P(2) and P(4) are oriented approximately parallel and are 6.46 Å apart at their midpoints. These rings and atoms P(1) and P(3) form a well-defined donor molecular cavity.

That **1** and **2** are obtained in only the cis isomeric form and in a boat conformation is surprising when compared to the fourfold-symmetric $(RNPR)_4$ (R = Me, Et)[10] and $[(n\text{-Pr})(NCH_2CH_2NP)]_4$[14] reported earlier which each contain only one type of phosphorus environment. Also, the integrity of the $P_4N_4$ ring in **1** and **2** appears to be maintained in solution and in the gas phase. No evidence for dissociation[14] of **1** or **2** to monomer, e.g., $[C_6H_4N_2(PhP)_2]$ or acyclic dimers, or for cis-trans isomerism is seen. After thermolysis at 100 °C for 10 days, no conversion of **1** or **2** to higher oligomers occurs. The exceptional thermal stability and advantageous P(1)-P(3) and Ph(2)-Ph(4) separations in **2** and **1** make them cavity-containing molecules into which selective coordination of other atoms or metal moieties is expected. **2**, with its exo phosphorus atoms oxidized, should show especially selective P(III) donor coordination. Elemental sulfur with **2** after 100 h at 100 °C yields only traces of trisulfide $[(C_6H_4N_2)_2(PhPS)_3(PhP)]$. **2** reacts with $(Ph_3P)_2Ni(CO)_2$ to form a **2**·$Ni(CO)_2$ complex, but not with $(CO)_5Mo(CH_3CN)$ or norbornadiene·$Mo(CO)_4$ possibly because the $Mo(CO)_5$ and $Mo(CO)_4$ units are too large for the cavity. This coordination selectivity, the differential reactivity of phosphorus atom pairs in the structure, and the possibility that higher order cyclooligomers of type $[C_6H_4N_2(PhP)_2]_n$ (e.g., $n$ = 3) might form are under investigation currently.

**Acknowledgment.** Support of this work by National Science Foundation Grants CHE-8312856 and CHE-8714191 is gratefully acknowledged.

**Supplementary Material Available:** Tables of crystal data, positional and isotropic thermal parameters, bond distances and angles, and anisotropic thermal parameters for **2** (9 pages). Ordering information is given on any current masthead page.

(16) Powell, P.; Timms, P. *The Chemistry of Non-Metals*; Chapman and Hall: London, 1974.

## Synthesis and X-ray Analysis of 1,2,4,5-Trioxazinane

Mitsuyuki Mori,[1a] Tomohito Sugiyama,[1a] Masatomo Nojima,*[,1a] Shigekazu Kusabayashi,[1a] and Kevin J. McCullough*[,1b]

*Department of Applied Chemistry, Faculty of Engineering, Osaka University, Suita, Osaka 565, Japan*
*Department of Chemistry, Heriot-Watt University, Edinburgh EH14 4AS, Scotland*

*Received March 7, 1989*

As a strategy for the synthesis of six-membered heterocyclic compounds, [3 + 3] cycloadditions between two different 1,3-dipoles would be attractive. The few examples of this type of reaction reported to date show some potential synthetic utility.[2] Although the dimerization of carbonyl oxides to give 1,2,4,5-tetroxanes is well-known,[3] we report, herein, the first example of [3 + 3] cycloadditions involving carbonyl oxides and nitrones which gave rise to 1,2,4,5-trioxazinanes, derivatives of a novel class of cyclic peroxides.

**Table I.** Synthesis of 1,2,4,5-Trioxazinane

| vinyl ether | nitrone | trioxazinane (% yield) |
|---|---|---|
| **1a**; $R^1$ = H, $R^2$ = $CH_2CH(CH_3)_2$ | **2a**; $R^3$ = $R^5$ = Ph, $R^4$ = H | **3a** (84) |
| **1a** | **2b**; $R^3$ = Ph, $R^4$ = H, $R^5$ = $CH_2Ph$ | **3b** (71) |
| **1a** | **2c**; $R^3$ = $(CH_2)_6CH_3$, $R^4$ = H, $R^5$ = $CH_2Ph$ | **3c** (52)[a] |
| **1a** | **2d**; $R^3$ = $R^4$ = $R^5$ = Ph | **3d** (80) |
| **1a** | **2e**; $R^3$ = $R^4$ = Ph, $R^5$ = $CH_3$ | **3e** (91) |
| **1b**; $R^1$ = Ph, $R^2$ = $CH_3$ | **2a** | **3f** (38)[b] |
| **1b** | **2b** | **3g** (41)[b] |
| **1b** | **2c** | **3h** (42)[a] |
| **1b** | **2d** | **3i** (96) |
| **1c**; $R^1$ = $(CH_2)_6CH_3$, $R^2$ = $CH_3$ | **2a** | **3j** (86)[c] |
| **1c** | **2c** | **3k** (70)[d] |
| **1c** | **2d** | **3l** (90) |
| **1c** | **2e** | **3m** (81) |

[a] **3k** was also produced in around 8% yield. [b] Benzaldehyde (around 30% yield) and 3,6-diphenyl-1,2,4,5-tetroxane (around 15% yield) were also isolated. [d] The cis/trans ratio = 51:49. [c] The cis/trans ratio = 66:34.

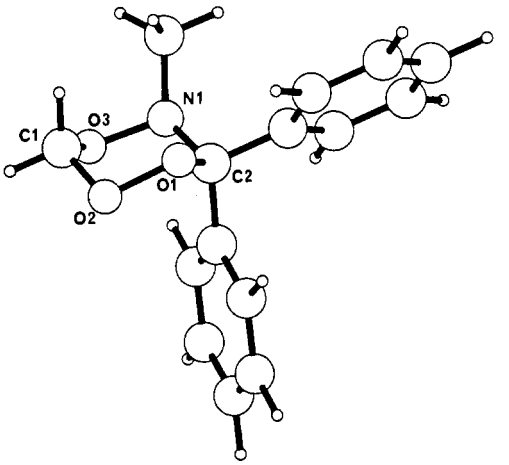



**Figure 1.** The X-ray crystal structure of the 1,2,4,5-trioxazinane **3e**. Some important geometrical parameters are as follows: O(1)-O(2) 1.474 (3), O(2)-C(1) 1.402 (5), C(1)-O(3) 1.414 (5), O(3)-N(1) 1.453 (4), N(1)-C(2) 1.458 (4), C(2)-O(1) 1.455 (4) Å; O(2)-C(1)-O(3) 110.8 (3), O(2)-O(1)-C(2) 105.7 (2), C(1)-O(2)-O(1) 105.0 (2), O(1)-C(2)-N(1) 110.7 (2), C(2)-N(1)-O(3) 107.9 (2), C(1)-O(3)-N(1) 111.4 (3)°.

After ozonation (2 mmol of ozone) of a mixture of the appropriate vinyl ether **1** (2 mmol) and nitrone **2** (1 mmol) in methylene chloride at 0 °C, the products, including the 1,2,4,5-trioxazinanes **3a-m**, were isolated by rapid column chromatography on silica gel (Table I). Since the new products could not be fully characterized by conventional analytical and spectroscopic techniques (Supplementary Material), an X-ray crystallographic study was undertaken of adduct **3e** to establish unambiguously the structure of the new ring system. The crystal structure (Figure 1) shows that the central 1,2,4,5-trioxazinane ring system adopts a chair conformation with the *N*-methyl being accommodated in an axial position. The bond distances around the heterocyclic ring are generally within expected ranges.

Cycloadditions involving unsymmetrically substituted dipolar components would be expected to give rise to the trioxazinanes

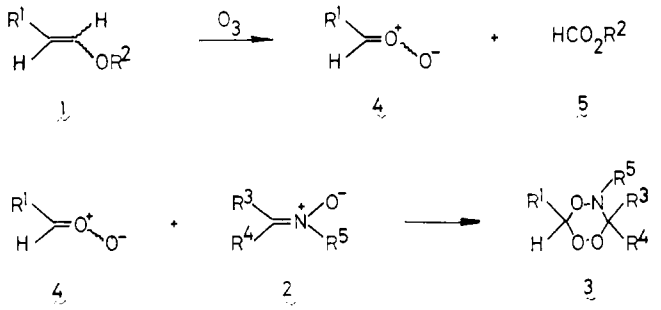
(1) (a) Osaka University. (b) Heriot-Watt University. All the correspondence for the X-ray analysis should be addressed to K.J.M.

(2) (a) Moody, C. J. Comprehensive Heterocyclic Chemistries; Katrizky, A. R., Rees, C. W., Eds.; Pergamon Press: Oxford, 1984; Vol. 3. (b) Crabb, J. N.; Storr, R. C. 1,3-Dipolar Cycloaddition Chemistry; Padwa, A., Ed.; Wiley: New York, 1984; Vol. 2. (c) Heine, H. W.; Heitz, L. *J. Org. Chem.* **1974**, *39*, 3192. (d) Kliegel, W. *Chem.-Ztg.* **1976**, *100*, 236. (e) Schultz, A. G.; Macielag, M.; Plummer, M. *J. Org. Chem.* **1988**, *53*, 391 and references therein.

(3) Bailey, P. S. Ozonation in Organic Chemistry; Academic Press: New York, 1978; Vol. 1, 1982; Vol. 2. (b) Murray, R. W.; Lin, W.-P.; Grumke, D. *Advs. Chem. Ser.* **1972**, *112*, 9. (c) Chiang, C.; Butler, W.; Kuczkowski, R. L. *J. Chem. Soc., Chem. Commun.* **1988**, 465.

0002-7863/89/1511-6884$01.50/0 

Scheme I



as mixtures of stereoisomers, e.g., compounds **3f-h,j,k**. In reality, the reaction of benzaldehyde *O*-oxide (**4b**) with nitrones **2a-c** afforded trioxazinanes **3f-h** as single isomers, whereas octanal *O*-oxide (**4c**) with nitrones **2a,c** gave the corresponding trioxazinanes **3j,k** as mixtures of isomers.[4] Since [3 + 3] cycloadditions between two 1,3-dipoles is predicted to be stepwise, unless one of the components is antarafacial, the trioxazinane isomer ratio is likely to be sensitive to the structures of either or both the carbonyl oxide and the nitrone. Although the cis and trans isomers of **3j** are formed in almost equal amounts, subsequent treatment of *cis*-**3j** [$^1$H NMR $\delta$ 5.65 (t, $J$ = 5 Hz, H-3) and 6.46 (s, H-6)] with chlorosulfonic acid (0.1 equiv) in methylene chloride afforded *trans*-**3j** [$^1$H NMR $\delta$ 5.69 (s, H-6) and 5.82 (t, $J$ = 5 Hz, H-3]. Under similar conditions, however, *trans*-**3k** [$^1$H NMR $\delta$ 4.1-4.2 (m, H-6) and 5.67 (t, $J$ = 5 Hz, H-3)] was isomerized to *cis*-**3k** [$^1$H NMR $\delta$ 4.7-4.8 (m, H-6) and 5.45 (t, $J$ = 5 Hz, H-3)].

In a nonparticipating solvent like methylene chloride, the carbonyl oxide **4**, generated in situ by selective ozonolysis of the vinyl ether **1**, reacted preferentially with the nitrone **2** to yield the corresponding 1,2,4,5-trioxazinane **3** (Scheme I). The alkyl formate **5**, coproduced from **1**, being a poor 1,3-dipolarophile,[5] did not combine with the carbonyl oxide. Ozonolyses of mixtures of the vinyl ether **1b** and nitrones containing 1 equiv of carbonyl compounds like benzaldehyde and benzophenone still gave the expected trioxazinanes **3** as the sole, isolable peroxidic products, albeit in reduced yield. Thus, for example, ozonolysis of $\beta$-methoxystyrene (**1b**) in the presence of a 1:1 mixture of nitrone **2d** and benzophenone afforded **3i** in 46% yield. In methanol, ozonolysis of a mixture of **1b** and nitrone **2d** gave the solvent derived $\alpha$-methoxy hydroperoxide (55%) together with a small amount of **3i** (1%) consistent with more efficient capture of the intermediate carbonyl oxide by methanol.[5]

1,2,4,5-Trioxazinanes, as exemplified by derivative **3h**, have chemical properties similar to other stable six-membered cyclic peroxides, e.g., 1,2,4,5-tetroxanes. Thermolysis of **3h** for 8 h in refluxing benzene afforded a mixture of ring cleavage products, benzaldehyde (78%), octanal (78%), and benzaldoxime (53%), together with unreacted **3h** (11%). Treatment of **3h** with sodium ethoxide (13 equiv) in ethanol for 1 day at room temperature gave benzoic acid (93%), the nitrone **2c** (49%), and octanal (33%). Reduction of **3h** with triphenylphosphine proceeded very slowly at room temperature (only 20% **3h** reacted after 88 h) yielding almost quantitatively a clean product mixture of benzaldehyde and nitrone **2c**. Under similar conditions, **3h** did not react with thioanisole.

Preliminary attempts to extend the [3 + 3] cycloaddition strategy by utilizing other 1,3-dipoles have thus far been unsuccessful, neither 2,4,6-trimethylbenzonitrile oxide nor phenanthrium *N*-benzoylimide nor azoxybenzene captures carbonyl oxides as efficiently as nitrones under the reaction conditions described above.

**Supplementary Material Available:** Crystal data for **3e**, spectral data ($^1$H NMR) for **3a-m**, and tables of bond lengths, bond angles, fractional coordinates, and anisotropic vibration parameters (7 pages); table of observed and calculated structure factors (8 pages). Ordering information is given on any current masthead page.

(4) We have tentatively assigned the stereochemistry on the basis that in $^1$H NMR spectra the equatorial proton would appear at a lower field compared with the axial one: Halls, P. J.; Jones, R. A. Y.; Katritzky, A. R.; Snarey, M.; Trepanier, D. L. *J. Chem. Soc. B* **1971**, 1320.

(5) (a) LaBarge, M. S.; Keul, H.; Kuczkowski, R. L.; Wallsch, M.; Cremer, D. *J. Am. Chem. Soc.* **1988**, *110*, 2081. (b) Nakamura, N.; Nojima, M.; Kusabayashi, S. *Ibid.* **1987**, *109*, 4969. (c) Mori, M.; Nojima, M.; Kusabayashi, S.; McCullough, K. J. *J. Chem. Soc., Chem. Commun.* **1988**, 1550.

## A Remarkable Pericyclic Mechanism for Enzyme-Catalyzed P-C Bond Formation

Michael S. McQueney, Sheng-lian Lee, Elise Bowman, Patrick S. Mariano,* and Debra Dunaway-Mariano*

*Department of Chemistry and Biochemistry*
*University of Maryland*
*College Park, Maryland 20742*

*Received April 26, 1989*

Recently,[1] we reported the isolation of the phosphorus-carbon bond-forming enzyme, PEP-phosphomutase, from *Tetrahymena pyriformis*. In *T. pyriformis* this enzyme plays a central role in 2-aminoethylphosphonate (AEP) biosynthesis through its catalysis of the first committed step involving C-P bond formation in the conversion of phosphoenolpyruvate (PEP) to phosphonopyruvate (PP). Since PEP and AEP are known to serve as precursors for a number of structurally diverse phosphonates,[2] the phosphoester-to-phosphonate rearrangement promoted by the phosphomutase might represent a common step in the biosynthesis of the phosphonate class of natural products.

Possible mechanisms for the PEP to PP rearrangement were suggested in our preliminary report.[1] These include a concerted sigmatropic phosphoryl migration, a stepwise double displacement route, and a stepwise cyclization-ring opening path through an oxaphosphatane intermediate (shown in Scheme I). We anticipated that an analysis of the stereochemical integrity of the migrating phosphoryl center would provide decisive information leading to elucidation of the mechanism for this important enzymatic transformation. Owing to a substantial driving force, the equilibrium between PEP and PP strongly favors PEP.[3] This feature coupled with the fact that procedures are known[4] for determining the stereochemistry of O-isotopically labeled thiophosphoenolpyruvate (TPEP) has led to a design of methodology to address the phosphomutase stereochemical problem which is based upon chiral [$^{18}$O,$^{16}$O]thiophosphonopyruvate (CTPP). Herein we report a solution to this problem involving the synthesis and configuration assignments of the separate enantiomers of CTPP, their phosphomutase-catalyzed isomerizations, and stereochemical analysis of the enantiomers of chiral [$^{18}$O,$^{16}$O$_2$]-thiophosphoenolpyruvate (CTPEP) which are products of these reactions.

The enantiomerically pure antipodes of CTPP were prepared by the sequence shown in Scheme II which advantageously utilizes HPLC separation of the diastereomeric phosphonamides **1**, derived

(1) Bowman, E.; McQueney, M.; Barry, R. J.; Dunaway-Mariano, D. *J. Am. Chem. Soc.* **1988**, *110*, 5575.

(2) Trebst, A.; Geike, F. Z. *Naturforsch., B: Anorg. Chem., Org. Chem., Biochem., Biophys., Biol.* **1967**, *22*, 989. Horiguchi, M. *Biochim. Biophys. Acta* **1972**, *261*, 102. Barry, R. J.; Bowman, E.; McQueney, M.; Dunaway-Mariano, D. *Biochem. Biophys. Res. Commun.* **1988**, *153*, 177. Rogers, T. O.; Birnbaum, J. *J. Antimicrob. Agents Chemother.* **1974**, *5*, 121. Sato, H. In *Mycotoxins and Phycotoxins*; Steyn, P. S., Vleggaar, R., Eds.; Elsevier: Amsterdam, 1986; p 77.

(3) This is due to a much larger BDE for the P-O vs P-C bond. Unpublished studies conducted in collaboration with Profesor Jack Tossell suggest an ca. 20 kcal/mol energy difference between the trianionic forms of these substances.

(4) Sheu, K.-F.; Ho, H.-T.; Nolan, L. D.; Markovitz, P.; Richard, J. P.; Utter, M. F.; Frey, P. A. *Biochemistry* **1984**, *23*, 1779.

0002-7863/89/1511-6885$01.50/0 