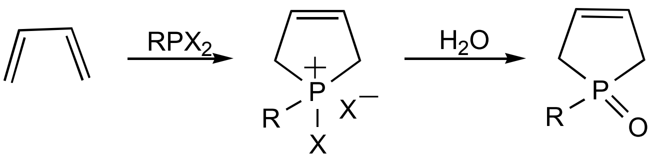
[1] Faculty of Pharmaceutical Sciences, Chiba Institute of Science, Choshi, Chiba 288-0025, Japan (E-mail:kmatsumoto@cis.ac.jp). [2] Faculty of Engineering, Shizuoka University, Hamamatsu, Shizuoka 432-8561, Japan

Dedicated to Professor Steven M. Weinreb on the occasion of his 65th birthday

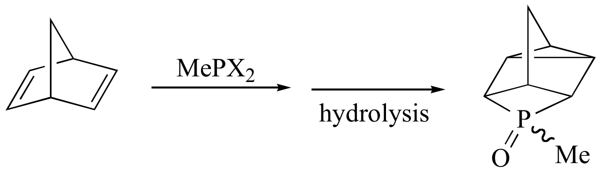
Abstract –A novel P-cage type of the title compounds were discussed in terms of X-Ray analyses and molecular orbital calculations. In solid state, *trans*-4-phenyl-4-phosphatetracyclo[3.3.0^{2,8}.0^{3,6}]octane 4-oxide (*trans*-**5**) is much more strained and asymmetric, whereas *cis*-6-phenyl-6-phosphapentacyclo[6.3.1.0^{2,4}.0^{3,7}.0^{5,10}]dodecane 6-oxides (*cis*-**4**) is less strained and highly symmetric. Molecular mechanics, semi-empirical, *ab initio*, and DFT calculations were used to estimate the relative energy of *cis*-**4**, *trans*-**4**, *cis*-**5**, and *trans*-**5**.

INTRODUCTION

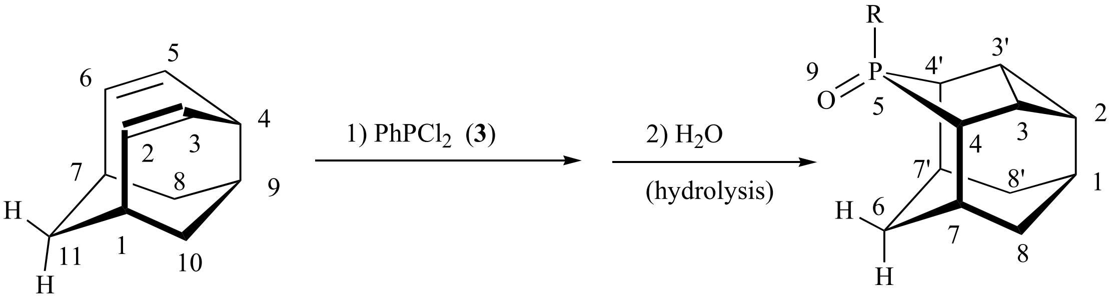
Among the large numbers of heterocyclic compounds, a relatively few caged heteropolycycles have been investigated. Although a few bridged aza-,[1] oxa-[2] and phosphacycles[3] have been reported, to the best of our knowledge, only a few caged heteropolycycles have been known. Among them, aza-[1a] and oxaiceanes (called as 3-oxawurtzitane by Swiss group)[2a,b] are classically notable examples. A more recent example is caged polynitrosamine.[1e] One of the simplest strategy for construction of such caged compounds would be homo-Diels-Alder reaction with bicyclo[2.2.1]heptadiene (norbornadiene)[1f] and thus the first caged phosphocycle, e.g. 4-phosphatetracyclo[3.3.0^{2,8}0^{3,6}]octane 4-oxides (**1**), was synthesized by an analogous cheletropic tactics (McCormack reaction; Scheme 1, 2).[3a-d, 4] Previously, we have briefly reported, employing McCormack reaction, a facile synthesis of *cis*-6-phenyl-6-phosphapentacyclo-[6.3.1.0^{2,4}.0^{3,7}.0^{5,10}]dodecane 6-oxide (*cis*-**4**) whose structure was unambiguously established by an X-Ray analysis (Scheme 3).[5,6] It occurred to us that a comparative study of X-Ray structures of the observed adducts as well as molecular orbital calculations of the phenyl analog of **1** and **4** is worthy of investigation. This is a subject of the present paper.



Scheme 1. McCormack cycloaddition reaction

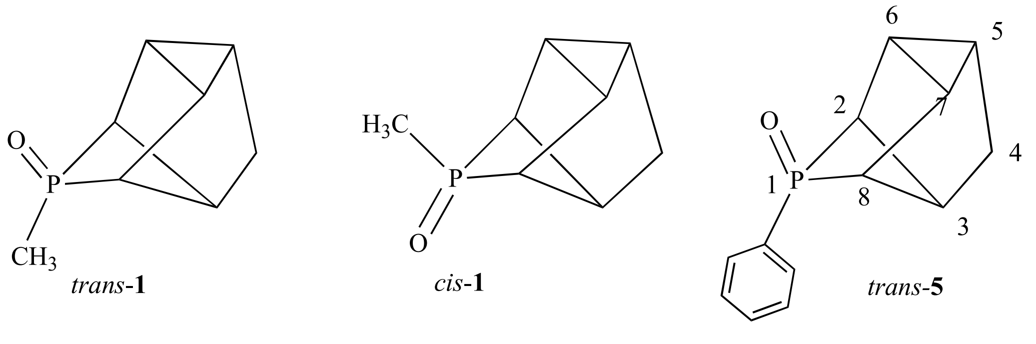


Scheme 2. Formation of 4-methylphosphatetracyclo[3.3.0,0^{2,8},0^{3,8}]octane 4-oxides



Scheme 3. Reaction of tricyclo[5.3.1.0.^{4,9}]undeca-2,5-diene (**2**) with dichlorophenylphosphine (**3**)

RESULTS AND DISCUSSION



Scheme 4. 4-Phosphatetracyclo[3.3.0^{2,8}.0^{3,6}]octane 4-oxides

Preparation, reactions, and stereochemistry of 4-methyl-4-phosphatetracyclo[3.3.0^{2,8}0^{3,6}]octane 4-oxides (**1**) and its derivatives have been intensively investigated by Cremer *et al.* in connection with phosphetanes which received an extensive attention for some times.[7] In contrast to earlier reports,[3a] they obtained a mixture of *trans*-**1** and *cis*-**1**, the former being proved thermodynamically stable, whereas employment of dibromophenylphosphine with norbornadiene at rt for 2 weeks followed by hydrolysis gave only *trans*-4-phenyl-4-phosphatetracyclo[3.3.0^{2,8}.0^{3,6}]octane 4-oxide (*trans*-**5**) in 13 % yield. It is reported, peculiarly enough that no reproducibility has been observed for this reaction. Stereochemical assignments for *trans*-**1** and *cis*-**1** were based upon NMR lanthanide shift experiments,[3d] while the structure of *trans*-**5** was later established by an X-Ray analysis.[8] In contrast with norbornadiene, tricyclo[5.3.1.$0^{4,9}$]undeca-2,5-diene (**2)** possessing the same 1,4-pentadiene moiety underwent smoothly a cheletropic reaction with dichlorophenylphosphine **(3**) to produce *cis*-**4** in 85 % isolated yield even at rt for 21 h. Unfortunately, among these interesting caged compounds, only *cis*-**4** and *trans*-**5** possessing a phenyl group on phosphorous are available for comparison of X-Ray structures. At a glance, *trans*-**5** is apparently much more strained than *cis*-**4** because the former has one 3 membered ring, one 4 membered ring, and two 5 membered rings, while the latter has one 3 membered ring and one 5 membered ring whose moieties are common in both molecule.

First, it is noted that only presumably thermodynamically stable *cis*-**4** and *trans***-5** was obtained in these reactions. Therefore, strictly considering, it might not be fair to compare *cis*-**4** with *trans*-**5**. Conversely, it is worthy to clarify why *cis*-**4** and *trans*-**5** are thermodynamically stable.

An inspection of Table 1 and Table 2 reveals that all of the chemically equivalent bond lengths and angles for *cis*-**4** were found to be exactly identical and thus quite highly symmetric, whereas this is not the case for *trans*-**5**, for example, two endocyclic P-C bonds are greatly different, e.g. 1.837(4) Å for C2-P1 and 1.789(6) Å for C8-P1. In addition, two endocyclic P-C bonds [C4-P5 and C4'-P5: 1.883(2) Å] of *cis*-**4** are exactly same and longer than those of *trans*-**5**. The further asymmetric character of *trans*-**5** is illustrated by the difference between the chemically equivalent bond lengths of C2-C3 [1.479(8) Å] and C3-C8 [1.616(8) Å], the latter of which is extremely long for a C-C single bond, though not unusual for a C-C bond in phosphetane rings (1.543 – 1.66 Å).[9] In *cis*-**4**, C3-C3'[1.528(3) Å] is significantly longer than C2-C3[and C2-C3':1.502(3) Å], whereas in *trans*-**5**, both C5-C6[1.527(9) Å] and C6-C7[1.523(4) Å] bonds are longer than C5-C7[1.493(7) Å] wherein another significant symmetry deviation takes place in the cyclopropane portion.

Table 1. Selected bond lengths for *cis*-**4** and *trans*-**5**

cis-**4**		*trans*-**5**	
Atoms	Bond length (Å)	Atoms	Bond length (Å)
C1-C2	1.515 (3)	C4-C5	1.479 (5)
C2-C3	1.502 (3)	C5-C6	1.527 (9)
C2-C3'	1.502 (3)	C5-C7	1.493 (7)
C3-C3'	1.528 (3)	C6-C7	1.523 (4)
C4-P5	1.883 (2)	C8-P1	1.789 (6)
C4'-P5	1.883 (2)	C2-P1	1.837 (4)
C10-P5	1.809 (2)	Ph-P1	1.794 (2)
C4-C7	1.568(2)	C3-C8	1.616(8)
C4'-C7'	1.568(2)	C2-C3	1.497(8)

The bond angles of *trans*-**5** reveal the same asymmetry and also highly strained nature while those of *cis*-**4** shows the same symmetry and less strained character as summarized in Table 2. The internal angle at the phosphorus (C8-P1-C2) of $74.63(10)^{\circ}$ for *trans*-**5** is much smaller than that [C4-P5-C4': $89.1(1)^{\circ}$] of *cis*-**4** and are smaller than those found for other phosphetanes [78.2-85.9° for C8-P1-C2][9,10] due to the presence of the tetracyclic system in *trans*-**5**. Thus, it is not unusual that two internal bonds [P1-C8-C3: 85.8(3)°, P1-C2-C3: 87.6(3)°] of *cis*-**5** are smaller than the corresponding bonds [P5-C4-C7 and P5-C4'-C7': 110.1(1)°] of *cis*-**4**. All angles in the cyclopropane portion are nearly 60° for both structures; the smallest angles [C5-C6-C7: 58.6(5)°] of *trans*-**5** also reflects its asymmetric structure. Large deviations for bond angles of chemically equivalent atoms in *trans*-**5** are observed, C7-C8-C3 [92.8(4)°] and C6-C2-C3 [100.0(4)°] C8-C7-C5 [111.6(4)°] and C5-C6-C2 [105.7(5)°], and C7-C6-C2 [99.9(5)°] and C8-C7-C6 [105.3(5)°], yet smaller for those of C7-C5-C4 [107.1(4)°] and C6-C5-C4 [109.5(5)°]. These were not at all in the case of *cis*-**4**. The apparent asymmetry of *trans*-**5** was attributed to forces in the solid state because these asymmetric characters were not observed in solution NMR studies.[8]

Table 2. Selected bond angles for *cis*-**4** and *trans*-**5**

cis-**4** Atoms	 Bond angles (°)	*trans*-**5** Atoms	 Bond angles (°)
C4 P5 C4'	89.1(1)	C8 P1 C2	74.63(10)
P5 C4 C7	110.1(1)	P1 C8 C3	85.8(3)
P5 C4' C7'	110.1(1)	P1 C2 C3	87.6(3)
C2 C3 C3'	59.4(1)	C5 C7 C6	60.8(5)
C2 C3' C3	59.4(1)	C5 C6 C7	58.6(5)
C3 C2 C3'	61.1(1)	C6 C5 C7	60.6(2)
C3 C4 C7	114.8(1)	C7 C8 C3	92.8(4)
C3' C4' C7'	114.8(1)	C6 C2 C3	100.0(4)
C4 C3 C2	120.0(1)	C8 C7 C5	111.6(4)
C4' C3' C2	120.0(1)	C2 C6 C5	105.7 (5)
C4' C3' C3	110.0(1)	C2 C6 C7	99.9(5)
C4 C3 C3'	110.1(1)	C8 C7 C6	105.3(5)
C3 C2 C1	119.6(1)	C7 C5 C4	107.1(4)
C3' C2 C1	119.6(1)	C6 C5 C4	109.5(5)

Next, we have performed molecular mechanics as well as molecular orbital calculations of *cis*-, *trans*-**4**, *cis*-, and *trans*-**5**. The results are summarized in Table 3. Geometrical optimization of both *cis*- and *trans*-**5** led to an exactly symmetric structure (C1) probably because effect of packing on structure was not under consideration in the present work.[11] The results indicate that *cis*-**4** is much more thermodynamically stable than *trans*-**4** except at PM3 level, while formation of *cis*-**5** and *trans*-**5** seems to be non-selective at MMFF, PM3, and AM1 levels, but slightly selective at *ab initio* levels (3-21G and 6-31G**). Exceptionally, at the DFT level (B3LYP), the energy of *trans*-**5** is as higher as 10.43 kcal/mol than *cis*-**5**. Rotational studies of **5** based on PM3 method were also unable to preclude the existence of the *cis*-**5**.[8] Tricyclo[5.3.1.0^{4,9}]undeca-2,5-diene (**2**) was much more reactive than norbornadiene since an equimolar mixture of **2** and norbornadiene with dichlorophenylphosphine (**3**) produced exclusively *cis*-**4**. This is partly because of unusually strong through-space interaction in a 1,4-cyclooctadiene system of **2**[12] and partly because of much more strained thus energetically higher transition state leading to the initial adduct of *trans*-**5**.

Table 3. Calculated energies and heats of formation for **4** and **5**.[a)]

Method	*cis*-**4** (Obsrvd)	*trans*-**4** (Not obsrvd)	ΔE[b)]	*cis*-**5** (Not obsrvd)	*trans*-**5** (Obsrvd)	ΔE[b)]
MMFF	119.18	121.48	2.30	151.87	152.51	-0.64
PM3	13.68	15.11	1.43	42.26	41.03	1.23
AM1	-52.25	-40.63	11.62	39.59	39.46	0.13
3-21G	-1064.77047	-1064.75979	6.70	-910.61231	-910.61692	2.89
6-31G**	-1070.43336	-1070.42525	5.09	-915.42235	-915.42575	2.13
B3LYP	-1075.81017	-1075.80285	4,59	-919.75976	-919.74314	–10.43

a) For calculation methods, see experimental. The units of MMFF, AM1, and PM3, methods are shown in kcal/mol, while *ab initio* methods are shown in au.

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

Table 4. Calculated energies and heats of formation for *trans*-**5** based upon X-Ray structure

Method	*trans*-**5**	ΔE[a)]
MMFF	216.82 kcal/mol	-64.31
AM1	95.44 kcal/mol	-55.98
3-21G	-910.54587 au	-44.58
6-31G**	-915.35615 au	-43.67
B3LYP	-919.69872 au	-27.87

a) Energy differences in kcal/mol with respect to the optimized structure of the observed product.

Although both the transition state structure of an initial McCormack reaction and the mechanism of hydrolysis of the initial adducts are unknown,[6,13,14] an exclusive formation of *cis*-**4** rather than *trans*-**4** is presumably responsible to the steric hindrance between phenyl group and C6-H. Indeed, an inspection of space filling model of *trans*-**4** reveals severe overlap between phenyl group and C6-H. This was not the case for *cis*-**4**.[15]

Finally, the energies and heats of formation for *trans*-**5** based upon its X-Ray structure were estimated by a single point calculation and are summarized in Table 4. Large deviations are noted for all the values, ranging from 28 to 64 kcal/mol. These differences might be attributed to "forces" in the solid state as suggested by Cremer *et al.*[8]

EXPERIMENTAL

Preparation of *cis*-4

A mixture of **2** (205 mg, 1.40 mmol) and **3** (2.0 mL, 14.7 mmol) was stirred at rt under argon for 21 h. The resulting mixture was poured into ice-water, then an excess of conc. aq.Na_2CO_3 was added and the mixture was stirred overnight. After extraction with CH_2Cl_2, the organic layer was dried over sodium sulfate. The solvent was evaporated in vacuo to give the crude *cis*-**4** (414 mg) which was recrystallized from benzene-hexane to give pure *cis*-**4** (259 mg). The filtrate was chromatographed on silica gel (EtOAc/benzene) afforded additional pure *cis*-**4** (63 mg). Total yield was 85 %. Mp 216 °C; ^{1}H NMR ($CDCl_3$) δ 0.36- 0,70 (m, 2H), 0.99 (d, 1H), 1.29 (s, 4H), 1,55-1.95(m, 1H), 1.95-2.30(m, 1H), 2.30-2.60 (m, 2H), 2.70-3.23(m, 3H), 7.24-7.70 (m, 5H). *Anal.* Calcld for $C_{17}H_{19}OP$: C, 75.54, H, 7.08. Found: C, 75.90, H, 7.04.

Calculations

Molecular mechanics, semi-empirical, *ab initio*, and DFT calculations were performed using a Spartan '04 Windows software package (Wavefunction, Inc.: MMFF, PM3, AM1, 3-21G, 6-31G**, and B3LYP using 6-31** as basis set). Geometry optimizations were carried out until convergence was attained.

ACKNOWLEDGEMENTS

This work was supported in part by the Ministry of Education, Science, and Culture, and Sports, Japan (to HH *et al.* C, No.18590104). Thanks are also extended to Professor Ryohei Yamaguchi (Graduate School of Human and Environmetal Studies, Kyoto University) for providing precursors of **2** with us, to Dr. Ikuko Miyahara and Professor Ken Hirotsu (Faculty of Science, Osaka City University) for performing an X Ray analysis of **4**, and also to Dr. Takahisa Machiguchi (Faculty of Science, Saitama University) for helpful discussions in the initial stage of this work. The authors are also grateful to Mr. N. Uchida (Wavefunction, Inc. Jpn) and Dr. Warren Hehre (Wavefunction, Inc. USA) for partial help of molecular orbital calculations by Spartan package. Finally, Special Grants (Education and Research Grants in 2004 and 2006 to KM and HI, respectively) from the Chiba Institute of Science (CIS) are greatly acknowledged.

REFERENCES AND NOTES

1. a) R. O. Klaus and C. Ganter, *Helv. Chim. Acta*, 1980, **63**. 2559; b) R. Furstoss, R. Tadayoni, and B. Waegell, *J. Org. Chem.*, 1977, **42**, 2844; c) A. T. Nielsen, S. L. Christian, and D. W. Moors, *J. Org. Chem.*, 1987, **52**, 1656.; d) J. Lacrampe, A. Heumann, R. Furstoss, and B. Waegell, *J. Chem. Res. Synopses,* 1978, 334; 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*, 1998, **54**, 11793; f) E. M. Burrage, R. C. Cookson, S. S. Gupte, and I. D. R. Stevens, *J. Chem. Soc., Perkin Trans 2*, 1975, 1325.
2. a) R. O. Klaus, H. Tobler, and C. Ganter, *Helv. Chim. Acta*, 1974, **57**, 2517; b) D. P. G. Hamon, G. F. Taylor, and R. N. Young, *Aust. J. Chem.*, 1977, **30**, 589; c) J. L. Jessen, C. Wolff, and W. Tochtermann, *Chem. Ber.*, 1986, **119**, 297; d) M. Sander and E. V. Dehmlow, *Org. Prep. Proc. Int.*, 2000, **32**, 189; e) S. Muthusamy, S. A. Babu, C. Gunanathan, E. Suresh, P. Dastidar, and R. V. Jasra, *Tetrahedron*, 2001, **57**, 7009.

3. a) M. Green, *Proc. Chem. Soc.*, 1963, 177; *J. Chem. Soc.*, 1965, 541; 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.*, 1975, 374; c) Mazhar-ul-Haque and S. E. Cremer, *J. Chem. Soc., Perkin Trans. 2,* 1978, 1115; 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.*, 1992, **57**, 511.
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.*, 1991, 1677.
6. For convenience, nomenclature regarding to *cis* and *trans* was adopted according to Cremer *et al.*[3d]
7. L. D. Quin, 'The Heterocylic Chemistry of Phosphorous,' Wiley-Interscience, New York, 1981, Chap.4 and references cited therein.
8. T. M. Lane, A. C. Peterson, S. E. Cremer, D. W. Bennett, and P. E. Fanwick, *Main Group Chemistry*, 1997, **2**, 43
9. For examples, see: C. R. Hockless, Y. B. Kang, M. A. MacDonald, M. Pabel, D. D. Pathak, A. C. Willis, and S. B. Wild, *Organometallics*, 1996, **15**, 1301; Mazhar-ul-Haque, W. Horne, S. E. Cremer, P. W. Cremer, and P. K. Kafarski, *J. Chem. Soc., Perkin Trans. 2*, 1981, 1138 and references cited.
10. A. Marinetti and D. Carmichael, *Chem. Rev.*, 2002, **102**, 201.
11. This aspect will be a subject of future communications.
12. R. Yamaguchi, M. Ban, M. Kawanisi, E. Osawa, C. Jaime, A. B. Buda, and S. Katsumata, *J. Am. Chem. Soc.,* 1984, **106**, 1512.
13. It is believed that thermodynamically stable phosphine oxides form predominantly in McCormack reaction regardless stereochemistry of an initial cheletropic adduct because of intervention of subsequent hydrolysis process.[3d,4]
14. Computational studies on transition state structures of a variety of cheletropic reactions are underway and the results will be reported in due course.
15. It is passing note that the predominant formation of *trans*-**1** over *cis*-**1** is generally in agreement with calculated energies for *trans*-**1** and *cis*-**1**: for example, 3-21G: *trans*-**1**, -721.17262; *cis*-**1**, -721.16892 au. 6-31G**: *trans*-**1**, -724.91606; *cis*-**1**, -724.91335 au. B3LYP: *trans*-**1**, -728.02810; *cis*-**1**, -728.02546 au. However, at AM1 level, the results are non-selective: *trans*-**1**, 2.56; *cis*-**1**, 2.22 kcal/mol.