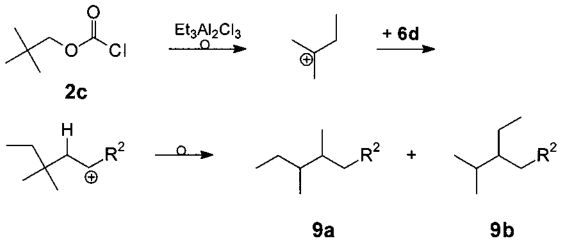

Scheme 6. Reaction of neopentyl chloroformate (**2c**) with 10-undecenoic acid (**6d**). The addition products **9a** and **9b** were formed in the ratio 2.2:1. $R^2 = (CH_2)_8COOH$.

obtained with 2-ethylhexyl chloroformate. In contrast, reactions with ethyl chloroformate led to oligomeric products.

Experimental Section

General method for the synthesis of **3a–c**: A mixture of the respective alkene **1a** (1.42 g, 4.2 mmol), **1b** (0.56 g, 5 mmol), or **1c** (1.56 g, 4.2 mmol) and isopropyl chloroformate (**2a**) (0.7 g, 5 mmol) in CH_2Cl_2 (10 mL) was stirred in a N_2 atmosphere (1 bar) for 5 min at −15 °C. Then $Et_3Al_2Cl_3$ (1.86 g, 7.5 mmol for **1a**, 1.24 g, 5 mmol for **1b**, and 2.47 g, 10 mmol for **1c**) was added dropwise over 1 h at −15 °C and the solution was stirred at room temperature for a further 1 h. Diethyl ether (100 mL), H_2O (40 mL), and 10% HCl to dissolve precipitated aluminum salts were then added. The organic phase was separated and washed with H_2O (3 × 30 mL). After the combined extracts had been dried over Na_2SO_4 the solvent was removed in vacuum. Purification of **3a** was achieved by column chromatography (silica gel 60, 70–230 mesh, 1.7 × 33 cm) with petroleum ether/ethyl acetate (7/3, 300 mL) to yield 0.99 g **3a** (73%). Pure **3b** (0.52 g, 67%) and **3c** (0.90 g, 60%) were obtained by kugelrohr distillation.

General method for the synthesis of **5** and **7a–c**: A mixture of the respective alkene **4**, **6a–c** (5 mmol), and **2a** (0.7 g, 5 mmol) in CH_2Cl_2 (10 mL) was stirred in a N_2 atmosphere (1 bar) for 5 min at −15°C. A mixture of triethylsilane (0.58 g, 5 mmol) and $Et_3Al_2Cl_3$ (1.24 g, 5 mmol) was then added dropwise over 1 h (2 h for **5**) at −15 °C and the mixture was stirred for a further 1 h at room temperature. Diethyl ether (100 mL), H_2O (40 mL), and 10% HCl to dissolve precipitated aluminum salts were then added. The organic phase was separated and washed with H_2O (3 × 30 mL). After the combined extracts had been dried over Na_2SO_4, the solvent was removed in vacuo, and the residues eluted over silica gel 60 with pentane. Evaporation of the pentane followed by kugelrohr distillation gave **5** (0.52 g, 82%), **7a** (0.50 g, 47%), **7b** (0.43 g, 55%), or **7c** (0.86 g, 72%).

General method for the synthesis of **8a/b** and **9a/b**: A mixture of **6d** (0.92 g, 5 mmol) and **2b** (0.68 g, 5 mmol) or **2c** (0.75 g, 5 mmol) in CH_2Cl_2 was stirred in a N_2 atmosphere (1 bar) for 5 min at −15 °C. Then $Et_3Al_2Cl_3$ (1.24 g, 5 mmol) was added as described for **3a–c**. The reaction mixtures were worked up as described and purified by column chromatography to give **8a/b**: (0.79 g, 65%) and **9a/b**: (0.89 g, 70%), respectively.

The products were identified by ^1H and ^{13}C NMR spectroscopy and mass spectrometry.

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van't Hoff–Le Bel Stranger: Formation of a Phosphonium Cation with a Planar Tetracoordinate Phosphorus Atom[**]

Matthias Driess,[*] Joachim Aust, Klaus Merz, and Christoph van Wüllen

Dedicated to Professor Gerhard Fritz
on the occasion of his 80th birthday

Molecular differentiation in nature would be strongly limited with respect to stereochemistry if a tetracoordinate carbon atom did not prefer a tetrahedral geometry.[1] It was the fundamental contribution of van't Hoff and Le Bel, in the final quarter of the nineteenth century, which predicted that the phenomenon of stereochemistry for tetracoordinated

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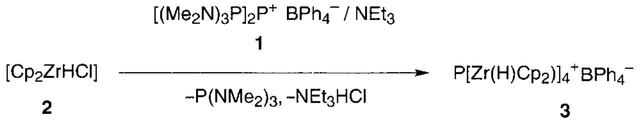
carbon compounds is based on the tetrahedron model of methane.[2] Nowadays this geometry is well known in molecular science. Moreover, isoelectronic molecules and ions usually adopt classical tetrahedral structures too. This can be rationalized by employing the far-reaching Lewis-bonding concept ("octet rule") and classical molecular orbital theory.[3] However, about 100 years after the finding of van't Hoff and Le Bel it was suggested that the seemingly impossible goal of stabilizing an "anti-van't Hoff–Le Bel" configuration of an eight valence electron molecule ER_4 (for example, planar methane, $E = C$, or silane derivatives, $E = Si$) or isoelectronic ions (for example, quarternary ammonium, NR_4^+, or phosphonium ions, PR_4^+; $R =$ organic or organometallic substituent) may not be out of reach.[4–7] While recent reports have shown that compounds with planar tetracoordinate carbon centers can be synthesized by employing organometallic substituents,[8–9] attempts to prepare planar isoelectronic ER_4 compounds with other main-group elements failed. Herein we describe the synthesis and structure of the first phosphonium cation, PR_4^+, which has exclusively electropositive organometallic zirconocene substituents R ($R = (C_5H_5)_2ZrH$, zirconocenyl hydride) and an "anti-van't Hoff–Le Bel" configuration. Furthermore we report the results of ab initio calculations on a series of isoelectronic model ER_4 compounds ($E = B^-$, C, N^+, Al^-, Si, and P^+), which show that this organometallic substituent R represents a facile and, at the same time, universal ligand for the stabilization of elusive "anti-van't Hoff–Le Bel" configurations of various main-group elements.

On the basis of the MO model of planar methane[4, 5] it is not difficult to understand why it is possible to stabilize planar tetracoordinate carbon atoms in methane derivatives: The mainly electronic trick to reduce and possibly reverse the energy gap between tetrahedral and planar configurations is to coordinate at least two electropositive metal centers at the four-coordinate carbon atom. At the same time these metal centers serve as strong σ-donor and π-acceptor ligands.[6–9] This enables delocalization of the unfavorable π electrons in the hypothetical planar CH_4 molecule and leads, therefore, to a substantial change in the energy difference between tetrahedral and planar geometry. Thus, one expects that strongly electropositive metal ligands with π-acceptor functions should support "anti-van't Hoff–Le Bel" structures of the isoelectronic ions NR_4^+ (ammonium), PR_4^+ (phosphonium), and AsR_4^+ (arsonium cation).[7] So far, only some gold(I) complexes $E(AuL)_4^+$ with $E = N$ and As ($L =$ neutral donor ligand such as $P(C_6H_5)_3$) have been isolated, of which the NR_4^+ ion possesses the classical tetrahedral structure, while the AsR_4^+ ion adopts a tetragonal pyramidal structure, with the arsenic atom sitting above the Au_4 square, as a result of its relatively large atom size and favorable Au-Au interactions.[10] The analogous PR_4^+ ion has not yet been prepared, but ab initio calculations predict the same tetragonal pyramidal geometry as observed for AsR_4^+.[11] In our search for a stable tetrametalated phosphonium salt ($PR_4^+X^-$, $R =$ metal ligand, $X =$ any counterion), we found that the tetrametalation of the triphosphenium salt **1**[12] with the Schwartz reagent $[(C_5H_5)_2ZrHCl]$ (**2**)[13, 14] in the molar ratio of 1:9 in THF and in the presence of triethylamine as an auxiliary base



$$\underset{\mathbf{2}}{[Cp_2ZrHCl]} \xrightarrow[-P(NMe_2)_3,\ -NEt_3HCl]{\underset{\mathbf{1}}{[(Me_2N)_3P]_2P^+\ BPh_4^-\ /\ NEt_3}} \underset{\mathbf{3}}{P[Zr(H)Cp_2]_4^+BPh_4^-}$$

surprisingly leads to the tetrazirconio-substituted phosphonium cation in **3**, which adopts an "anti-van't Hoff–Le Bel" configuration. Compound **3** is diamagnetic, sparingly soluble in aromatic solvents, THF, and CH_2Cl_2, but soluble in DMF (but slow decomposition occurs), and has been isolated in an analytically pure state (correct C,H combustion analysis) in the form of green crystals in 11 % yield.

The mechanism for the formation of **3** is not yet known, but paramagnetic reactive intermediates have been observed, but which could not be characterized. Apparently, **1** is a source of phosphorus cations in this reaction, since the only detectable phosphorus-containing product in the ^{31}P NMR spectrum of the reaction mixture, besides **3**, is merely the "free" triaminophosphane $P(NMe_2)_3$ ($\delta(^{31}P) = 123.9$). The latter is liberated from **1** through a ligand substitution reaction (metathesis). The ^{31}P NMR spectrum of solutions of **3** in $[D_6]DMF$ shows a quintet resonance signal at relatively low field ($\delta = 254.2$) as a result of $^2J(P, H)$ couplings with four chemically equivalent ZrH protons ($J = 29.5$ Hz), and a singlet in the $^{31}P\{^1H\}$ spectrum. The expected sets of phenyl, C_5H_5, and ZrH proton resonances are observed in the ^1H NMR spectrum, with the characteristic high-field resonance of the ZrH protons ($\delta = -3.8$ ($^2J(H,P) = 29.5$ Hz)) clearly indicating the presence of Zr-H-Zr bridges. This has been confirmed by a single-crystal X-ray diffraction analysis of **3**.[15] It crystallizes in the monoclinic space group $C2/c$ with four ion pairs in the unit cell and the phosphorus atoms as symmetry centers in the cations. The most striking feature of the structure is the planar tetracoordinate phosphorus atom in the cation (Figures 1 and 2) along with its isoelectronic, classical tetraphenylborate counterion. The Zr-P (2.616(1) and 2.610(2) Å) and Zr-H bond lengths (1.93, 2.07, and 2.12 Å) are unremarkable and resemble those values reported for zirconium phosphanides[16] and μ-hydrido zirconium hydrides.[14, 17] The Zr1-P-Zr2 and Zr1a-P-Zr2 angles of 89.84(4) and 90.16(4)°, respectively, are almost ideal for such a coordination mode. The bridging

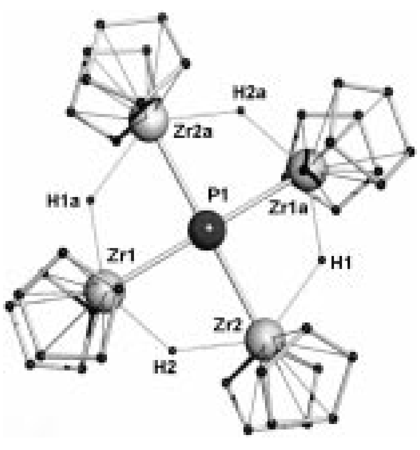


Figure 1. Molecular structure of the phosphonium cation $P[Zr(H)(C_5H_5)_2]_4^+$ in the tetraphenylborate salt **3**; the hydrogen atoms of the C_5H_5 groups are omitted for clarity.

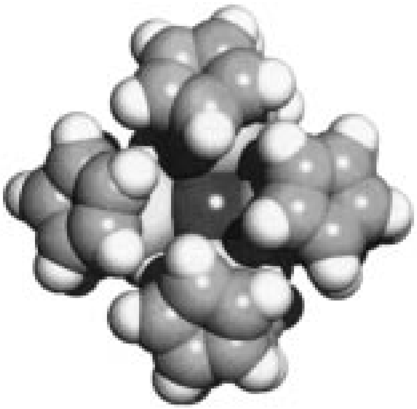


Figure 2. van der Waals model of the phosphonium cation in **3** (see also Figure 1).

hydride centers facilitate the formation of an almost planar eight-membered Zr_4H_4 cycle, which can be regarded as an "anti crown ether" ligand[18] for the phosphorus cation. The endocyclic H-Zr-H angles of 132–138° reflect the almost equidistant bridging mode of the hydride centers.

What are the reasons for the unprecedented geometry of the phosphonium cation? Apparently, steric congestion by the C_5H_5 groups of the zirconocene moieties plays a role in the energy gap between the planar and tetrahedral form. However, ab initio calculations[19] of the model cation $P[Zr(H)Cl_2)]_4^+$, in which the C_5H_5 groups have been fully replaced by chlorine atoms, clearly show that the planar ("anti-van't Hoff–Le Bel") structure (D_{4h} symmetry) is still favored by 74 kcal mol^{-1} (!) with respect to the classical tetrahedral one (S_4 symmetry). Interestingly, the Zr-H hydride atoms in the optimized S_4 structure prefer terminal coordination sites. Apparently, the Zr-H-Zr hydrogen bridges contribute to the energy gap, but they probably do not make a substantial contribution. It seems crucial, as in the case of stable, planar methane derivatives, that the p_z lone-pair electrons of phosphorus in the HOMO (*H*ighest *O*ccupied *M*olecular *O*rbital) can be delocalized by π-backbonding to symmetry-adopted empty d orbitals of the four metal centers (Figure 3). According to its MO model the planar cation possesses Zr,P,Zr-three-center σ-bonds in the molecular plane (Figure 3), which are mostly responsible for the unusual low-field chemical shift of the ^{31}P nucleus. It should be mentioned that previous calculations of the very unfavorable planar PH_4^+ form (energy gap between tetrahedral and planar configuration (D_{4h}) 276 kcal mol^{-1} (!)) revealed its spontaneous distortion to an tetragonal pyramidal structure (C_{4v}), which is still 163 kcal mol^{-1} less stable with respect to the tetrahedral form.[7] This result underlines the remarkable incommensurability of the phosphonium cation in **3** versus PH_4^+. Furthermore, our calculations of the hypothetical silane SiR_4 and of the corresponding alanate AlR_4^- with $R = Zr(H)Cl_2$ revealed that the planar configuration is, in analogy to the PR_4^+ analogue, 66 and 60 kcal mol^{-1} more stable, respectively, than the tetrahedral geometry. This large energy gap is intriguing, since the structural preference of such planar entities is almost independent of the electronegativities of the central main-group atoms. It is therefore very surprising, that the isoelectronic species of elements of the second period (ER_4, $E = B^-$, C, N^+) prefer a strongly distored tetrahedral geometry with one large Zr-E-Zr angle of about 140° and Zr-H-Zr hydride bridging.

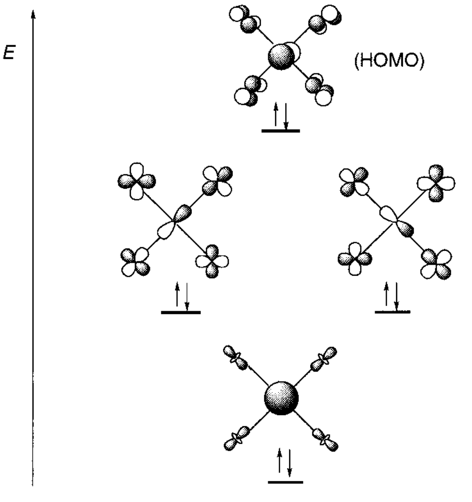


Figure 3. Molecular orbital representation of the σ and π interactions between zirconium and phosphorus atoms in the PZr_4^+ core of the cation in **3**.

These structures are 6–13 kcal mol^{-1} more stable than their planar D_{4h} forms. The energy gap is probably reduced or even reversed as a result of steric influence if C_5H_5 ligands instead of chlorine substituents are bonded to the metal. Apparently, the different behavior of second versus third period elements is a consequence of the smaller size of boron, carbon, and nitrogen atoms and reflects their preference to undergo s,p hybridization in contrast to aluminum, silicon, and phosphorus atoms.[20] Compound **3** is clearly important as a starting material for studies of structure–reactivity relationships of this rare class of compounds. The simple and, at the same time, universal organometallic ligand R in **3** offers tremendous advantages for the preparation of other "anti-van't H-Hoff–Le Bel"-configured eight valence electron ER_4 molecules and ions.

Experimental Section

A slurry of **2** (2.56 g, 9.93 mmol) in THF (40 mL) and NEt_3 (10 mL) at −70 °C was treated with **1** (0.73 g, 1.08 mmol). The reaction mixture was then slowly warmed up to room temperature whereby the red suspension was stirred for four days. Filtration and subsequent evaporation of solvents left a solid residue, which was disolved in CH_2Cl_2 (30 mL). This solution was then layered with hexane (10 mL), whereby the product precipitated in the form of analytically pure green crystals (yield: 0.14 g, 0.12 mmol; 11 %); m.p. 178 °C (decomp). ^1H NMR (250 MHz, $[D_6]$DMF, 300 K): $\delta = -3.80$ (d, 4H, Zr-H, ^2J(H,P) = 29.5 Hz), 6.31 (s, 40H, C_5H_5), 7.00 (m, 4H, *p*-C_6H_5), 7.10 (m, 8H, *m*-C_6H_5), 7.50 (m, 8H, *o*-C_6H_5); ^{31}P NMR (101 MHz, $[D_6]$DMF, 300 K): $\delta = 254.2$ (quint., ^2J(P,H) = 29.5 Hz).

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[15] Crystal structure data: monoclinic, space group $C2/c$, $a = 25.484(18)$, $b = 13.219(8)$, $c = 18.109(11)$ Å, $\beta = 120.400(17)^\circ$, $V = 5262(6)$ Å^3, $Z = 4$, $\rho = 1.565$ g cm^{-3}, $\mu = 0.842$ mm^{-1}, $F(000) = 2512$, crystal size $= 0.2 \times 0.2 \times 0.1$ mm. Crystals were mounted on a glass capillary with perfluorinated hydrocarbons and immediately chilled to 203 K. Data collection was performed with a Bruker axs SMART diffractometer ($\mathrm{Mo}_{K\alpha}$ grahite monochromator). A total of 11158 reflections ($1.80 < \theta \leqslant 25.37^\circ$) were collected, of which 4690 unique reflections ($R_{\text{int}} = 0.100$) were used. The structure was solved using the program SHELXS-97 and refined (326 parameter) using the program SHELXL-97 to $R1 = 0.0525$, $wR2 = 0.1137$ (all data) ($I > 2\sigma(I)$; both programs from G. M. Sheldrick, Universität Göttingen, **1997**). The positions of the Zr-H hydrogen atoms were localized in the difference fourier map and refined; non-hydrogen atoms were anisotropically refined. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Centre as supplementary publication no. CCDC-116996. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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Lectin-Mediated Drug Targeting: Discrimination of Carbohydrate-Mediated Cellular Uptake between Tumor and Liver Cells with Neoglycoconjugates Carrying Fucose Epitopes Regioselectively Modified in the 3-Position[**]

Hans-Georg Lerchen,[*] Joerg Baumgarten,
Norbert Piel, and Victoria Kolb-Bachofen

Dedicated to Dr. Pol Bamelis
on the occasion of his 60th birthday

The specific interaction between carbohydrate epitopes and corresponding endogenous cell-surface lectins plays a fundamental role in a variety of intercellular recognition processes such as sperm–egg adhesion, leucocyte adhesion to platelets and endothelium, cancer metastasis, and microorganism adhesion to host cells.[1] Various lectins have been identified and characterized with respect to carbohydrate specificity on rat, mice, and mammalian tissues, particularly on the liver.[2] The utility of these carbohydrate–lectin interactions for receptor-mediated drug targeting has already been explored mainly focussing on liver targeting.[3] Also tumor cells express a distinct lectin pattern on their surfaces.[4] However, to our knowledge, so far no tumor-specific lectins have been described, and a lectin-mediated drug targeting to tumor cells is extremely challenging.[5] Prerequisites are the discrimination of the targeting moiety between tumor cells and healthy tissue and the circumvention of an efficient scavenging of glycoconjugates by liver cells as described for Kupffer cells and hepatocytes.[6]

The goal of this work was the identification of carbohydrate residues appropriate for tumor targeting. A fucose-binding receptor has been identified on colon cancer cells such as SW480 and was considered to be an appropriate target mediating tumor cell binding and uptake.[7] However, fucose also efficiently binds to lectins in the liver, particularly on Kupffer cells.[2] Therefore a discrimination between the recognition of tumor and liver cell had to be achieved. Neoglycoconjugates such as glycoconjugates of bovine serum albumin (BSA) are appropriate tools for studying lectin–carbohydrate interactions and carbohydrate-mediated cellu-

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