A new class of purely inorganic ligands: carboranylphosphinic acids
Una nova classe de lligands purament inorgànics: els àcids carboranilfosfínics

Elena Oleshkevich, Francesc Teixidor and Clara Viñas
Institut de Ciència de Materials de Barcelona (ICMAB-CSIC)

Abstract: Dicarba–*closo*–dodecaboranes (or carboranes) are icosahedral clusters of empirical formula $C_2B_{10}H_{12}$. Depending on the relative position of the carbon atoms in the cluster, three isomers can be distinguished: *ortho*– (1,2), *meta*– (1,7) and *para*– (1,12). Our group focused this research on the first two: *ortho*– and *meta*–carborane isomers. The high symmetry, remarkable stability and versatile reactivity of these clusters allow their functionalization according to a desired application. Our group and others were interested in carboranylphosphorus compounds, mostly due to their properties as ligands for organometallic chemistry and enantioselective catalysis. Among them are carboranylphosphines and carboranylphosphines with P(V) moieties, except carboranyl phosphinates and carboranyl phosphonates. Few studies are found in the literature on carboranyl phosphinic and phosphonic acids. Our research goal has been devoted to developing preparation and characterization of carboranyl phosphinates, aiming towards the designing of purely inorganic ligands that are capable to coordinate to metals producing stable water–soluble polynuclear systems. The influence of the boron cluster on the reactivity of the phosphinate group was studied as well.

Keywords: Carboranes, phosphinates, phosphonates.

*Resum: Els dicarba–*closo*–carborans (o carborans) són poliedres icosaèdrics de fórmula empírica $C_2B_{10}H_{12}$. Depenent de la posició dels dos àtoms de carboni en els diferents vèrtexs del clúster, podem tenir tres isòmers diferents: orto– (1,2–$C_2B_{10}H_{12}$), meta– (1,7–$C_2B_{10}H_{12}$) i para– (1,12–$C_2B_{10}H_{12}$). Aquests clústers són molt estables i mostren una gran simetria i una capacitat de ser substituïts, sigui als vèrtexs de carboni, als de bor o a ambdós, de manera que s'obtenen així diferents clústers funcionalitzats per emprar–los en l'aplicació desitjada. El grup de recerca té una llarga experiència en la síntesi de lligands tipus fosfina que contenen el clúster de carborà que van emprar–se en la preparació de complexos de metalls de transició per usar–los en catàlisi homogènia. L'oxidació d'aquestes fosfines, de P(III) a P(V), és difícil, cal forçar–la. Aquesta és una propietat important de cara a la seva aplicació com a catalitzadors. Pocs exemples es troben a la literatura sobre àcids fosfònics i fosfínics que continguin clústers de carborà. En aquest treball, s'han sintetitzat i caracteritzat àcids fosfònics i fosfínics de clústers icosaèdrics de carborà fent servir com a reactius de partida els isòmers orto– i meta– del closo–carborà. S'ha estudiat la capacitat coordinant d'aquestes noves famílies de lligands que són purament inorgànics amb metalls amb l'objectiu d'obtenir complexos de coordinació polimèrics solubles en aigua. La influència dels clústers de bor en la reactivitat dels lligands també s'ha estudiat.*

Paraules clau: Carborans, àcid fosfònic, àcid fosfínic.

Introduction

n the periodic table of elements, boron lies next to carbon. Both boron and carbon have the property of catenating. Carbon forms cycles and polymers and is the base of organic chemistry. Boron forms clusters and induces a huge discipline of chemistry: Boron science. Boranes, boron clusters and, in particular, icosahedral dicarba-*closo*-dodecaboranes with empirical formula $C_2B_{10}H_{12}$ are of special interest. Boron clusters were considered as electron deficient compounds till Lipscomb's discovery. William N. Lipscomb was awarded with the Nobel Prize in Chemistry 1976 "for his studies on the structure of boranes illuminating problems of chemical bonding". Lipscomb proposed the mechanism to understand the three-center two-electron (3c-2e) bond in boron clusters [1]. In 3c-2e, a pair of electrons is shared between three atoms. The three atoms can be a boron atom at either end and a hydrogen atom in the middle, as in the case of the diborane B–H–B bonds, or the three atoms, can be three boron atoms, as in the polyhedral clusters. 3D aromaticity of boron or carborane clusters gives them unique properties that are not common in organic chemistry [2].

A relation between hydrocarbon and borohydride chemistries has been recently reported [3]. The idea is based on keeping

Contact address: Clara Viñas
Institut de Ciència de Materials de Barcelona (ICMAB-CSIC)
Campus de la UAB, Bellaterra. 08193 Cerdanyola del Vallès
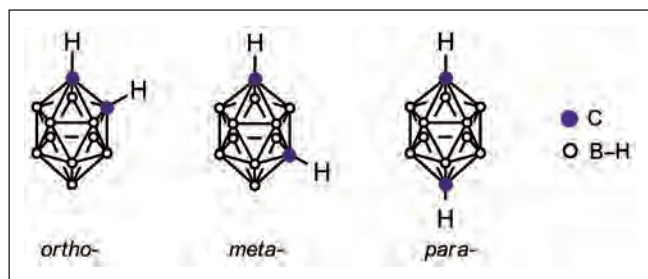Tel.: +34 935 801 853. Fax: +34 935 805 729
E-mail: *clara@icmab.es*

FIGURE 1. The three isomers of icosahedral dicarba–*closo*–dodecarboranes ($C_2B_{10}H_{12}$).

the same number of valence electrons in a confined space. Thus, the «addition» of an extra electron to each boron atom in borohydrides yields molecular analogues of hydrocarbons. As a result, for any given hydrocarbon in organic chemistry, its borohydride analogue can be found in boron chemistry. Along this line, work was recently reported that establishes a direct connection between Wade-Mingos rule of tridimensional aromatic *closo* boron hydride clusters and Hückel's rule of planar aromatic annulenes, showing that they share a common origin regulated by the number of valence electrons in an electronic confined space [4].

Chemical reactivity of *ortho*- and *meta*-carboranes: electrophilic substitutions on *ortho*- and *meta*-carboranes

Although *ortho*- and *meta*-carborane clusters are remarkably stable, in certain reaction conditions they exhibit high synthetic reactivity. From the point of view of electrophilic sub-

stitution at the C_c–H vertices (C_c: carbon atom belonging to carborane cluster), both isomers display similar chemical reactivity. In both carborane isomers the hydrogen atoms of the C_c–H units are more acidic than the ones bonded to B–H vertices, due to the more electronegative character of carbon with respect to boron (2.5 and 2.0, respectively, according to the Pauling scale). Thus, hydrogen atoms attached to carbon can be considered acidic while those bonded to boron are considered hydride. The acidity of the C_c–H vertices decreases in the order of *ortho*-, *meta*- and *para*-carborane. Its vulnerability to become deprotonated decreases in the same order.

This relatively acidic character of C_c–H units allows their deprotonation by strong alkali and alkaline earth metal bases, like for example *n*-butyllithium or Grignard reagents. The generated negative charge on the carbon atom of the cluster, C_c, attracts electrophilic reagents, opening the way to the introduction of functional groups at the C_c position of the cluster.

Figure 2 shows the two possible pathways for substitutions at one or both of the C_c atoms. After dilithiation of the carborane cluster (bottom pathway) it is possible to introduce simultaneously twice the same substituent, which leads to symmetrically substituted carborane. The other pathway (top) demonstrates monosubstitution of the carborane cluster or unsymmetrical disubstitution. The synthesis of monosubstituted carborane derivatives is more complicated compared to the sythesis of disubstituted carborane derivatives. The reason is the disproportionation of Li[$1,2–C_2B_{10}H_{11}$] into Li$_2$[$1,2–C_2B_{10}H_{10}$] and $1,2–C_2B_{10}H_{12}$, as it was found for *ortho*-carborane [5]. Several approaches have been developed to overcome this problem. They include the use of protection/deprotection methodol-
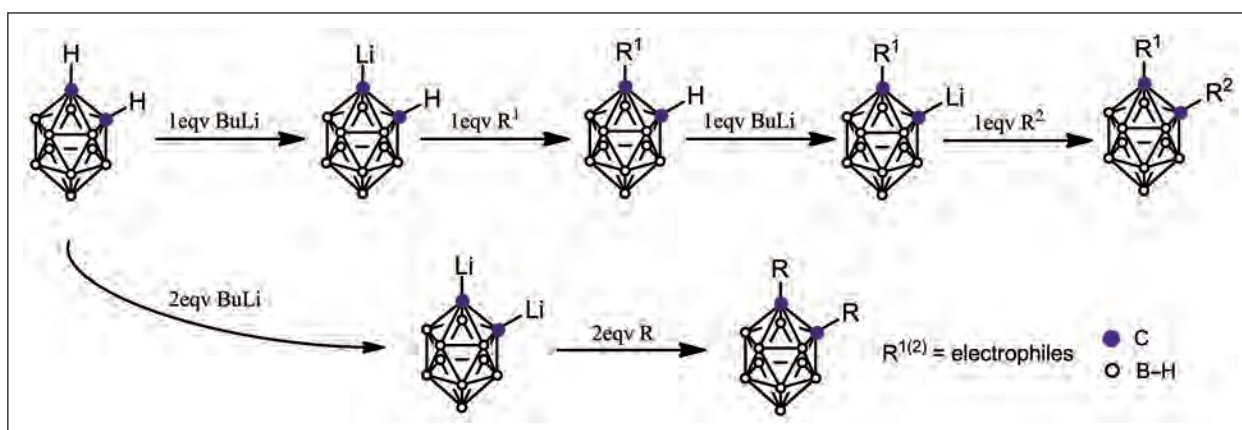

FIGURE 2. Deprotonation reaction of C_c–H units followed by substitution with electrophilic agents.

ogies with dimethoxyethane as the solvent or by doing the reaction at high dilution [6]. Perhaps a simpler method is performing the monosubstitution reactions in ethereal solvents at low temperature and specific carborane concentration. It was suggested that, depending on the type of electrophile, it is possible to find a combination of conditions (ethereal solvent, temperature, carborane concentration) that facilitates the largest degree of monosubstitution [7].

Phosphorus-substituted carboranes and carboranyl phosphinic acids

Substituting conventional organic entities by boron clusters to produce new compounds could deliver remarkable properties such as high rigidity and space occupancy. Carboranylphosphines is one example [8]. Phosphines are prominent ligands in coordination chemistry. By changing groups bonded to phosphorus, the steric and electronic effects are modified, so it is possible to «tailor» properties of the phosphines as ligands.

Our group and others were interested in the exploration of the properties of phosphinate ligands synthesized on the *ortho*-carborane platform [8], including P(III) and P(V) derivatives of *ortho*-carboranylphoshines [9]. The first derivatives

that contain pentavalent phosphorus, phosphinic acids of *ortho*- and *meta*-carboranes were synthesized many years ago [10]. However, neither their characterization nor reproducible procedures of their synthesis were available. As a consequence, their coordination chemistry still remained unexplored till recently [11]. A representative drawing of the carboranyl phosphines, carboranyl phosphine oxides, carboranyl phosphinates and carboranyl phosphonates is shown in Figure 3.

Synthetic pathway of carboranyl phosphinic acids

As previously mentioned, due to the acidic character of C_c–H vertices of the cluster, they can be deprotonated with strong bases and then functionalized by means of electrophilic reagents. In our case, the deprotonation of the *meta*-carborane clusters **1–2** by *n*-BuLi followed by reaction with ClP(NMe$_2$)$_2$ gave *closo*-carboranyldiaminophosphine derivatives **3–4**. The reaction of compounds **3–4** with dry HCl gas in benzene gives *closo*-carboranyldichlorophosphines **5–6** that can be further hydrolyzed to the corresponding phosphinic acids **7–8** in aqueous solution at room temperature. The general reaction is given in Scheme 1.

Compounds **3–10** were characterized by multinuclear NMR and FT-IR spectroscopic techniques, mass spectrometry and elemental analysis. Table 1 shows the ^{31}P chemical shifts of
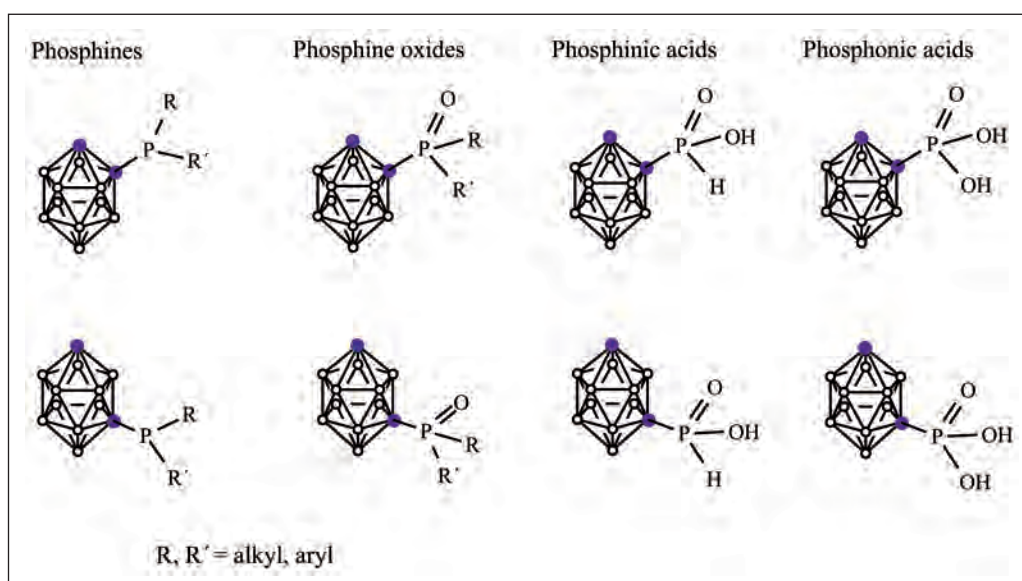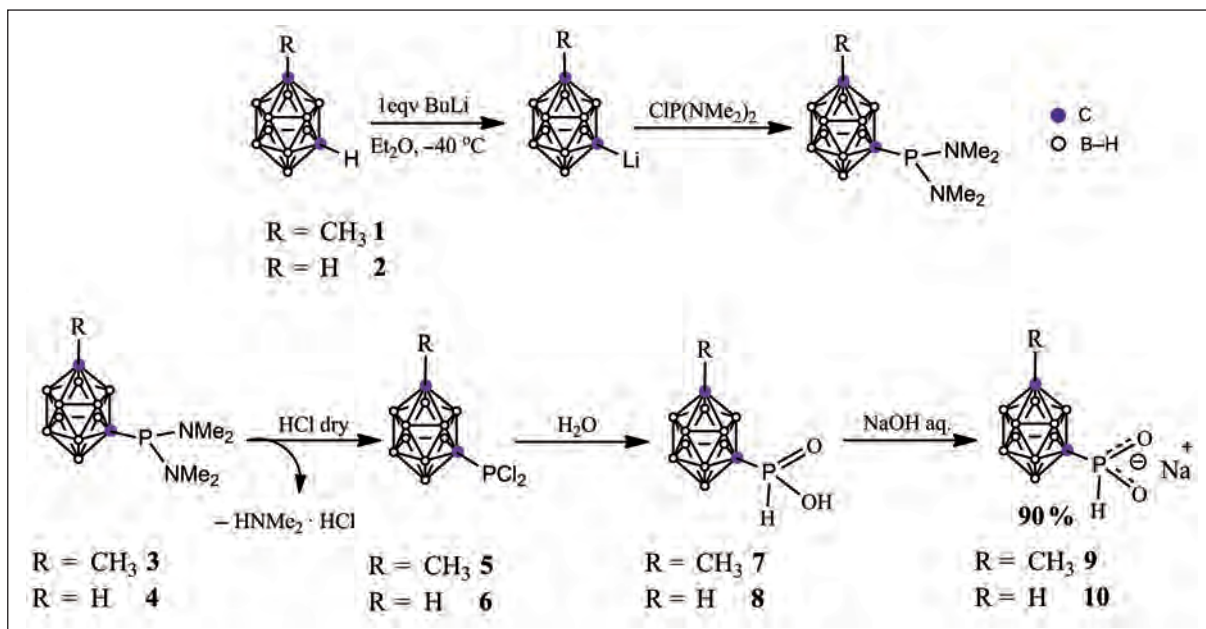

FIGURE 3. Phosphorus-substituted *closo*-carboranes.

Scheme 1. Synthesis of *closo*–carboranylphosphinic acids.

these phosphorus compounds derived from *ortho-* and *meta*-carborane, which appear in the region between δ +162.20/ +14.66 ppm. The ³¹P resonances in all *ortho*-carborane derivatives appear at higher frequency compared with those of the *meta*-carborane derivatives. From Table 1, it is clear when comparing the two cluster isomers that the difference in

the ³¹P chemical shift is the same: entries 1 and 2, entries 4 and 5 or entries 7 and 8. These experimental data display that a P(V) atom bonded to a *meta*-carboranyl cluster is more deshielded than if it is bonded to a *ortho*-carboranyl one; the difference being 6.45, 6.82 and 3.70 ppm, respectively. The same trend is observed in the anionic sodium salts, entries 10

Entry	Compound	Solvent	δ (³¹P), ppm (*J*, MHz)	Δδ (³¹P), ppm	
TABLE 1. ³¹P NMR chemical shifts (in ppm) for intermediates and products					
1	1–CH₃–2–P(NMe₂)₂–1,2–*closo*–C₂B₁₀H₁₀	CDCl₃	99.32	+6.45	−0.12
2	1–CH₃–7–P(NMe₂)₂–1,7–*closo*–C₂B₁₀H₁₀	CDCl₃	105.77		
3	1–P(NMe₂)₂–1,7–*closo*–C₂B₁₀H₁₁	CDCl₃	105.65		
4	1–CH₃–2–PCl₂–1,2–*closo*–C₂B₁₀H₁₀	CDCl₃	155.38	+6.82	−0.11
5	1–CH₃–7–PCl₂–1,7–*closo*–C₂B₁₀H₁₀	CDCl₃	162.20		
6	1–PCl₂–1,7–*closo*–C₂B₁₀H₁₁	CDCl₃	162.09		
7	1–CH₃–2–OPH(OH)–1,2–*closo*–C₂B₁₀H₁₀	CDCl₃	17.08 (640)	+3.70	+0.28
8	1–CH₃–7–OPH(OH)–1,7–*closo*–C₂B₁₀H₁₀	CDCl₃	20.78 (633)		
9	1–OPH(OH)–1,7–*closo*–C₂B₁₀H₁₁	CDCl₃	21.06 (635)		
10	[Na·(H₂O)₄][1–CH₃–2–OPH(O)–1,2–*closo*–C₂B₁₀H₁₀]	D₂O	9.21 (449)		
11	[Na][1–CH₃–7–OPH(O)–1,7–*closo*–C₂B₁₀H₁₀]	D₂O	14.63 (t, (¹*J*(P, D) = 89)	+5.42	+0.01
		H₂O	14.65 (d, ¹*J*(P, H) = 589)		
12	[Na][1–OPH(O)–1,7–*closo*–C₂B₁₀H₁₁]	D₂O	14.66 (d, ¹*J*(P, H) = 583)		
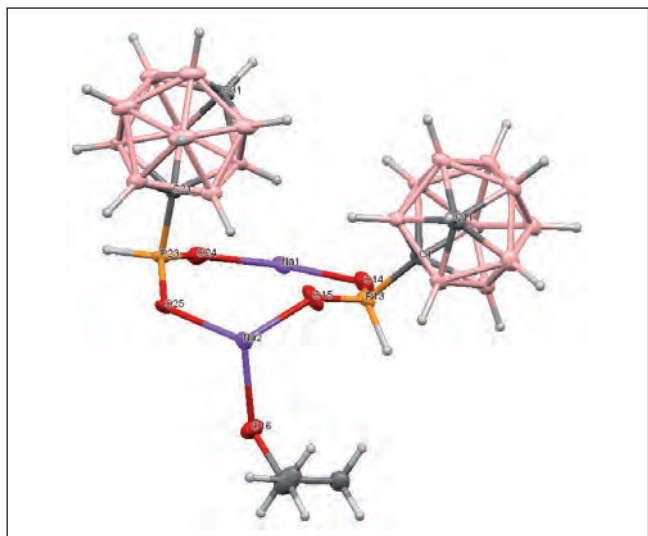
Figure 4. Molecular structure of [Na$_2$][1−OPH(O)−1,7−*closo*−C$_2$B$_{10}$H$_{10}$]$_2$CH(OH)(CH$_3$)$_2$.

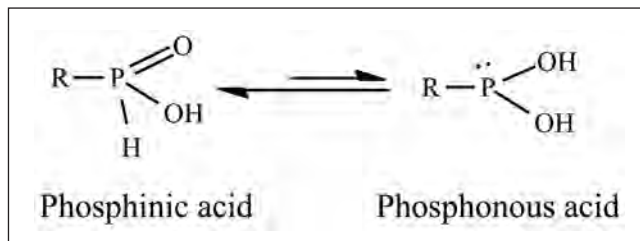
Figure 5. Tautomeric equilibrium between phosphinic and phosphonous acid isomers.

Good crystals of sodium salt of *meta*-carboranylphosphinic acid **10** (Figure 4) suitable for X-ray diffraction were grown from *i*PrOH/water solution, fully confirming its molecular structure.

Isotopic exchange with deuterium and tautomerization

It is well known that pentavalent phosphinic acid derivatives R(O)PH(OH) are involved in the tautomerization process with the corresponding trivalent phosphonous acid form RP(OH)$_2$ [12]. This tautomeric equilibrium (Figure 5) is completely shifted to P(V) tautomer, so free phosphonous acid normally cannot be detected by spectroscopic methods.

It was suggested that phosphorus-bonded hydrogen of phenylphosphinic acid undergoes isotopic exchange with deuterium from the deuterated solvent due to the presence of tautomeric equilibrium [13]. The compounds 1−OPH(OH)−1,7−
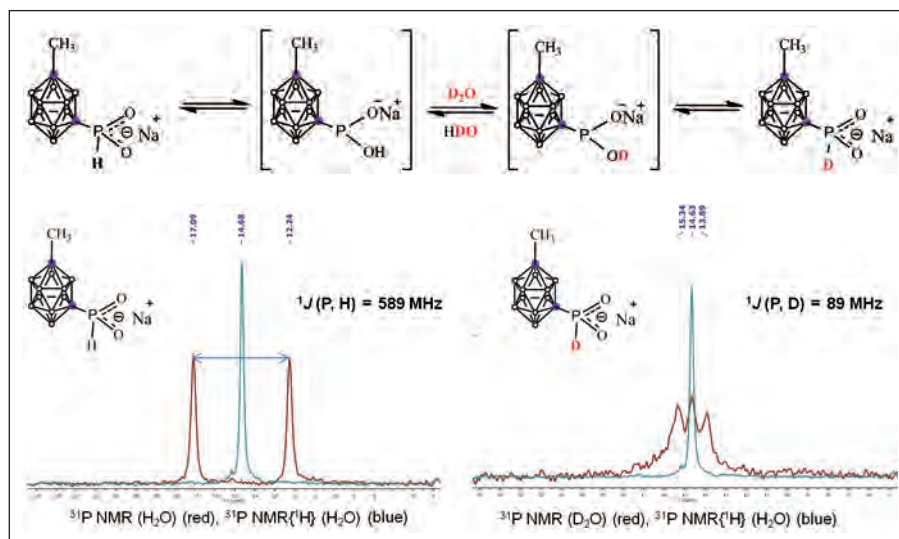
and 11. It is also important to note when comparing entries 2 and 3, entries 5 and 6 or entries 8 and 9 on Table 1 that there is no influence on the nature of the R group (R = Me, H) bonded to the second C$_c$, the difference being 0.11 ppm in all cases. There is no difference in the chemical shifts for the sodium salts, entries 11 and 12.

Closo-carboranylphosphinic acids, compounds **7–9**, displayed a singlet around 17 ppm (for *ortho*-isomer) and 21 ppm (for *meta*-isomer) on ^{31}P{^{1}H} NMR spectrum that turns to a doublet in the ^{31}P NMR spectrum with coupling constant in the range of ^1J(P, H) = 635 Hz, indicating the presence of a P–H bond in the compounds.

Figure 6. P–H/P–D exchange in D$_2$O observed by ^{31}P NMR spectra for Na[1−Me−7−OPH(O)−1,7−C$_2$B$_{10}$H$_{10}$].
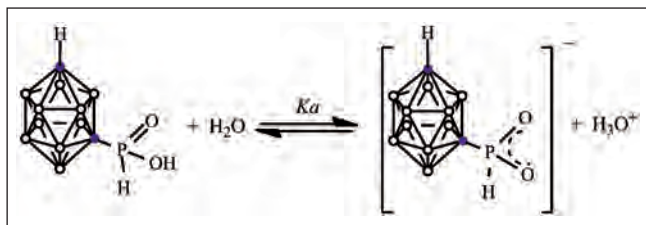
FIGURE 7. *Meta*–carboranylphosphinic acid and the corresponding conjugate base (phosphinate).

$C_2B_{10}H_{11}$ (**8**), $Na[1–Me–7–OPH(O)–1,7–C_2B_{10}H_{10}]$ (**9**), and $Na[1–OPH(O)–1,7–C_2B_{10}H_{11}]$ (**10**) display the same isotopic exchange.

To know the influence of the *meta*-carboranyl ligand, the kinetics of this acid–base isotopic exchange reaction between the hydrogen atom bound to phosphorus and deuterium from the D_2O solvent, was studied by means of $^{31}P\{^1H\}$ and ^{31}P NMR spectra for the compounds **8–10** (Figure 6).

A point to note is that the ^{31}P and $^{31}P\{^1H\}$ NMR spectra of **9** in D_2O after 3.5 h exhibit a triplet (1:1:1) at $d = 14.63$ ppm with a $^1J(P, D)$ of 89 Hz as a result of the completed isotopic exchange, whereas no exchange was observed for **10** after 2 days in D_2O. The phosphinic acid form of 1–OPH(OH)–1,7–$C_2B_{10}H_{11}$ disappears under isotopic exchange but the reaction is not as fast as in the case of $Na[1–Me–7–OPH(O)–1,7–C_2B_{10}H_{11}]$. After 48 h in D_2O, a triplet (1:1:1) at $d = 12.96$ ppm with a $^1J(P, D)$ of 87 Hz was observed.

Acidity, pK_a comparison

Phosphinic acids possess one acidic P–OH group; the acidity of organophosphinic acids varies in the range of 1.3-2.5 pK_a.
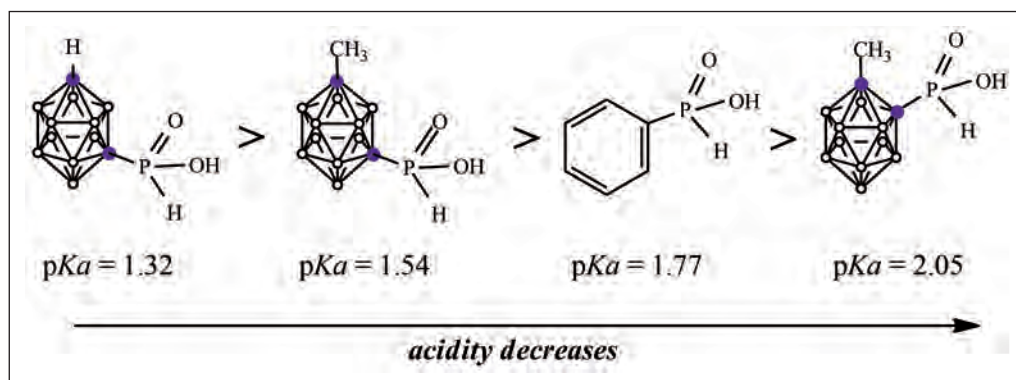
In a similar way as carboxylic acids, pK_a values of phosphinic acids depend on the backbone molecule and the presence of other functional groups. We compared acid strengths of different carboranylphosphinic acids and their organic analogue phenylphosphinic acid. To our surprise, *meta*-carborane enhances the acidity of corresponding phosphinic acid compared to *ortho*-carborane and phenyl group (Figure 8). Also the presence of CH_3 group on the other C_c decreases the acidity of the corresponding carboranylphosphinic acid.

Conclusions

This work has shown that, in a manner similar to organic phosphinates, purely inorganic carboranyl phosphinates can be prepared in very good to excellent yields. Carboranylphosphinic acids have been prepared with both isomers, *ortho*- and *meta*-carborane. The hydrogen in the H–P unit of the carboranylphosphinate has been easily exchanged by D from the deuterated NMR solvent, although rate differences have been noticed depending on the adjacent carborane carbon substituent and the salt or acid form utilized. The carborane influence has been observed in the pK_a of the phosphinate, which is more negative for the *meta*-carboranyl than for the «comparable» phenyl and *ortho*-carborane. It is expected that these enhanced electronic properties will be accompanied by others derived from the hydrophobicity and space-filling efficiency of the carboranyl fragment, making the physicochemical properties of the generated metal complexes attractive for applications in medicine or in materials science.

FIGURE 8. pK_a values of *ortho*-, *meta*–carboranylphosphinic acids and phenylphosphinic acid.

Acknowledgements

References

[1] EBERHARDT, W. H.; CRAWFORD, B.; LIPSCOMB, W. N. "The valence structure of the boron hydrides". *J. Chem. Phys.*, No. 22 (1954), p. 989-1001.

[2] *a)* TEIXIDOR, F.; VIÑAS, C.; DEMONCEAU, A.; NÚÑEZ, R. "Boron clusters: do they receive the deserved interest?". *Pure App. Chem.*, No. 75 (2003), p. 1305-1313. *b)* SCHOLZ, M.; HEY-HAWKINS, E. "Carbaboranes as pharmacophores: properties, synthesis, and application strategies". *Chem. Rev.*, No. 111 (2011), p. 7035-7062.

[3] *a)* POATER, J.; SOLÀ, M.; VIÑAS, C.; TEIXIDOR, F. "A simple link between hydrocarbon and borohydride chemistries". *Chem. Eur. J.*, No. 19 (2013), p. 4169-4175. *b)* POATER, J.; SOLÀ, M.; VIÑAS, C.; TEIXIDOR, F. "π aromaticity and three-dimensional aromaticity: two sides of the same coin?". *Angew. Chem. Int. Ed.*, No. 53 (2014), p. 12191-12195.

[4] POATER, J.; SOLÀ, M.; VIÑAS, C.; TEIXIDOR, F. "Hückel's rule of aromaticity categorizes aromatic *closo* boron hydride clusters". *Chem. Eur. J.* (2016). DOI: 10.1002/chem.201600510.

[5] GRIMES, R. N. *Carboranes.* 2nd ed. Burlington: Academic Press, 2011.

[6] *a)* GÓMEZ, F. A.; HAWTHORNE, M. F. "A simple route to C-monosubstituted carborane derivatives". *J. Org. Chem.*, No. 57 (1992), p. 1384-1390. *b)* VIÑAS, C.; BENAKKI, R.; TEIXIDOR, F.; CASSABÓ, J. "Dimethoxyethane as a solvent for the synthesis of C-monosubstituted o-carborane derivatives". *Inorg. Chem.*, No. 34 (1995), p. 3844. *c)* VALLIANT, J. F.; GUENTHER, K. J.; KING, A. S.; MOREL, P.; SCHAFFER, P.; SOGBEIN, O. O.; STEPHENSON, K. A. "The medicinal chemistry of carboranes". *Coord. Chem. Rev.*, No. 232 (2002), p. 173.

[7] POPESCU, A. R.; MUSTETI, A. D.; FERRER-UGALDE, A.; VIÑAS, C.; NÚÑEZ, R.; TEIXIDOR, F. "Influential role of ethereal solvent on organolithium compounds: the case of carboranyllithium". *Chem. Eur. J.*, No. 18 (2012), p. 3174-3184.

[8] POPESCU, A. R.; TEIXIDOR, F.; VIÑAS, C. "Metal promoted charge and hapticities of phosphines: the uniqueness of carboranyl-phosphines". *Coord. Chem. Rev.*, No. 269 (2014), p. 54-84 and cited references.

[9] POPESCU, R.; LAROMAINE, A.; TEIXIDOR, F.; SILLANPÄÄ, R.; KIVEKÄS, R.; LLAMBIAS, J. I.; VIÑAS, C. "Uncommon coordination behaviour of P(S) and P(Se) units when bonded to carboranyl clusters: experimental and computational studies on the oxidation of carboranyl phosphine ligands". *Chem. Eur. J.*, No. 17 (2011), p. 4429-4443.

[10] *a)* ZAKHARKIN, L. I.; KAZANTSEV, A. V.; ZHUBEKOVA, M. N. *Izv. Akad. Nauk SSSR, Ser. Khim.*, No. 9 (1969), p. 2056-2057. *b)* KAZANTSEV, A. V.; ZHUBEKOVA, M. N.; ZAKHARKIN, L. I. *Zh. Obshch. Khim.*, No. 42 (1971), p. 1570-1571.

[11] OLESHKEVICH, E.; TEIXIDOR, F.; CHOQUESILLO-LAZARTE, D.; SILLANPÄÄ, R.; VIÑAS, C. "Carboranylphosphinic acids: a new class of purely inorganic ligands". *Chem. Eur. J.*, No. 11 (2016), p. 3665-3670.

[12] *a)* MARTIN, R. B. "The rate of exchange of the phosphorus bonded hydrogen in phosphorous acid". *J. Am. Chem. Soc.*, No. 81 (1959), p. 1574-1576. *b)* SILVER, R. B.; LUZ, Z. "Oxidation of phosphorous acid". *J. Phys. Chem.*, No. 66 (1962), p. 1356-1359.

[13] REUBEN, J.; SAMUEL, D.; SILVER, B. L. "Deuterium exchange between phenylphosphonous acid and water". *J. Am. Chem. Soc.*, No. 85 (1963), p. 3093-3096.
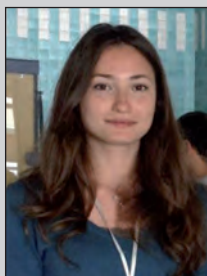
E. Oleshkevich

F. Teixidor
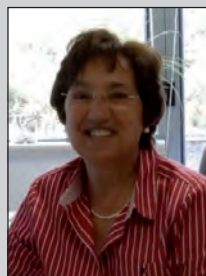
C. Viñas

Elena Oleshkevich is a graduate in Chemical Technology of Biologically Active Synthetic Substances (2011) at the D. I. Mendeleev University of Chemical Technologies of Russia (Российский химико-технологический университет имени Д. И. Менделеева). She is now preparing her doctoral thesis under the direction of Prof. Clara Viñas at the Institute of Materials Science of Barcelona (ICMAB-CSIC). The subject of her thesis is the synthesis of carboranyl phosphinic acids for use as purely inorganic ligands and the study of the properties of their metallic complexes for their possible application in medicine and in materials science.

Francesc Teixidor graduated in Chemistry at the Autonomous University of Barcelona (UAB) in 1975 and took his doctorate there in 1979. Then he did a post-doctoral fellowship at the University of Michigan with Prof. Ralph W. Rudolph for two and half years. Back in Barcelona, he joined the UAB as lecturer in Chemistry. In 1987 he won a place as scientific researcher of the Higher Council of Scientific Research (CSIC) at the Institute of Materials Science of Barcelona and he has been a research professor there since 1999. He has directed 25 doctoral theses and 24 research projects, and he has published over 350 scientific papers in SCI journals, 24 book chapters and one encyclopedia chapter, among other scientific contributions. His field of research is inorganic chemistry, with a special focus on the formation of B–C and B–P bonds and the application of boron clusters as molecular materials for energy production.

Clara Viñas is a graduate in Chemistry at the Autonomous University of Barcelona (UAB, 1975) and in Pharmacy at the University of Barcelona (UB, 1980). She began her research work at the laboratories of Prof. Ralph W. Rudolph at the University of Michigan for one year. On returning to Barcelona, she worked in industry and subsequently won a place at the Municipal Laboratory of Sabadell, where she came to be the director. She took a PhD in Pharmacy at the University of Barcelona in 1991. In 1992 she won a place as tenured scientist of the Higher Council of Scientific Research (CSIC) at the Institute of Materials Science of Barcelona. There she was promoted to the category of scientific researcher in 2002 and she has been a research professor at this institution since 2006. Over the course of her scientific career she has directed 11 doctoral theses and 12 research projects, and she has published over 295 scientific papers in SCI journals, 17 book chapters and one encyclopedia chapter, among other contributions. Her research is based on the synthesis of boron compounds, carboranes and metallacarboranes for use in advanced medical applications.