Table 1. Pore volume occupied by the different $n$-alkanes at 293 K.[a]

| | propane | butane | pentane | hexane | heptane |
|---|---|---|---|---|---|
| $V_{ads}$ [mL g$^{-1}$] | 0.15 | 0.16 | 0.17 | 0.10 | 0.10 |

[a] The values were calculated by using the density of the liquid $n$-alkane at 293 K relative to that of water at 277 K. A Setaram TG-DSC 111 instrument operating under a helium flow of about 3.8 L h$^{-1}$ was used in these adsorption experiments. The FER samples were dehydrated at 723 K for 10 min. After cooling, adsorption was performed by either saturating 20% of the helium flow with the liquid $n$-alkanes or by replacing 20% of the helium flow by the gaseous $n$-alkanes. This means that the adsorption pressure of the liquid $n$-alkanes was 20% of the saturation pressure, while the propane and butane pressure was 20 kPa.

occurs after the formation of coke residues in the FER pores.[9,10,13] The results presented here imply that FER behaves as a one-dimensional pore system for long-chain molecules, while its full two-dimensional pore system can be exploited only by the shorter molecules. Pore blocking due to the formation of coke will therefore have a large inhibiting effect on the movements of the long-chain molecules, which are limited by one-dimensional (single-file) diffusion; the movements of shorter molecules are far less restricted. The resulting long residence time of the long-chain molecules causes them to crack. The combination of ten-ring channels with intersecting eight-ring channels, from which the longer molecules are excluded, is a unique feature of the FER pore structure. The results presented provide an excellent demonstration of the importance of understanding adsorption effects in zeolites for predicting differences in catalytic performance of zeolites.

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[1] J. E. Naber, K. P. de Jong, W. H. J. Stork, H. P. C. E. Kuipers, M. F. M. Post, *Stud. Surf. Sci. Catal.* **1994**, *84*, 2197–2219.

[2] J. M. Thomas, *Sci. Am.* **1992**, *266*(4), 82–88.

[3] W. O. Haag, *Stud. Surf. Sci. Catal.* **1994**, *84*, 1375–1394.

[4] B. Smit, J. I. Siepmann, *Science* **1994**, *264*, 1118–1120.

[5] S. P. Bates, W. J. M. van Well, R. A. van Santen, B. Smit, *J. Am. Chem. Soc.* **1996**, *118*, 6753–6759.

[6] E. J. Maginn, A. T. Bell, D. N. Theodorou, *J. Phys. Chem.* **1995**, *99*, 2057–2079.

[7] E. Hernández, C. R. A. Catlow, *Proc. R. Soc. Lond. A* **1995**, *448*, 143–160.

[8] R. C. Runnebaum, E. J. Maginn, *J. Phys. Chem. B* **1997**, *101*, 6394–6408.

[9] H. H. Mooiweer, K. P. de Jong, B. Kraushaar-Czarnetzki, W. H. J. Stork, B. C. H. Krutzen, *Stud. Surf. Sci. Catal.* **1994**, *84*, 2327.

[10] P. Meriaudeau, V. A. Tuan, N. H. Le, G. Szabo, *J. Catal.* **1997**, *169*, 397–399.

[11] B. Smit, T. L. M. Maesen, *Nature* **1995**, *374*, 42–44.

[12] D. Frenkel, B. Smit, *Understanding Molecular Simulations: from Algorithms to Applications*, Academic Press, Boston, USA, **1996**.

[13] G. Seo, H. S. Jeong, S. B. Hong, Y. S. Uh, *Catal. Lett.* **1996**, *36*, 249–253.

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# The First Delocalized Phosphole Containing a Planar Tricoordinate Phosphorus Atom: 1-[Bis(trimethylsilyl)methyl]-3,5-bis(trimethylsilyl)-1,2,4-triphosphole**

F. Geoffrey N. Cloke, Peter B. Hitchcock, Philip Hunnable, John F. Nixon,* Lászlo Nyulászi,* Edgar Niecke,* and Vera Thelen

The generally accepted view that phospholes are not aromatic[1, 2] must now be revised in light of the first example of a fully delocalized 1,2,4-triphosphole containing a planar tricoordinate phosphorus atom, which is described here. Theoretical calculations predict that a planar phosphole would be strongly aromatic,[3, 4] and that planarity can be achieved by partial[5, 6] or full replacement[6–8] of CH groups by dicoordinate phosphorus atoms in the five-membered phosphole ring. Both the sum of the bond angles (342°)[9] and the complexing behavior[10, 11] of the recently described 1-[bis(trimethylsilyl)methyl]-3,5-di-*tert*-butyl-1,2,4-triphosphole (**1**), indeed show the expected increase in the planarity of the tricoordinate phosphorus atom and the enhanced aromaticity of the ring system. Likewise, the incorporation of bulky substituents[12–15] at the tricoordinate phosphorus atom of a phosphole resulted in characteristic changes both in the photoelectron spectrum[16] and in the chemical reactivity,[15] providing the first example of a phosphole that undergoes electrophilic substitution. Schmidpeter et al. recently reported phospholes substituted by electron-withdrawing cationic moieties,[17, 18] which exhibited NMR spectroscopic characteristics[17] or structural features (sum of bond angles at the tricoordinate phosphorus atom 338°),[18] which is in accordance with partial flattening of the phosphorus pyramid. However, a totally planar phosphole which would lead to full aromaticity has not been previously achieved.

Treatment of the recently reported[19] 3,5-bis(trimethylsilyl)-1,2,4-triphospholide anion (**2**) with $(SiMe_3)_2CHBr$ in 1,2-dimethoxyethane (DME) readily affords yellow 1-[bis(trimethylsilyl)methyl]-3,5-bis(trimethylsilyl)-1,2,4- triphosphole [**3**, Eq. (a)]. As anticipated, the compound exhibits a molecular ion at $m/z$ 422 in the mass spectrum, four expected resonances in the $^1H$ NMR spectrum, and three resonances in the ratio 2:1:1 in the $^{29}Si$ NMR spectrum. The $^{31}P\{^1H\}$ NMR spectrum of **3**, however, is completely different from that of the corresponding 1,2,4-triphosphole **1**.[9] Whereas the latter

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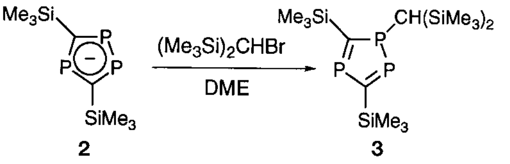

(a)

shows the expected widely spaced pattern of lines for an AMX spin system (where A represents the tricoordinate phosphorus atom attached to the dicoordinate phosphorus atom M and X is the other dicoordinate phosphorus atom), in the spectrum of **3** the signal of phosphorus atom A is significantly shifted so that it now almost overlaps with the signal of the adjacent dicoordinate phosphorus atom. The $^{31}$P{1H} NMR spectrum of **3** is therefore best described as an ABX spin system and was analyzed accordingly.

Particularly noteworthy is the similarity in chemical shifts of the two adjacent tri- and dicoordinate phosphorus atoms in **3** which to our knowledge is unprecedented. The differences in chemical shifts between **1** and **3** clearly reflect the effect of the significant delocalization of the lone pair electrons of the tricoordinate phosphorus atom into the ring system of **3** (see below).

Good quality crystals of **3** were obtained for a single-crystal X-ray diffraction study (Figure 1).[28] The structure reveals a number of features of considerable interest. The most dramatic aspect of the structure is the planarity of the five-membered 1,2,4-triphosphole ring system with a sum of angles at the tricoordinate phosphorus atom of 358.7°. This value contrasts previously reported values of 342.3° for the analogous 3,5-di-*tert*-butyltriphosphole **1**,[9] 302.7° for 1-benzyl phosphole,[20] and 331.7° for the recently described 2,4,6-tri-*tert*-butylphenyl-3-methylphosphole (**4**).[15] Interestingly, the shortest P–C bond length in **3**, namely P1–C1 (1.684(7) Å), involves the tricoordinate phosphorus atom P1 and is significantly shorter than P2–C2 (1.745(7) Å), P3–C2 (1.715(7) Å), or P3–C1 (1.743(7) Å), which all involve dicoordinate phosphorus atoms. The corresponding values for **1** are 1.734(4), 1.718(4), 1.763(4), and 1.720(3) Å. The P1–C1 bond length in **3** is similar to those found in bis(methylene)phosphoranes (e.g. 1.661 and 1.674 Å in Ph$_2$CP(2,4,6-MeC$_6$H$_2$)C(SiMe$_3$)$_2$).[21]

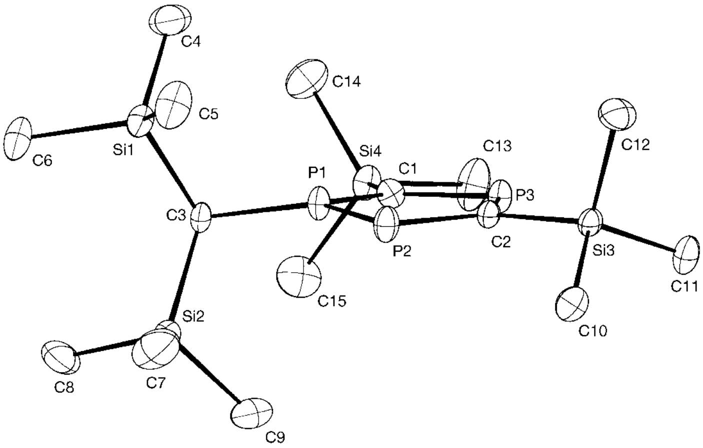

Figure 1. Molecular structure of **3**. Selected bond lengths [Å] and angles [°]: P1–C1 1.684(7), P1–C3 1.811(6), P1–P2 2.056(3), P2–C2 1.745(7), P3–C2 1.715(7), P3–C1 1.743(7); C1-P1-C3 125.1(4), C1-P1-P2 110.5(3), C3-P1-P2 123.1(3), C2-P2-P1 92.3(2), C2-P3-C1 103.8(3).

The observed bond lengths within the triphosphole ring of **3** are also consistent with a contribution of a (canonical) phosphanediylmethylenephosphorane unit, as discussed together with a localized C=P bond by Schmidpeter et al.[18] The aromaticity indices, which are larger for **3** than for other five-membered phosphorus heterocycles (see below), are also in agreement with a description of a formalism that takes into account the conventional resonance structure (1,3-diphosphabutadiene and the lone pair of the tricoordinate phosphorus atom) and one involving the bis(methylene)phosphorane unit.

To understand the planarity about the tricoordinate phosphorus atom in **3** better, ab initio quantum-chemical calculations were carried out.[22] While 1,2,4-triphosphole **1** turned out to be nonplanar at the HF/3-21G* level of theory,[23] the geometry optimization of **3** resulted in a planar structure even when starting from an initial nonplanar geometry. The optimized bond lengths for **3** are in very good agreement with those obtained by X-ray structure analysis (Table 1). This behavior indicates that the planarity of **3** is unlikely to be attributed to solid-state interactions. The calculated structure is very similar to that obtained at the same level of theory (with one imaginary frequency) for the unsubstituted 1,2,4-triphosphole calculated under planarity constraint. A comparison of the structures of **1** and **3** shows that silyl substituents lengthen while alkyl substituents shorten the neighboring bonds.

Table 1. Selected bond lengths [Å] in **3** (X-ray structure and ab initio calculations) and the unsubstituted 1,2,4-triphosphole (calculated under planarity constraint).

| | X-ray | calcd (HF/3-21G*) | H-substituted, planar |
|---|---|---|---|
| P1–P2 | 2.056 | 2.054 | 2.061 |
| P2–C2 | 1.745 | 1.739 | 1.717 |
| C2–P3 | 1.715 | 1.725 | 1.735 |
| P3–C1 | 1.743 | 1.750 | 1.722 |
| C1–P1 | 1.684 | 1.692 | 1.692 |

The resulting structure is not only fully planar, but also aromatic, in agreement with previous conclusions drawn for planar phospholes from theoretical studies.[3–8] The Bird aromaticity index[24] for **3** is 84, which is significantly larger than the values of 46 calculated (HF/3-21G*) for nonplanar phosphole and 35.5 obtained from the X-ray structure of 1-benzyl phosphole[25] as well as 56 for **1** and 56.5 for **4**. Likewise, the bond-shortening index[26] of **3** is 60 (compared to 67 for benzene,[26] 68 for pentaphosphole P$_5$H,[7] 57 for thiophene,[7] and 50 for nonplanar phosphole and **1**). This reflects the strong π-donor properties of the planar tricoordinate phosphorus atom, as predicted by the previous theoretical work.[4, 27] The trimethylsilyl substituent is a π-electron acceptor, as is the BH$_2$ group. The latter reduces the inversion barrier of both phosphole[4] and 1,3,4-triphosphole[5] when attached to the 2- and 5-positions of those rings. Presumably the decrease of the π-electron density caused by the substituent is compensated by an increased contribution of the lone pair of the tricoordiate phosphorus atom, which can be accomplished only by an enhanced flattening of the phosphorus pyramid.

To model the electronic effect of the different substituents on phosphole ring systems, calculations were carried out with a methyl substituent in the 1-position and silyl substituents in the 3- and 5-positions. For 1-methyl-3-silyl-1,2,4-triphosphole and 1-methyl-5-silyl-1,2,4-triphosphole, inversion barriers of 1.92 and 1.89 kcal mol$^{-}$ were obtained, which are about 1 kcal mol$^{-}$ lower than that for 1-methyl-1,2,4-triphosphole (2.77 kcal mol$^{-}$; all calculations at the MP2/6-31G* level). For 1-methyl-3,5-disilyl-1,2,4-triphosphole a further decrease of the inversion barrier results, but full planarity was not attained. These results indicate that the effect of the silyl substituent alone is not enough to stabilize the planar structure. Similarly, 2,5-diboryl-1,3,4-triphosphole was found to be nonplanar at the MP2/6-31G* level.[5]

The bis(trimethylsilyl)methyl group was shown to flatten the *tert*-butyl-substituted triphosphole ring.[22] The effect can be attributed to the electron-donor effect of the bis(trimethylsilyl)methyl group and to steric repulsion of the two trimethylsilyl groups which are situated above and below the ring. To examine this effect the structure of 1-[bis(silyl)methyl]-3,5-disilyl-1,2,4-triphosphole was also optimized. This turns out to be nonplanar; the sum of bond angles around the tricoordinate phosphorus atom is 324.3°. Optimization of 1-[bis(trimethylsilyl)methyl]-3,5-disilyl-1,2,4-triphosphole, on the other hand, results in a planar structure, showing that the steric bulk of the substituent in the 1-position of the phosphole ring plays a significant role in making the ring planar.

The 1,2,4-triphosphole **3** is the first example of a neutral five-membered ring containing a tricoordinate phosphorus atom that is fully planar. Furthermore, according to the available measurements, **3** is the most aromatic of all the known neutral five-membered phosphorus heterocycles. The new planar triphosphole is likely to show aromatic chemical behavior, such as formation of $\eta^5$-transition metal complexes. An analysis of the various factors that result in the planarity of the ring indicates that the effects of the dicoordinate phosphorus atoms incorporated into the ring, the π-electron acceptors substituted at the ring atoms (other than the tricoordinate phosphorus), and the sterically demanding groups on the tricoordinate phosphorus atom should all be taken into account.[23]

## *Experimental Section*

A solution of **2** (0.65 g, 2.5 mmol) in DME (10 mL) was cooled to −78 °C. $(SiMe_3)_2CHBr$ (0.7 mL, 2.6 mmol) was then added. The solution was warmed to room temperature slowly and stirred for 24 h. The volatile components were removed under vacuum, and the product extracted with hexane (30 mL). Purification by column chromatography with hexane as eluent followed by recrystallization in heptane yielded yellow crystals of **3** suitable for X-ray crystallography. Yield: 54 % after purification. $^{31}P\{^1H\}$ NMR (121.5 MHz, $C_6D_6$): $\delta = 288.3$ (dd, $^2J(P_X,P_A) = 14.3$, $^2J(P_x,P_B) = 11.5$ Hz; $P_x$), 180 (dd, $^1J(P_B,P_A) = 571.2$ Hz; $P_B$), 179 (dd; $P_A$); $^1H$ NMR (300 MHz, $C_6D_6$): $\delta = 2.24$ (dd, $^2J(H,P_A) = 8.5$, $^3J(H,P_B) = 1.1$ Hz; $(Me_3Si)_2CH$), 0.55 (s; $Si(CH_3)_3$), 0.46 (s; $Si(CH_3)_3$), 0.07 (s; $CH(Si(CH_3)_3)_2$); $^{13}C\{^1H\}$ NMR (75.5 MHz, $C_6D_6$): $\delta = 180.2$ (ddd, $^1J(C,P_X) = 86.4$, $^1J(C,P_B) = 52.6$, $^2J(C,P_A) = 22.8$ Hz; $P_BCP_X$), 153.4 (ddd, $^1J(C,P_X) = 95.5$, $^1J(C,P_A) = 32.4$, $^2J(C,P_B) = 25.3$ Hz; $P_ACP_X$), 22.1 (ddd, $^1J(C,P_A) = 31.1$, $^2J(C,P_B) = 17.6$, $^3J(C,P_X) = 5.7$ Hz; $CH(SiMe_3)_2$), 3.3 (br d; $Si(CH_3)_3$), 2.9 (m; $Si(CH_3)_3$), 0.8 (br s; $CH(Si(CH_3)_3)_2$); $^{29}Si$ NMR (49.7 MHz, $C_6D_6$): $\delta = -5.4$ (br m), −1.9 (br m), 2.7 (br s); MS (EI, 70 eV): $m/z$ (%): 422 [$M^+$], 349 [$M^+ - SiMe_3$], 218 [$P_3C_2(SiMe_3)Si^+$], 73 [$Me_3Si^+$].

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[1] F. Mathey, *Chem. Rev.* **1988**, *88*, 437; A. N. Hughes, *Handbook of Organophosphorus Chemistry* (Ed.: R. Engel) Marcel Dekker, New York, **1992**, chap. 10; L. D. Quin, *Comprehensive Heterocyclic Chemistry, Vol. 2* (Eds.: A. R. Katritzky, C. W. Rees, E. F. V. Scriven), Pergamon, Oxford, **1996**, p. 757.

[2] F. Mathey, *J. Organomet. Chem.* **1990**, *400*, 149.

[3] D. B. Chesnut, L. D. Quin, *J. Am. Chem. Soc.*, **1994**, *116*, 5779.

[4] L. Nyulászi, *J. Phys. Chem.* **1995**, *99*, 586.

[5] L. Nyulászi, *J. Phys. Chem.* **1996**, *100*, 6194.

[6] A. Dransfeld, L. Nyulászi, P. von R. Schleyer *Inorg Chem.*, submitted.

[7] L. Nyulászi, *Inorg. Chem.* **1996**, *35*, 4690.

[8] M. N. Glukhotsev, A. Dransfeld, P. von R. Schleyer, *J. Phys. Chem.* **1996**, *100*, 13447.

[9] V. Caliman, P. B. Hitchcock, J. F. Nixon, *J. Chem. Soc. Chem. Comm.* **1995**, 1661.

[10] P. B. Hitchcock, J. F. Nixon, N. Sakarya, *Chem. Commun.* **1996**, 2751.

[11] V. Caliman, P. B. Hitchcock, J. F. Nixon, L. Nyulászi, N. Sakarya, *Chem. Commun.* **1997**, 1305.

[12] L. D. Quin, Gy. Keglevich, A. S. Ionkin, R. Kalgutkar, G. Szalontai, *Phosphorus Sulfur Silicon Relat. Elem.* **1996**, *109–110,* 433.

[13] L. D. Quin, Gy. Keglevich, A. S. Ionkin, R. Kalgutkar G. Szalontai, *J. Org. Chem.* **1996**, *61*, 7801.

[14] Gy. Keglevich, L. D. Quin, Zs. Böcskei, Gy. M. Keserü, R. Kalgutkar, P. M. Lahti, *J. Organomet. Chem.* **1997**, *532*, 109.

[15] Gy. Keglevich, Zs. Böcskei, Gy. Keserü, K. Ujszászi, L. D. Quin *J. Am. Chem. Soc.* **1997**, *119*, 5095.

[16] L. Nyulászi, Gy. Keglevich L. D. Quin, *J. Org. Chem.* **1996**, *98*, 7808.

[17] A. Schmidpeter, M. Thiele, *Angew. Chem.* **1991**, *103*, 333; *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 308.

[18] G. Jochem, H. Noth, A. Schmidpeter, *Chem. Ber.* **1996**, *129*, 1083.

[19] V. Thelen, D. Schmidt, M. Nieger, E. Niecke, W. W. Schoeller, *Angew. Chem.* **1996**, *108*, 354; *Angew. Chem. Int. Ed. Engl.* **1996**, *35,* 313.

[20] P. Coggon, J. F. Engel, A. T. McPhail, L. D. Quin, *J. Am. Chem. Soc.* **1970**, *92,* 5779.

[21] R. Appel, *Multiple Bonds and Low Cordination in Phosphorus Chemistry* (Eds.: M. Regitz, O. J. Scherer), Thieme, Stuttgart, **1990**, pp 367–390.

[22] Quantum-chemical calculations were carried out with the GAUSSIAN 94 suite of programs. Gaussian 94, Revision B.2: M. J. Frisch, G. W. Trucks, H. B. Schlegel, P. M. W. Gill, B. G. Johnson, M. A. Robb, J. R. Cheesman, T. Keith, G. A. Petersson, J. A. Montgomery, K. Raghavachari, M. A. Al-Laham, V. G. Zakrzewski, J. V. Ortiz, J. B. Foresman, J. Cioslowski, B. B. Stefanov, A. Nanayakkara, M. Challacombe, C. Y. Peng, P. Y. Ayala, W. Chen, M. W. Wong, J. L. Andres, E. S. Replogle, R. Gomperts, R. L. Martin, D. J. Fox, J. S. Binkley, D. J. Defrees, J. Baker, J. P. Stewart, M. Head-Gordon, C. Gonzalez, J. A. Pople, Gaussian, Inc., Pittsburgh, PA, 1995. Geometry optimization was carried out at the HF/3-21G(*)level for 1-[bis(trimethylsilyl)methyl]-3,5-bis(trimethylsilyl)-1,2,4- triphosphole (**3**) and for 1-[bis(trimethylsilyl)methyl]-3,5-disilyl-1,2,4-triphosphole. For the rest of the compounds optimizations were carried out at the HF/6-31G* and MP2/6-31G* levels of theory. Second derivatives of these compounds were calculated at the HF/6-31G* level, resulting in all positive harmonic frequencies.

[23] L. Nyulaszi, J. F. Nixon, unpublished results.

[24] C. W. Bird, *Tetrahedron*, **1985**, *41*, 1409.

[25] C. W. Bird, *Tetrahedron*, **1990**, *46*, 5697.

[26] L. Nyulászi, P. Várnai, T. Veszprémi, *THEOCHEM* **1995**, *358*, 55.

[27] J. Kapp, K. Schade, A. M. El-Nahasa, P. von R. Schleyer, *Angew. Chem.* **1996**, *108*, 2373; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2236.

[28] Crystal data for **3** ($C_{15}H_{37}P_3Si_4$): $M_r = 422.7$, monoclinic, space group $P21/c$ (no. 14), $a = 9.887(3)$, $b = 20.310(3)$, $c = 14.129(2)$ Å, $\beta = 108.21(2)°$, $V = 2695.1$ Å$^3$, $Z = 4$. $Mo_{(K\alpha)}$ radiation, data collection with an Enraf-Nonius CAD4 diffractometer. Of 4727 reflections measured, 2127 were observed ($I > 2\sigma(I)$). $R = 0.083$, $wR2 = 0.182$. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC-101105. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44)1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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# Facile Synthesis of Cyclic Tetrapeptides from Nonactivated Peptide Esters on Metal Centers**

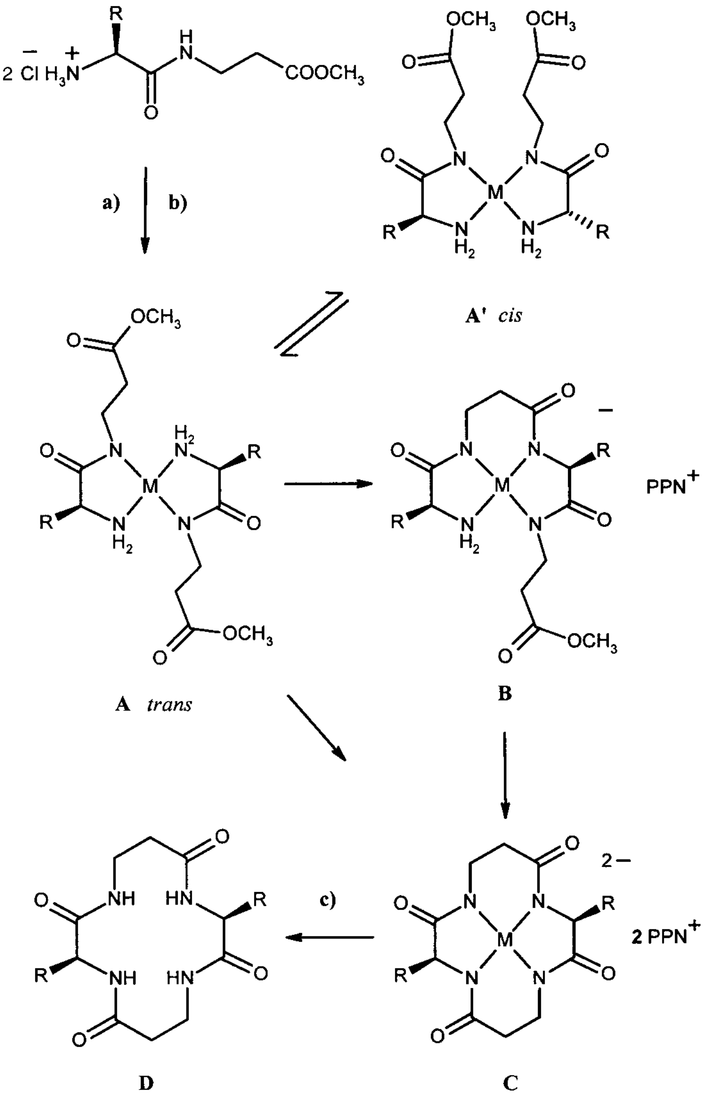
Katharina Haas, Werner Ponikwar, Heinrich Nöth, and Wolfgang Beck*

*Dedicated to Professor Dieter Seebach*
*on the occasion of his 60th birthday*

The search for a comprehensive understanding of the structure–activity relationship for conformationally rigid peptides has led to a greater interest in cyclic peptides.[1, 2] Synthetic cyclopeptides are interesting target molecules owing to their biological activity, their model character for conformational analyses, and their potential as drugs, among other things.[3] Synthetic analogues of hormones[4] show the link between reduced peptide flexibility due to cyclization and increased receptor specificity in a particularly impressive fashion. As the metabolic degradation of peptides begins preferably at the C or N terminals,[1] cyclic peptides are expected to have a longer biological availability than their linear analogues. Cyclic tetrapeptides with biological activity are also found in nature.[5]

Present methods for the cyclization of peptides generally require a completely protected peptide precursor, which is cyclized in solution or at a solid phase by using a coupling agent, as well as a strongly activated acyl component. In order to avoid intermolecular oligomerizations, the cyclization of small peptides, in particular (e.g., tetrapeptides), must be performed under high dilution conditions.[6]

In the course of our continuing studies into the formation of oligopeptides at metal centers,[7] we have found a facile, metal-mediated synthesis of 12-, 14-, 16-, and 18-membered cyclic tetrapeptides or macrolactams from readily accessible nonactivated dipeptide ester precursors. The reaction of $Ni^{II}$, $Pd^{II}$, and $Cu^{II}$ salts with two equivalents of dipeptide ester in methanol in the presence of NaOMe as base results in dianionic complexes, which can be isolated by precipitation with suitable cations (e.g., $Ca^{2+}$, $Cs^+$, $PPN^+ = (Ph_3PNPPh_3)^+$ (**1**–**11**, see Scheme 2). The cyclization of the dipeptides coordinated to the metal probably occurs as shown in Scheme 1. The crucial step is the same as that assumed for the oligomerization of peptides at metal centers,[7, 8] namely



Scheme 1. Postulated mechanism of the metal-supported synthesis of $C_2$-symmetrical cyclic tetrapeptides, exemplified for a 14-membered ring. a) $Na_2[PdCl_4]$, $NiCl_2 \cdot 6H_2O$ or $CuCl_2 \cdot 2H_2O$, 6NaOMe, MeOH, 24 h, 65 °C; b) [PPN]Cl, $H_2O$; c) HCl/MeOH (saturated), room temperature, 15 min.

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