Novel α-functionally substituted amino acids: diphenylphosphinoglycines†‡

Joachim Heinicke,*[a] Normen Peulecke[a] and Peter G. Jones[b]

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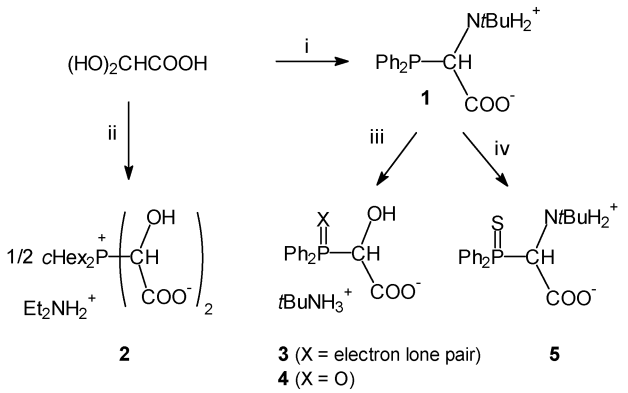
The three-component one-pot reaction of glyoxalic acid hydrate with P–H and N–H compounds allows a convenient access to phosphinoglycines. The molecular structure of 1, determined by X-ray crystallography, some reactions and an alternative formation of phosphinoglycolates are reported.

Synthetic amino acids are of interest in various fields of chemistry and pharmacology.[1] Recently, amino acids with phosphino substituents at the phenyl group of phenylglycine and phenylalanine[2,3] or in the β-position ("phosphinoserines"[4,5] and 4-phosphinoprolines[6,7]) have been reported, likewise the synthesis of the oligopeptides thereof and their catalytic applications,[8] but acyclic α-phosphino amino acids with the trivalent phosphorus atom directly attached to the asymmetric carbon atom are to the best of our knowledge unknown. Only an ester, iPr$_2$PCH(NEt$_2$)COOMe, prepared from chlorodiisopropylphosphine and the sodium enolate of *N*,*N*-diethylglycine methyl ester,[9] has been described.

We now report a first representative of the novel α-phosphino amino acids, *N*-(*tert*-butyl)diphenylphosphinoglycine **1**, and its single crystal X-ray molecular structure.§ **1** is conveniently accessible by addition of an ethereal solution of glyoxylic acid hydrate to equimolar amounts of diphenylphosphine and *tert*-butylamine at ambient temperature (Scheme 1). The zwitterionic compound precipitates from the solution and can be purified by crystallisation from methanol as monosolvate **1·MeOH**. Since changes in the substitution pattern can lead to other products, a generalisation of the scope of this synthetic method requires further investigations of the factors controlling the reaction course. Thus, despite identical conditions and equimolar amounts of the reagents, the reaction of (HO)$_2$CHCOOH with the dialkylphosphine cHex$_2$PH and Et$_2$NH provides the zwitterionic dicyclohexylphosphonium bis(glycolate) **2**. Here, the addition of glyoxylic acid to the phosphino group of the first-formed cHex$_2$PCH(OH)COO$^-$ is preferred to the acid catalysed replacement of the hydroxy by the diethylamino group, even in the presence of water binding agents such as CaCl$_2$ or MgSO$_4$.



Scheme 1 Synthesis of the phosphinoglycine **1**, the phosphonio bis(glycolate) **2** and reactions of **1**. *Reagents and conditions*: i. Ph$_2$PH, tBuNH$_2$, Et$_2$O, 4–15 h, 20 °C; ii. cHex$_2$PH, Et$_2$NH, Et$_2$O, 15 h, 20 °C; iii. for **3**: D$_2$O, few min, 20 °C; for **4**: 30% H$_2$O$_2$, H$_2$O/THF (2 : 1), 0→20 °C, 24 h; iv. S, THF, 12 h, 20 °C.¶

The three-component reaction of $(HO)_2CHCOOH$ with P–H and N–H compounds with aldehydes or ketones, and restricted so far to formaldehyde in the case of P^{III}–H derivatives. Kabachnik–Fields reactions with α-keto carboxylic acids have, as far as we know, not yet been reported.[12] The presence of the COOH group implies acid catalysis, and thus particularly easy condensation, but also hydrolysis. If both reactions are fast, the nature of the product is controlled by the solubility, *i.e.* the least soluble zwitterionic compound precipitates and is isolated. The high sensitivity to hydrolysis (deuterolysis) follows from the exclusive detection of **3** by NMR measurements of freshly prepared solutions of **1** in D$_2$O (H$_2$O) and by formation of **4** in the oxidation of **1** with aqueous H$_2$O$_2$ (30%), while oxidation of **1·MeOH** with sulfur in THF under anhydrous conditions furnishes the thiophosphinoglycine **5**.†

Compounds **1–5** gave satisfactory microanalyses as well as conclusive ^{1}H, ^{13}C and ^{31}P NMR spectra in suitable solvents.† The X-ray crystal structure analysis of the monosolvate **1·MeOH**§ (Figs. 1 and 2) shows hydrogen bonds from the carboxylate group to the acidic protons of methanol and the NH$_2$$t$Bu group. The P–C bond lengths and C–P–C angles are in the usual ranges. The angles N–C(1)–C(2) and N–C(1)–P are close to the ideal tetrahedral angle while the angle C(2)–C(1)–P is slightly widened. The N–C(1) bond length is slightly shorter than N–C(3), and the C(1)–C(2) bond length slightly longer than the C–C bonds within the *tert*-butyl group.

The facile decarboxylation of **1** to Ph$_2$PCH$_2$NHtBu (**6**) (^{31}P NMR $\delta = -15.7$) in THF (relative ^{31}P signal intensity of **6**: 15, 40, 57% after 3 h, 1 day, 7 days) and particularly in CDCl$_3$ solution (70% after 1 h) even at room temperature is not reflected in the solid state structural data. Indeed, the thermal degradation of crystalline **1·MeOH** becomes substantial only above 95–100 °C,

† Electronic supplementary information (ESI) available: experimental details, ^{1}H, ^{13}C and ^{31}P NMR data for **1–5**, DTA/TG data for **1** and **5**, details of oligomerisation experiments and single crystal X-ray data. See http://www.rsc.org/suppdata/cc/b4/b412860e/

‡ This paper is dedicated to Prof. Dr. Dr.h.c. W. Keim on the occasion of his 70th birthday.

*heinicke@uni-greifswald.de

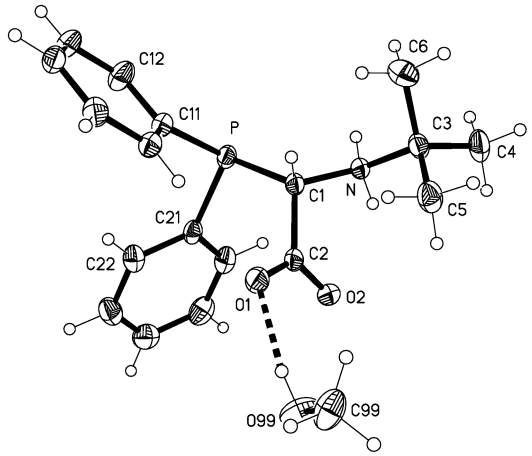


Fig. 1 Molecular structure of **1·MeOH** (ellipsoids with 50% probability) and the atom labelling scheme. Selected bond lengths (Å) and angles (°): P–C(11) 1.8299(11), P–C(21) 1.8306(12), P–C(1) 1.8927(11), N–C(1) 1.5021(13), N–C(3) 1.5281(13), C(1)–C(2) 1.5347(15); C(11)–P–C(21) 103.14(5), C(11)–P–C(1) 101.57(5), C(21)–P–C(1) 103.68(5); hydrogen bridging bond O(99)O(1) 2.725(2), H(99)O(1) 1.89, O(99)–H(99)O(1) 170.3.

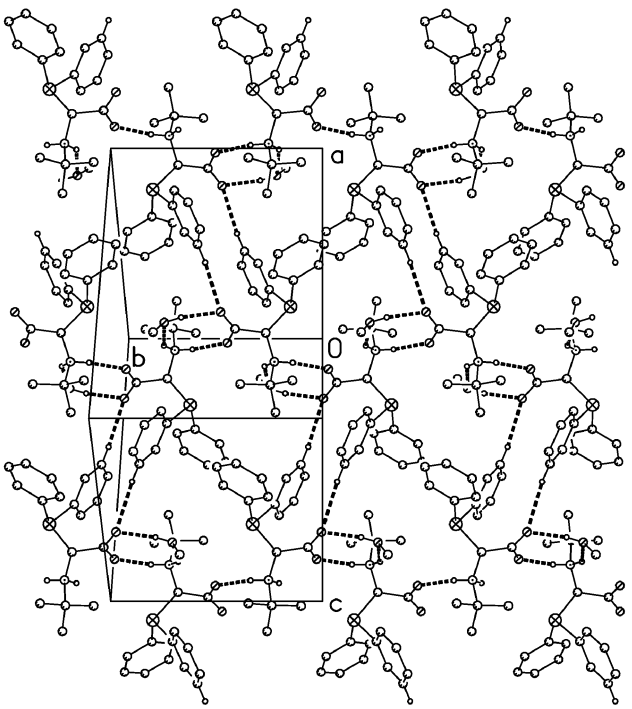
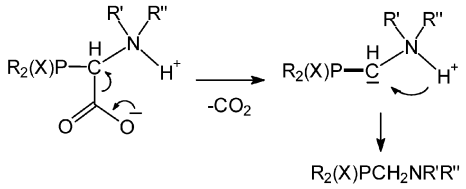


Fig. 2 A view of the unit cell and intermolecular association within **1·MeOH**.

particularly near the exothermic peak at 114 °C (DTA) and the melting point (123–125 °C (dec.)), and reaches a mass loss of 22%, corresponding to the formation of **6**, at 140 °C. The much easier decarboxylation in aprotic solvents may be favoured by a less stable solution structure lacking the hydrogen bonds to both oxygen atoms of the carboxylate group. This assumption is supported by mechanistic studies on the thermal decarboxylation of diphenylphosphinoacetic acid,[13] which starts by proton



Scheme 2 Proposed decomposition path for phosphinoglycines.

transfer from the COOH to the phosphino group in a five-membered transition state and involves an intermediate *P*-ylide. For the decarboxylation of **1** and **5** a similar process may be anticipated, but *via* an intermediate *N*-ylide, favoured by stabilisation of the α-carbanion intermediate by the phosphino group (Scheme 2).

Despite the low stability of **1** in solution, its use as a ligand in coordination chemistry and transition metal catalysis appears to be promising. Suspensions or solutions prepared from equimolar amounts of **1** and Ni(1,5-COD)$_2$ in toluene or THF catalyse the oligomerisation of ethylene, in non-optimised batch procedures at 100 °C with conversions of 88% (p_{start} 50 bar, TON 4530) and 85% (p_{start} 30 bar, TON 2230), respectively. The products are waxy polyethylenes (M_{NMR} 900 and 1230), mainly α-olefins (90 and 93%) with very low branching (Me/C=C 1.3 and 1.5). The similarity to the behaviour of Shell Higher Olefin Process-catalysts derived from diphenylphosphinoacetic acid[14] suggests formation of five-membered nickel P$^{\frown}$O-chelate complexes, and the activity at 100 °C gives evidence of higher thermal stability of these complexes than of dissolved **1** itself.

In conclusion, the facile synthesis of **1** shows a route to novel functionally substituted asymmetric α-amino acids that are suitable hybrid ligands for transition metal complexes and catalysts. Further studies are in progress.

Joachim Heinicke,*[a] Normen Peulecke[a] and Peter G. Jones[b]
[a]*Institut für Chemie und Biochemie, Ernst-Moritz-Arndt-Universität Greifswald, 17487, Greifswald, Germany.*
E-mail: heinicke@uni-greifswald.de; Fax: +49 3834 864319;
Tel: +49 3834 864318
[b]*Institut für Anorganische und Analytische Chemie der Technischen Universität Braunschweig, 38023, Braunschweig, Germany.*
E-mail: p.jones@tu-bs.de; Fax: +49 0531-391 5387;
Tel: +49 0531-391 5382

Notes and references

§ Crystal data for **1·MeOH** $C_{19}H_{26}NO_3P$ (347.38), monoclinic, space group $P2_1/n$, a = 12.6440(11), b = 9.7680(8), c = 15.2660(11) Å, β = 96.853(4)°, U = 1872.0(3) Å^3, Z = 4, specimen 0.40 × 0.15 × 0.15 mm^3, T = 133(2) K, Bruker SMART 1000 CCD diffractometer, λ(Mo Kα) 0.71073 Å, 25111 reflections collected to 2θ = 60°, independent reflections 5481 [R(int) = 0.0423], refinement (SHELXL-97) by full-matrix least-squares on F^2, data/restraints/parameters 5481/40/251, goodness-of-fit on F^2 = 1.030, final R indices [$I > 2\sigma(I)$] $R1$ = 0.0339, $wR2$ = 0.0888, R indices (all data) $R1$ = 0.0518, $wR2$ = 0.0948, largest diff. peak and hole 0.379 and −0.192 e Å^{-3}. The methanol molecule is disordered over two positions (only one shown in Fig. 1). Crystallographic data for **1·MeOH** have been deposited with the Cambridge Crystallographic Data Centre, CCDC 247779. See http://www.rsc.org/suppdata/cc/b4/b412860e/ for crystallographic data in .cif or other electronic format.

¶ Selected substances and $^{31}P\{^1H\}$ NMR data (121.5 MHz). For **1**: yield 3.25 g (92%), mp. 123–125 °C (dec.), δ(D_8-THF) 3.4. For **2**: yield 750 mg (48%), δ(D_2O) 33.2, 34.0 (diastereoisomers, *ca.* 2 : 1). For **3**: δ(D_2O) 6.7. For **4**: yield 350 mg (88%), mp. 177–179 °C, δ($CDCl_3$) 32.0. For **5**: yield 55 mg (62%), mp. 109–110 °C (dec.), δ($CDCl_3$) 51.5.

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