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The effect of N-substituent on the relative thermodynamic stability of unionized and zwitterionic forms of α-diphenylphosphino-α-amino acids

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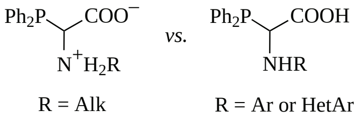
The relative thermodynamic stability of unionized and zwitterionic forms of α-phosphino-α-amino acids is governed by the substituent R at the nitrogen atom, namely, (het)aryl substituents favour the formation of the unionized form RHNCH(PPh$_2$)COOH, while in the case of alkyl analogues the zwitterions RH$_2$N$^+$CH(PPh$_2$)COO$^-$ predominate. The experimentally observed trends have been supported by quantum-chemical calculations. The synthesis and X-ray crystal structure analysis of a new unionized α-phosphino-α-amino acid [α-diphenylphosphino-*N*-(2-methoxycarbonyl-phenyl)glycine] are reported.



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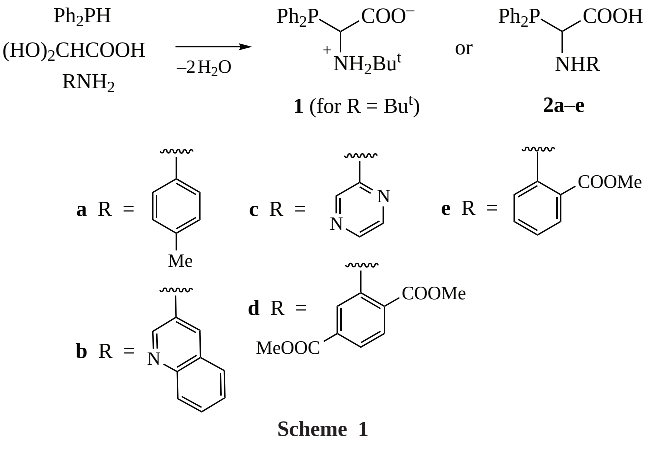
Many types of non-natural α-amino acids synthesized over the last decades[1] have found application in modern chemistry and materials science as synthetic building blocks, organocatalysts, ligands for transition metal catalysts for preparation of new drugs, fine chemicals, and new materials. In recent years, a growing trend has emerged to introduce the organophosphorus group into the side chain of α-amino acids. Such a synthetic modification of natural α-amino acids has a significant effect on their properties, *e.g.*, shifts of the isoelectric point by additional acidic, basic or simply polar groups[2] or, in the case of *P*,*N*-acetalic α-phosphino-α-amino acids,[3] decreased kinetic stability towards hydrolysis of reactive OH-compounds and lowered sensitivity to thermolytic cleavage of CO$_2$.[3] Natural and closely related α-amino acids are known to be crystallized mostly in zwitterionic form.[2] The thermodynamic stability of unionized and zwitterionic forms of N-substituted α-amino acids was explained by resonance structures.[4] In this communication, the effect of N-substituent on the relative thermodynamic stability of unionized and zwitterionic forms of α-phosphino-α-amino acids is reported and quantified by quantum-chemical calculations.

Organophosphorus derivatives of α-amino acids possess the PCCO-motif of the diphenylphosphinoacetic acid, which is known to form active nickel catalysts for the ethylene oligomerization.[5] They can be obtained by three-component one-pot reactions, which are usually carried out by adding solutions of the corresponding amine and secondary phosphine to a solution of glyoxylic acid hydrate in the same solvent (or by adding in the reversed order). This is the simplest and the most convenient way to obtain phosphorylated derivatives of α-amino acids (Scheme 1).[6] The first representative of this chemotype, α-diphenylphosphino-*N*-(*tert*-butyl)glycine **1**, was reported in 2005.[7] Later, the scope was expanded by various derivatives differing by the substituent at the nitrogen atom.[8–12] For solid-state molecular structures of known compounds (**1** and **2a–d**), see Online Supplementary Materials.

For some time, it was believed that α-phosphino-α-amino acids, similarly to α-amino acids, are ampholytes. Thorough studies performed for N-substituted α-diphenylphosphinoglycines have shown that the formation of the zwitterionic form RH$_2$N$^+$CH(PPh$_2$)COO$^-$ is observed only in the case of alkyl [R = Bu^t,[7] Bu^n,[8(*a*)] Pr^i (ref. 9)] or alkyl/aryl [R = Me(4-MeOC$_6$H$_4$)CH][9] substituents at the nitrogen atom.



Scheme 1

In contrast, derivatives with aryl (R = *p*-tolyl, **2a**)[8(*a*)] and (het)aryl (R = quinolin-3-yl, **2b**)[8(*b*)] substituents are crystallized in the unionized form RHNCH(PPh$_2$)COOH, that is not typical of α-amino acids. Recently, we reported on two α-diphenylphosphinoglycines with aromatic substituents [R = pyrazin-2-yl,[11] **2c** and R = 2,5-(MeO$_2$C)$_2$C$_6$H$_3$,[12] **2d**]. In both cases, a combination of experimental methods (NMR spectroscopy and X-ray diffraction analysis) detected the formation of the unionized form. Based on these data, one can suppose that all *N*-(het)aryl-substituted α-amino acids are not zwitterionic because of a too low basicity due to mesomeric interactions of the nitrogen lone pair with the (het)aryl π-electronic system.

In this work, to contribute an additional support to this hypothesis, the series of α-diphenylphosphinoglycines was extended by a new derivative **2e** (see Scheme 1). The structure of **2e** has been unambiguously proven by ^{1}H, ^{13}C and ^{31}P NMR spectroscopy[†] and X-ray diffraction analysis[‡] (Figure 1). These results confirm the above assumption of the formation of the unionized form when aromatic substituent is located at the nitrogen atom. Compound **2e** crystallizes in the triclinic space group $P\bar{1}$. Bond lengths are within the corresponding standard values. The only exception is the (H)C–N bond, whose length (1.431 Å) is shorter compared to its standard value (1.455 Å).

To get more insight into the influence of the aromatic substituent at the nitrogen atom and to figure out the factors favouring the formation of the unionized form, we performed a quantum-chemical analysis of molecular structures and the relative thermodynamic stability of various unionized conformers and the corresponding zwitterionic counterparts of **2a**–**e** (for results of quantum-chemical calculations and their detailed discussion, see Online Supplementary Materials). Our results fully support the assumption that the stabilization of the unionized form in the case of aromatic substituent is due to the presence of the (het)aryl π-electronic system capable of involving the nitrogen lone pair into the conjugation. The flatter the (H)C–NH–C$_{\text{Ar}}$ fragment (*i.e.*, the higher the p-character of the nitrogen lone pair) and the larger the π-electronic system of the substituent, the more efficient is the conjugation of the nitrogen lone pair with the (het)aryl π-electronic system and the more stable is the unionized form compared to the zwitterionic one. This trend is observed for all compounds within any series associated with a given conformation of the unionized form (see Online Supplementary Materials, Table S6). The same analysis was also performed for **1** for comparison. In the absence of conjugation, the unionized form is destabilized, and the zwitterionic form becomes more stable (Table S8). Note that more polar solvent increases the stability of the charge-separated (zwitterionic) state.

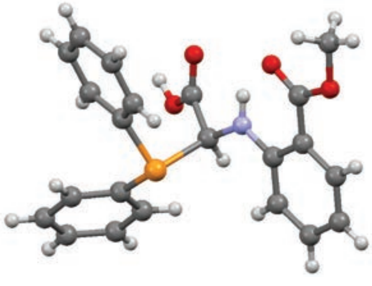


Figure 1 The solid-state molecular structure of α-diphenylphosphino-*N*-(2-methoxycarbonylphenyl)glycine **2e**.

To conclude, we have shown that the relative thermodynamic stability of possible forms of α-diphenylphosphino-α-amino acids is governed by the substituent at the nitrogen atom, where (het)aryl substituents favour the formation of the unionized form whereas alkyl substituents stabilize the zwitterionic one. The experimentally observed results have been supported by quantum-chemical calculations.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2020.07.038.

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[†] For synthesis details and NMR data for **2e**, see Online Supplementary Materials.

[‡] *Crystal data for* **2e**. C$_{22}$H$_{20}$NO$_4$P (*M* = 393.36), triclinic, space group $P\bar{1}$ at 294 K: a = 8.2651(7), b = 9.7114(8) and c = 13.1428(9) Å, α = 75.352(3), β = 88.534(3) and γ = 68.600(3)°, V = 947.66(13) Å^3, Z = 2, d_{calc} = 1.378 g cm^{-3}, μ(Mo-Kα) = 0.174 mm^{-1}, F(000) = 412. Total of 12747 reflections were collected (4126 independent reflections with $\theta < 27°$, R_{int} = 0.065) and used in the refinement, which converged to wR_2 = 0.1357, GOOF = 0.83 for all independent reflections [R_1 = 0.0390 was calculated for 3359 reflections with $I \geqslant 2\sigma(I)$].

The X-ray diffraction analysis was carried out at room temperature on a Bruker Kappa Apex II CCD automatic diffractometer using graphite monochromated Mo-Kα (0.71073 Å) radiation and ω-scan rotation. Data collection: images were indexed, integrated, and scaled using the APEX2[13] data reduction package and corrected for absorption using SADABS.[14] The structure was solved by the direct methods and refined using SHELX.[15] Non-hydrogen atoms were refined anisotropically. The hydrogen atoms of the OH and NH groups were revealed by means of the difference electron density maps and refined in the isotropic approximation. Other hydrogen atoms were calculated at idealized positions and refined as riding atoms. All calculations were performed using WinGX.[16] Intermolecular interactions were analyzed using the PLATON program.[17] All the figures were produced by the MERCURY program.[18]

CCDC 1996686 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.

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