considered, a binding pocket from the structurally unrelated subtilisin family was detected. Further examples from this family followed together with other members of the trypsin family. The trypsin and subtilisin superfamily are representatives of the major class of serine proteases, that is, they share functional similarity without sequence and fold homology.

The entire NADPH cofactor binding pocket of a carbonyl reductase[28] was taken as the query and screened against a set of 5377 cavities extracted from proteins with no significant sequence homology. The top-scoring cavities also accommodate NADPH; subsequent cavities host ligands with decreasing similarity, but which contain parts of the NADPH skeleton. The large cavity of an NADPH-dependent steroid dehydrogenase[29] is detected at rank 41 (Figure 3), although the crystal structure had been determined in the absence of the bound co-factor. A cavity from a phenol hydrolase is found at rank 116 which accommodates FAD as a co-factor. In this case, the adenine recognition site is shared with the original NADPH query pocket.

Surprisingly, in another search we detected a surface patch of an adenine-binding pocket that was similar to an unoccupied binding-site region in HIV protease. In the proteinase structure, a macrocyclic peptidomimetic is bound to the active site,[30] and leaves a binding-site region that is similar to a patch in the catalytic subunit of protein kinase A unoccupied.[31] In the latter case, this patch accommodates the adenine portion of adenylimino diphosphate. This surprising finding is of potential interest for drug design, as an adenyl moiety might be used to supplement the macrocycle in the unoccupied binding niche in HIV protease. It is likely that a large database of binding-site cavities can be used to generate interesting suggestions for new molecular portions that can be used as potential bioisosters in skeletons of novel leads.

Received: March 19, 2001 [Z16803]

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Unusual Formation of an Azaphospholene from 1,3,4,5-Tetramethylimidazol-2-ylidene and Di(isopropyl)aminophosphaalkyne**

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During recent studies of the reactivity of N-heterocyclic carbenes[1] towards phosphaalkynes, we found that the anellated compound *N*,*N*′-bis(2,2-dimethylpropyl)benzimid-

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[**] This project was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.

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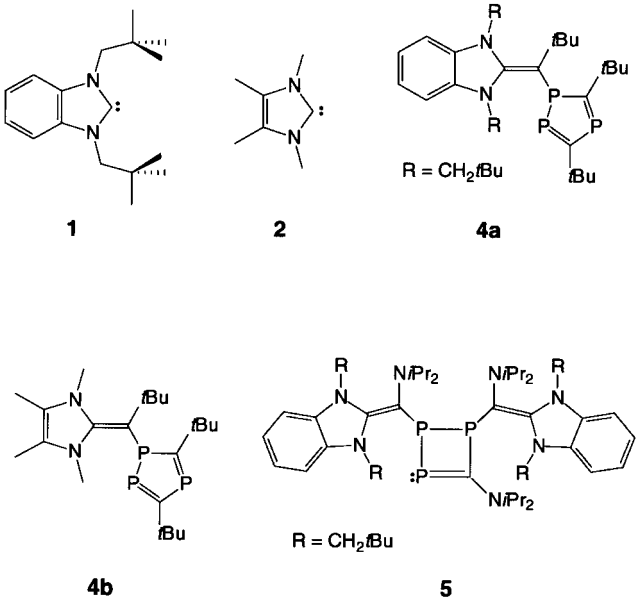
  1433-7851/01/4017-3144 $ 17.50+.50/0

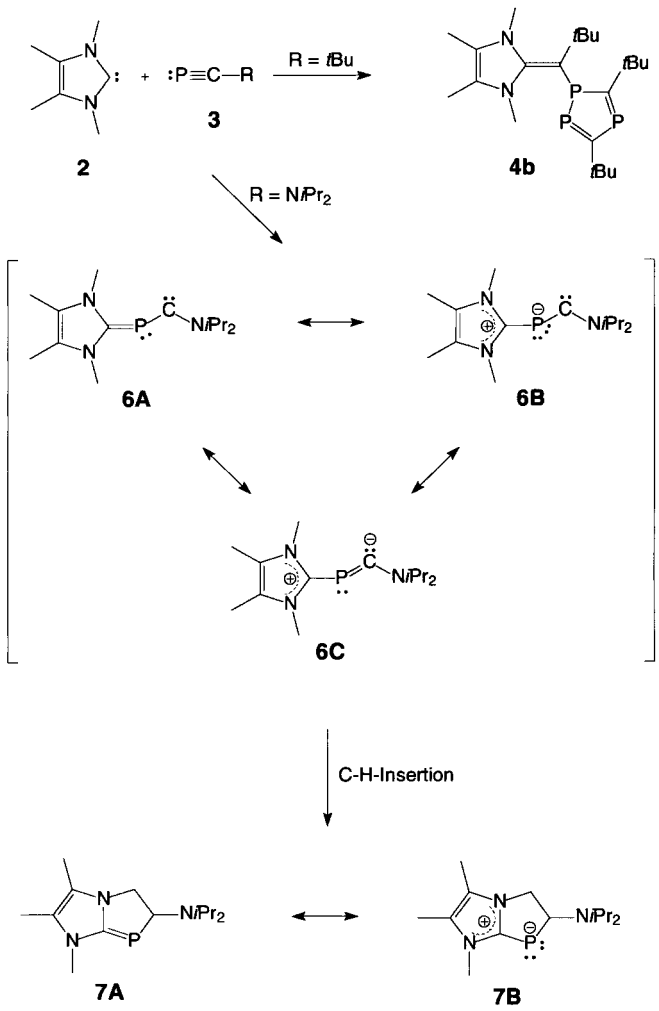
azolin-2-ylidene (**1**)[2] reacts quantitatively with P≡C*t*Bu (**3a**), to form the triphosphole **4a**, and with P≡CN*i*Pr$_2$ (**3b**), to yield the 1,2,3-triphosphetene **5**.[3] Similarly, Nixon et al.[4] have synthesized the triphosphole derivative **4b** by treating the Arduengo carbene 1,3,4,5-tetramethylimidazol-2-ylidene (**2**) with the 2,4,6-tri-*tert*-butyl-1,3,5-triphosphabenzene. These



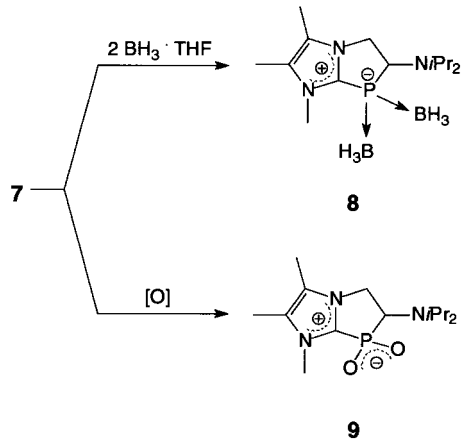
results demonstrate that the bond formation between the unsaturated carbon of the P–C multiple-bond system and the carbene carbon atom is favored. The reaction of the Bertrand phosphanylsilyl carbene with the phosphaalkyne **3a** proceeds in the same manner. The primarily formed 2-phosphanyl-2*H*-phosphirene is stabilized by ring opening under preservation of the C–C$_{carbene}$ bond, and breaking of the P–C$_{carbene}$ bond to yield the $1\lambda^5,2\lambda^3$-diphosphetene.[5] Herein we report the synthesis of an isolable 1:1 adduct between the N-heterocyclic carbene **2** and the phosphaalkyne **3b**, which results in the formation of a P–C$_{carbene}$ bond, and we propose a mechanism for this novel reaction on the basis of quantum-chemical calculations.

The main product of the reaction of the carbene **2** with **3a** (carried out in toluene at room temperature) is the triphosphole **4b**[4] (ca. 70%). However, when **2** is treated with the aminophosphaalkyne **3b**, the bicyclic compound **7** is formed in almost quantitative yield (Scheme 1).

Compound **7** was isolated as pale yellow, air and moisture sensitive microcrystals. The ^{13}C NMR spectrum shows the resonance signal of the carbene carbon at $\delta = 178.9$ (^1J(P,C) = 81.5 Hz), which is strongly shifted to higher field when compared to **2** ($\Delta\delta = 33.8$). The ^{31}P{^{1}H} NMR signal is observed as a singlet at $\delta = -64.8$ which is in the region characteristic for C-diaminophosphaalkenes.[6] The bonding situation in the new azaphosphole **7** is best described by the two resonance structures **7A** and **7B**, in which **7B** represents an inversely polarized phosphaalkene with a π electron-density distribution of P$^{\delta-}$=C$^{\delta+}$.[7] This interpretation is supported by the derivatization of **7** with the Lewis acid BH$_3$ · THF, which yields exclusively the complex **8** with two coordinated BH$_3$ groups on the phosphorus atom (Scheme 2).



Scheme 1. Proposed mechanism for the formation of the azaphospholene **7** from **2** and **3b** (DFT calculations: B3LYP/6-311G(2d)).



Scheme 2. Formation of **8** and **9** through reaction of **7** with BH$_3$ · THF or air.

Cowley et al.[8] have recently described an analogous diborane complex with an acyclic diaminophosphaalkene.

In further support of these experimental data, we obtained a small amount of the oxidation product **9** (Scheme 2), with two oxygen atoms bound to the phosphorus atom, from a solution of **7**, kept for several weeks in benzene at room temperature (obviously because of the effect of air and moisture).

  1433-7851/01/4017-3145 $ 17.50+.50/0

The ^{31}P NMR spectra of **8** and **9** (δ_P (**8**): 2.8; δ_P (**9**): 90.5) show, as expected, a strong low-field shift compared to the azaphospholene **7**. The $^{13}C\{^1H\}$ NMR spectrum signal of the carbene center of **8** appears as a doublet at $\delta = 151.7$ with a remarkably small $^1J(P,sp^2\text{-}C)$ coupling of only 9.0 Hz.

The crystal-structure analysis[9] confirms the mass spectrometry (MS) and NMR data, which demonstrates that both BH_3 groups or oxygen atoms in the bicyclic species **8** and **9** are bonded to the phosphorus atom (Figures 1 and 2). In both cases the phosphorus atom assumes a distorted tetrahedral geometry. The P–B and P–O bond lengths are comparable to those of related acyclic derivatives.[8, 10] The $P-C_{carbene}$ distances (**8**: 1.818(5); **9**: 1.824(3) Å), shortened C–N bond lengths in comparison to the free carbene **2**,[1d] and the planar environment of the ring nitrogen atoms suggest a strongly polarized $P-C_{carbene}$ bond with the formal positive charge localized in the imidazole ring.

The mechanism of the surprising formation of compound **7** was studied by quantum-chemical density functional theory (DFT) calculations (B3LYP/6-311G(2d) optimizations and zero-point energy corrections ΔZPE; all stationary points were characterized by vibrational frequency calculations, Program GAUSSIAN 98;[11] the methods B3LYP/6-311G(d,p) and B3LYP/6-31G* give similar results). Because of computing-time considerations the slightly simplified model systems **2′** (H instead of CH_3 at C=C in **2**) and **3b′** (CH_3 instead of *i*Pr at the nitrogen atom in **3b**) were used. According to the calculations the initial adduct, which is formed by an attack of the phosphorus atom of **3b′** on the carbene **2′**, has structure **6′** with significant bending at both the newly formed carbene center (Scheme 1) and at the phosphorus atom (Figure 3). The bonds from phosphorus to the heterocycle (1.82 Å) and to the former phosphaalkyne carbon atom (1.77 Å) are calculated to be unusually long. A natural bond orbital (NBO) analysis of **6′** indicates a substantial negative charge on the carbene carbon atom as in resonance structure **6C** (Scheme 1). According to the calculations the CH-insertion[12] to produce the bicyclic compound **7′** proceeds in two steps: first, an intramolecular 1,5-H shift takes place, which leads to the 1,5-dipolar intermediate **6″**. The corresponding transition state is quite low in energy (14.8 kcal mol^{-1}) and can be reached at room temperature. The resulting intermediate **6″** is calculated to be 10.4 kcal mol^{-1} higher in energy than **6′**. It is transformed to **7′** in a 1,5 ring-closure reaction by passing over an activation energy barrier of 18.5 kcal mol^{-1}. Compound **7′** is 26.9 kcal mol^{-1} lower in energy than the intermediate **6′**. For **7′** again unusual long P–C bonds are calculated ($P-C_{heterocycle}$: 1.76, $P-CHNMe_2$: 1.96 Å (bond – no bond resonance)).

According to the calculations we interpret the attack of the imidazol-2-ylidene **2′** at the phosphorus atom of **3′** as a result of a kinetically controlled reaction. The thermodynamically favored C–C bond formation leading to a vinylphosphinidene (3.7 kcal mol^{-1} lower than **6′**) is not observed. An isomeric 2*H*-phosphirene structure does not correspond to a minimum on the potential-energy surface.

According to the DFT calculations benzimidazol-2-ylidene is a harder nucleophile than **2′** (HOMO energy is 0.25 eV more negative than for imidazol-2-ylidenes). It undergoes exclusively the thermodynamically favored P–C attack.[3] Specific solvation effects may additionally contribute to the remarkable selectivity observed.

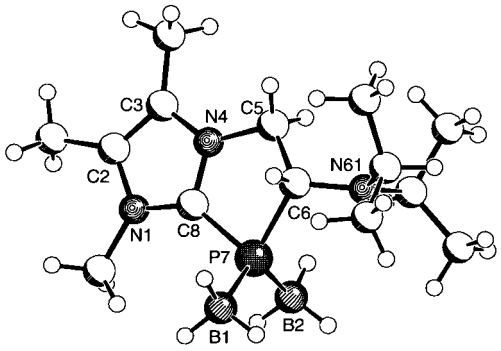


Figure 1. Molecular structure of **8**. Selected bond lengths [Å] and angles [°]: P7-C8 1.818(5), P7-C6 1.899(5), P7-B1 1.934(5), P7-B2 1.953(6), C8-N1 1.337(6), C8-N4 1.330(5), N1-C2 1.385(6), C2-C3 1.356(6), N4-C3 1.388(6), N4-C5 1.462(6), C5-C6 1.546(6); C8-P7-C6 86.8(2), C8-P7-B1 112.2(3), C6-P7-B1 107.8(2), C8-P7-B2 102.7(2), C6-P7-B2 118.5(2), B1-P7-B2 122.6(3), N1-C8-N4 107.3(4), P7-C8-N1 137.7(4), P7-C8-N4 114.6(3), C2-N1-C8 109.1(4), C3-N4-C8 110.4(4), N1-C2-C3 107.7(4), N4-C3-C2 105.5(4).

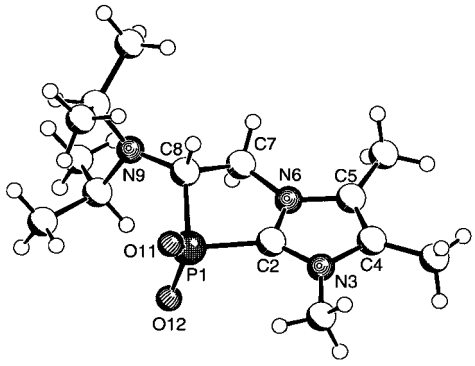


Figure 2. Molecular structure of **9**. Selected bond lengths [Å] and angles [°]: P1-C2 1.824(3), P1-C8A 1.861(4), P1-C8B 1.878(8), P1-O11 1.471(2), P1-O12 1.468(2), C2-N3 1.325(3), C2-N6 1.329(3), C4-C5 1.353(4), N3-C4 1.388(3), N6-C5 1.382(3), N6-C7 1.463(3), C7A-C8A 1.532(5); C2-P1-C8A 86.5(2), C2-P1-C8B 90.5(3), C2-P1-O11 110.64(12), C2-P1-O12 107.32(12), C8A-P1-O11 109.1(2), C8B-P1-O11 126.5(5), C8A-P1-O12 117.3(2), C8B-P1-O12 96.5(5), O11-P1-O12 120.55(13), N3-C2-N6 107.1(2), N6-C5-C4 105.9(2), C5-C4-N3 106.9(2), P1-C2-N3 139.5(2), P1-C2-N6 113.3(2), C2-N6-C7A 117.3(2), N6-C7A-C8A 104.9(2), C7A-C8A-P1 107.7(2).

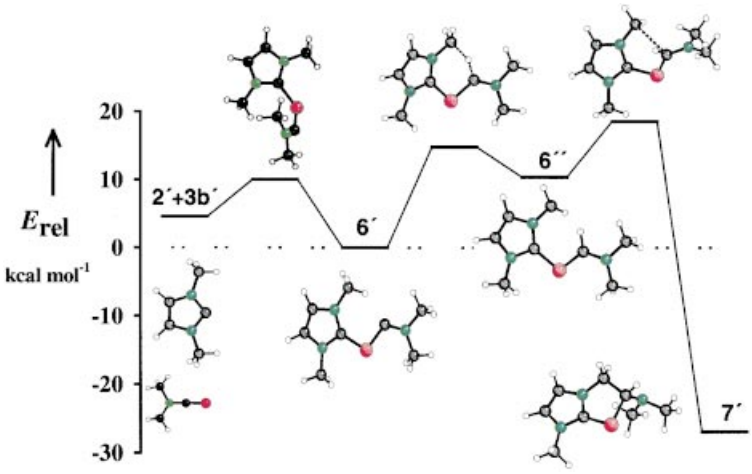


Figure 3. Relative energies for the intermediates in the reaction of the carbene **2′** with the phosphaalkyne **3b′** to **7′**.

  1433-7851/01/4017-3146 $ 17.50+.50/0 *Angew. Chem. Int. Ed.* **2001**, *40*, No. 17

The results presented here demonstrate clearly that both the electronic structures of the phosphaalkyne (with or without π-donor substituents),[13] as well as those of the N-heterocyclic carbenes determine the reaction pathway of the adduct formation. In general the formation of three different types of phosphaheterocycles (type **4**, **5**, or **7**) may be expected. By treating a soft carbene (**2**) with an electron-rich phosphaalkyne (**3b**) we could direct the course of the reaction towards primary attack of the carbene carbon atom at the phosphorus atom of the phosphaalkyne. This allowed the subsequent unusual C–H activation at the nitrogen substituent of the Arduengo carbene.

Experimental Section

All reactions were carried out under argon using standard Schlenk techniques. Reactions were monitored by using ^{31}P NMR spectroscopy.

Preparation of **4b**: A solution of **2**[15] (0.058 g, 0.47 mmol) in [D$_8$]toluene (1 mL) was added dropwise, at room temperature, to a stirred solution of **3a**[14a] (0.140 g, 1.40 mmol) in [D$_8$]toluene (1 mL). The mixture was stirred continuously and afterwards transferred into the NMR tube. ^{31}P NMR measurements indicated a complete reaction of **3a** and the formation of **4b** after 2 days. After removal of the solvent in vacuo and recrystallization from pentane, **4b** was obtained as an red powder (0.135 g, 68% yield). **4b** was characterized by comparison of the NMR data with those in the literature.[4]

7: A solution of **3b**[14b] (0.100 g, 0.70 mmol) in [D$_8$]toluene (1 mL) was added dropwise, at room temperature, to a solution of **2** (0.087 g, 0.70 mmol) in [D$_8$]toluene (1 mL) under stirring. At the beginning of the reaction, the mixture changed from yellow to red. ^{31}P NMR measurements indicated a complete reaction of **3b** and a nearly quantitative formation of **7**. After removal of the solvent in vacuo and recrystallization from pentane, **7** was obtained as pale yellow, air and moisture sensitive powder (0.153 g, 82% yield). ^{1}H NMR (200.1 MHz, [D$_8$]toluene, 25 °C): $\delta = 1.04$ (d, J(H,H) = 7.0 Hz, 6H, CHCH_3), 1.23 (d, J(H,H) = 6.2 Hz, 6H, CHCH_3), 1.36 (s, 3H, CCH_3), 1.53 (s, 3H, CCH_3), 2.67 (s, 3H, NCH_3), 3.38 (m, 3H, NCH_2 and CHCH$_3$), 3.52 (dsept, J(H,H) = 7.0, ^4J(P,H) = 3.2 Hz, 1H, CHCH$_3$), 5.06 (dt, J(H,H) = 8.0, ^2J(P,H) = 7.2 Hz, 1H, PCH); ^{13}C{^{1}H} NMR (50.3 MHz, [D$_8$]toluene, 25 °C): $\delta = 8.1$ (s, C=CCH_3), 8.8 (s, C=CCH_3), 22.5 (s, CHCH_3), 21.6 (s, CHCH_3), 32.4 (s, NCH_3), 52.0 (d, ^2J(P,C) = 10.7 Hz, NCH_2), 55.2 (s, CHCH$_3$), 55.3 (s, CHCH$_3$), 60.0 (d, ^1J(P,C) = 38.7 Hz, PCH), 125.4 (s, C=C), 129.3 (s, C=C) 178.9 (d, ^1J(P,C) = 81.5 Hz, C=P); ^{31}P{^{1}H} NMR (81.0 MHz, [D$_8$]toluene, 25 °C): $\delta = -64.2$ (s); MS (70 eV): m/z (%): 267 (60) [M^+], 224 (10) [$M^+ - $ CH(CH$_3$)$_2$], 194 (11) [$M^+ - $ CH(CH$_3$)$_2$ – 2CH$_3$], 166 (100) [$M^+ - i$Pr$_2$NH].

8: A 1M solution of BH$_3$ · THF (1.0 mL, 1.12 mmol) was added dropwise, at room temperature, to a stirred solution of **7** (0.150 g, 0.56 mmol) in [D$_8$]toluene (1 mL). After 3 h colorless crystals precipitated from the reaction mixture (0.126 g, 76% yield). Their quality was sufficient for a single-crystal X-ray structure analysis. ^{1}H NMR (200.1 MHz, CDCl$_3$, 25 °C): $\delta = 1.03$ (d, J(H,H) = 6.5 Hz, 6H, CHCH_3), 1.15 (d, J(H,H) = 7.1 Hz, 6H, CHCH_3), 1.63 (br, 6H, BH$_3$), 2.20 (s, 3H, CCH_3), 2.22 (s, 3H, CCH_3), 3.46 (sept, J(H,H) = 6.5 Hz, 1H, CHCH$_3$), 3.79 (s, 3H, NCH_3), 3.46 – 4.1 (m, 3H, NCH_2 and CHCH$_3$), 4.53 (dt, J(H,H) = 8.0, ^2J(P,H) = 10.3 Hz, 1H, PCH); ^{13}C{^{1}H}NMR (50.3 MHz, CDCl$_3$, 25 °C): $\delta = 8.6$ (s, C=CCH_3), 9.0 (s, C=CCH_3), 22.9 (s, CCH_3), 23.3 (s, CCH_3), 32.9 (s, NCH_3), 46.1 (s, CHCH$_3$), 46.2 (s, CHCH$_3$), 49.0 (d, ^2J(P,C) = 2.2 Hz, NCH_2), 61.4 (d, ^1J(P,C) = 24.3 Hz, PCH), 124.7 (s, C=C), 129.0 (s, C=C), 151.7 (d, ^1J(P,C) = 9.0 Hz, C=P). ^{31}P{^{1}H} NMR (81.0 MHz, CDCl$_3$, 25 °C): $\delta = 2.8$ (br s); MS (70 eV): m/z (%): 295 (1) [M^+], 281 (14) [$M^+ - $ BH$_3$], 267 (100) [$M^+ - $ 2BH$_3$].

Received: March 26, 2001 [Z16849]

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[9] a) X-ray structure analysis of **8** (C$_{14}$H$_{32}$B$_2$N$_3$P): $M = 295.02$, colorless crystals $0.20 \times 0.20 \times 0.15$ mm, $a = 10.394(1)$, $b = 16.959(2)$, $c = 11.189(1)$ Å, $\beta = 111.52(1)°$, $V = 1834.8(3)$ Å^3, $\rho_{calcd} = 1.068$ g cm^{-3}, $\mu = 1.45$ cm^{-1}, empirical absorption correction with SORTAV ($0.972 \le T \le 0.979$), $Z = 4$, monoclinic, space group $P2_1/n$ (No. 14), $\lambda = 0.71073$ Å, $T = 198$ K, ω and φ scans, 7778 measured reflections ($\pm h, \pm k, \pm l$), $(\sin\theta)/\lambda = 0.59$ Å^{-1}, 2648 independent ($R_{int} = 0.095$) and 1689 observed reflections ($I \ge 2\sigma(I)$), 190 refined parameters, $R = 0.077$, $wR^2 = 0.180$, max. residual electron density 0.40/ – 0.26 e Å^{-3}, hydrogen atoms calculated and refined as riding atoms.[16] b) X-ray structure analysis of **9** (C$_{14}$H$_{26}$N$_3$O$_2$P · 1.5 C$_6$H$_6$): $M = 416.51$, yellow crystals $0.35 \times 0.15 \times 0.05$ mm, $a = 6.866(1)$, $b = 28.907(1)$, $c = 12.439(1)$ Å, $\beta = 104.68(1)$, $V = 2388.2(4)$ Å^3, $\rho_{calcd} = 1.158$ g cm^{-3}, $\mu = 1.37$ cm^{-1}, without absorption correction ($0.954 \le T \le 0.993$), $Z = 4$, monoclinic, space group $P2_1/c$ (No. 14), $\lambda = 0.71073$ Å, $T = 198$ K, $\omega/2\theta$ scans, 14554 measured reflections ($\pm h, \pm k, \pm l$), $(\sin\theta)/\lambda = 0.65$ Å^{-1}, 5417 independent ($R_{int} = 0.054$) and 3943 observed reflections ($I \ge 2\sigma(I)$), 293 refined parameters, $R = 0.078$, $wR^2 = 0.144$, max. residual electron density 0.34/ – 0.31 e Å^{-3}, disorder of the atoms C7, C8, N9 and the *iso*-propyl groups are refined with restrains, hydrogen atoms calculated and refined as riding atoms.[16]

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and SCHAKAL (E. Keller, Universität Freiburg, **1997**) for molecular graphics. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-155454 (**8**) and CCDC-155453 (**9**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

Towards Synthetic Adrenaline Receptors—Shape-Selective Adrenaline Recognition in Water**

Michael Herm, Oliver Molt, and Thomas Schrader*

Dedicated to Professor Günter Wulff on occasion of his 66th birthday

The adrenergic receptor family is one of the most intensively investigated receptor types. Its G-protein-coupled signal transduction influences a broad range of vital body functions—from respiration to blood pressure.[1] Every year about 3000 research articles appear dealing with biochemical, medicinal, and pharmaceutical aspects of this important class of receptors. However, mainly because of the lack of X-ray crystal structures of these integral membrane proteins, their tertiary structure and mechanism of action have not been fully elucidated to date.[2] A synthetic model which imitates the postulated receptor–ligand interactions could shed new light on the efficiency of the specific combination of selected weak attractive forces. Such a model could also become a new prototype for artificial adrenaline sensors. Many attempts have been made to create synthetic receptor molecules for catecholamines. Most of these are monotopic: in some recent developments dopamine selectivity has been achieved with a pyrazol-containing podand, a homocalix[3]arene triether, as well as with a sol–gel process.[3] Enantioselective 3,4-dihydroxyphenylalanine (DOPA) recognition has been achieved by a peptide–bipyridinium cyclophane.[4] Boronic acids have been used in newer ditopic receptors for molecular recognition of the catechol ring.[5a,b] In an alternative design the catechol has been bound by a symmetric hydrophobic cavity with peripheral carboxylate groups for dopamine recognition.[5c] All these artificial host molecules, however, are far from biomimetic and not selective for catecholamino alcohols.

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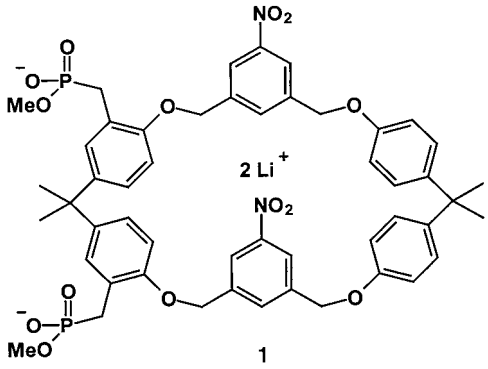
[**] Towards Synthetic Adrenaline Receptors, Part 4. This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie. Part 3: ref. [6].

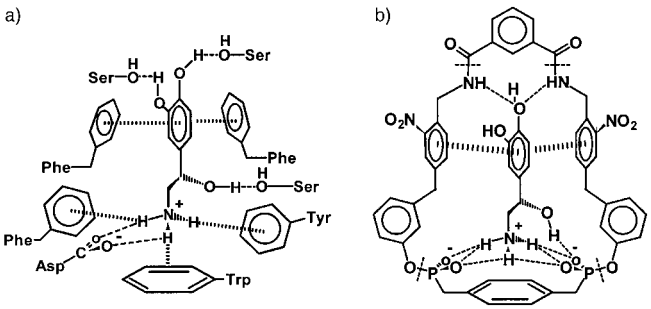
Recently, we introduced macrocyclic receptor molecule **1** with a hydrophobic cavity for the strong binding of adrenaline derivatives in methanol.[6] However, the amphiphilic host molecule undergoes strong self-association in water and is not



1

selective for adrenaline derivatives. We felt, that in order to imitate the natural binding site, an artificial biomimetic adrenaline host should be able to provide—at least after an induced-fit process—a microenvironment with a shape complementary to the geometrical form of its guest. A high number of van der Waals contacts would help desolvation in water and lead to a strong hydrophobic attraction.[7] In addition, the functional groups of the artificial receptor molecule should be positioned much more precisely, so that multiple noncovalent interactions could become effective in a cooperative fashion simultaneously after docking of the substrate. Extensive modeling experiments suggested a new approach, namely incorporation of the xylylene bisphosphonate moiety in a macrocycle, which should also be able to form the sandwich arrangement found in the natural example, as well as provide binding sites for the catechol hydroxyl groups at its opposite end.

Scheme 1 shows our solution to this problem: the nitroarene groups in the macrocyclic receptor molecule **2** can undergo double π-stacking interactions with the catechol ring of adrenaline without producing any significant ring strain in the receptor molecule, while the isophthalic amide group is ideally preoriented to form hydrogen bonds to the phenolic OH groups. Molecular mechanics calculations predict high binding enthalpies resulting from the interplay of noncovalent interactions operating simultaneously.[8] Monte–Carlo simu-



Scheme 1. a) Noncovalent interactions between noradrenaline and the β-adrenergic receptor; b) energy-minimized structure of the complex formed between noradrenaline and macrocyclic bisphosphonate **2**. The dashed lines indicate retrosynthetic cuts.

  1433-7851/01/4017-3148 $ 17.50+.50/0