Revisitation of the PCl_5-Chlorination Reaction of α-Amino Acids: Spectroscopic and DFT Insights, and Synthesis of the *L*-Proline-Derived 2,5-Diketopiperazine

Marco Bortoluzzi,[a] Fabio Marchetti,*,[b] Maria Grazia Murrali,[b] Guido Pampaloni [b]

[a] Dipartimento di Scienze Molecolari e Nanosistemi, University of Venezia Ca' Foscari, Dorsoduro 2137, I-30123 Venezia.

[b] Dipartimento di Chimica e Chimica Industriale, University of Pisa, Via Risorgimento 35, I-56126 Pisa.

* E-mail: fabmar@dcci.unipi.it. Tel: +39 050 2219 245. Webpage: http://www.dcci.unipi.it/~fabmar/

Abstract

The traditional chlorination reaction of α-aminoacids with PCl_5 was elucidated by means of spectroscopic and DFT studies. Thus $[\overline{NH_2(CH_2)_3}CHC(O)Cl]Cl$, **1**, and $[RCH(NH_3)C(O)Cl][Cl]$ (R = H, **3**; R = CH_3, **4**; R = CH_2Ph, **5**; R = CH_2CHMe_2, **6**) were obtained in high yields from equimolar amounts of PCl_5 and *L*-proline, glycine, *L*-alanine, *L*-phenylalanine and *L*-leucine, respectively. Compounds **3-6** resulted to be stable at room temperature under nitrogen atmosphere, whereas **1** rapidly degraded under the same conditions, both in the solid state and in solution. The 1:2 molar reaction of PCl_5 with *L*-proline selectively afforded the salt $[\overline{NH_2(CH_2)_3}CHC(O)Cl][PCl_6]$, **2**, showing better inertness than the homologous **1**. The slow degradation reaction of **2** may represent a strategy for the clean synthesis of the *L*-proline-derived 2,5-diketopiperazine, which was recovered in *ca.* 60% yield from a dichloromethane solution stirred at room temperature for several days and purged with nitrogen gas in order to remove the released HCl. Compounds **1-6** were characterized by elemental analysis and IR spectroscopy, and by NMR spectroscopy in the cases of soluble **1** and **2**. Furthermore, the structures of **1-6** were computationally optimized by means of DFT functionals. According to the spectroscopic and DFT outcomes, **1-6** exist in solution as tight ion pairs featured by NH---Cl cation-anion interactions, leading to possible HCl formation and consequent condensation reactions. The less stability observed for **1-2** respect to **3-6** should be associated with the relatively high ΔG value of the condensation step.

Keywords: Phosphorus pentachloride; α-Amino acids; 2,5-Diketopiperazine; Chlorination Reaction; α-Ammonium-Acylchloride

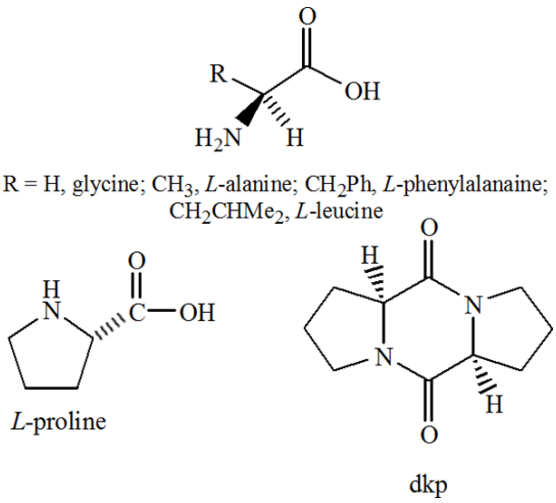
Introduction

The activation of the carboxylic acid function by a chlorinating agent may be a crucial, preliminary step for the subsequent functionalization of α-amino acids.[1] The resulting acylchloride species are reactive intermediates which are frequently used for *in situ* derivatization, however their solid state isolation has been accomplished by using PCl_5 as typical Cl transfer agent (*Fischer procedure*).[1a,2] The resulting products have been generally described as "hydrochloride salts", notwithstanding the characterization has relied on limited analytical data [1a,2] and spectroscopic information are still missing in the literature. In addition, some ambiguity exists about the stoichiometry to be employed in the reaction α-amino acid/PCl_5, especially for what regards *L*-proline: for instance, Morán and co-workers used approximate 1:1 molar ratio in chloroform,[1a] instead Liwschitz *et al.* used a two-fold excess of PCl_5 in acetyl chloride.[2b] The derivative obtained from PCl_5/*L*-proline, independently on the preparation method, was described as a particularly unstable compound, for which storage at temperatures below −10 °C was recommended.[1a]

In the framework of our research on the reactivity of high-valent metal chlorides,[3] we came interested in the interaction of PCl_5 with naturally occurring α-amino acids. Here we revisit such piece of chemistry, showing the first IR and NMR characterization of the products obtained by 1:1 and 1:2 combination of *L*-proline with PCl_5, respectively, and thus giving insight into their identity. The study has been extended to glycine, *L*-alanine, *L*-phenylalanine and *L*-leucine (Scheme 1), whose acylchloride derivatives are non soluble compounds which have been characterized by elemental analysis and IR spectroscopy. DFT calculations have been carried out in order to optimize the structures of the products and to understand their different stabilities at room temperature.

Furthermore, we show a new, simple route to obtain the *L*-proline derived 2,5-diketopiperazine (dkp, Scheme 1). Indeed dkp belongs to the extensive family of homologous compounds, that possess valuable

biologic properties [4] and are considered as promising scaffolds for drug discovery.[5] Although the 2,5-diketopiperazine skeleton is easily available in nature, being found either alone or embedded in more complex architectures,[5a] there is currently high interest in developing new synthetic strategies to access 2,5-diketopiperazines.[5a,6]



Scheme 1. Amino acids and the cyclic dipeptide of *L*-proline (dkp).

Results and discussion

The 1:1 and 1:2 molar reactions of *L*-proline with PCl_5 were conducted under nitrogen atmosphere in CH_2Cl_2 at 0 °C, and afforded colourless solutions in *ca.* 1 hour. Thus air sensitive, colourless solids were isolated upon removal of the volatile materials. The solids were maintained at low temperature (0-5 °C) and quickly analyzed by IR spectroscopy. The IR spectra showed a strong absorption due to the carbonyl moiety, occurring at slightly higher wavenumber in **1** respect to **2** (**1**: 1790 cm^{-1}; **2**: 1778 cm^{-1}). This absorption decreased in intensity with time, on keeping the samples at room temperature under nitrogen; it completely disappeared after 1 hour in the case of **1**, and after 24 hours in the case of **2**.

The different inertness exhibited by **1** and **2**, respectively, reflects the different nature of the anion in the two salts. This observation is clearly supported by the outcomes of the elemental analyses (C, H, N, Cl;

see Experimental) and NMR experiments. Indeed we reproduced the 1:1 and 1:2 molar reactions of *L*-proline with PCl_5 in CD_2Cl_2. The resulting solutions were analyzed by NMR (^1H, ^{13}C, ^{31}P) spectroscopy. Phosphorous oxychloride, $POCl_3$, (^{31}P NMR resonance at 4.6 ppm [7] in CD_2Cl_2) was the only phosphorous-species resulting from the 1:1 reaction (Eqn. 1): in agreement with elemental analysis, this fact indicates that Cl^- acts as counterion in **1**, presumably due to the estimated low $Cl–POCl_3$ bond energy.[8] Otherwise, both $POCl_3$ and $[PCl_6]^-$ (resonance at –295 ppm,[9] detected at 198 K) were clearly identified in the 1:2 reaction mixture (Eqn. 1). In the spectrum recorded at room temperature, the resonance of $[PCl_6]^-$ appeared as a broad one centred at –190 ppm; this fact suggests that, in solution, the anion is probably involved in $Cl_5PCl\cdots H–N$ interaction with the ammonium group belonging to the cation (*vide infra*).

L-proline + $nPCl_5 \rightarrow$ $[\overline{NH_2(CH_2)_3CHC(O)Cl}][X] + POCl_3$ (1)

n = 1 X = Cl, **1**

n = 2 X = PCl_6, **2**

The ^1H and ^{13}C NMR spectra of the reaction mixtures evidenced the clean formation of the pyrrolidinium-2-carbonylchloride cation (Eqn. 1). The chemical shift values related to **1** are very close to the corresponding ones found for **2**. The only exception is given by the nitrogen-bound protons (**1**: δ = 10.45, 9.42 ppm; **2**: δ = 9.85, 8.73 ppm); since the nitrogen formally hosts the positive charge of the cation, this NMR feature is in accord with the different nature of the anion in the two salts (*i.e.*, Cl^- in **1** and $[PCl_6]^-$ in **2**). The ^{13}C resonances related to the CH_2 moieties resemble those exhibited by *L*-proline in D_2O,[10] while the resonances due to the carbonyl (**1**: 171.8 ppm; **2**: 172.4 ppm; *L*-proline: 175.8 ppm) and CH groups (**1**: 67.6 ppm; **2**: 67.8 ppm; *L*-proline: 62.4 ppm) undergo significant shift with respect to *L*-proline, as consequence of the chlorination.

In order to shed light into the structural aspects, the structures of **1** and **2** were optimized by DFT calculations in the presence of an implicit salvation model. The graphical representations are given in Figure 1, while the main bond lengths are compared in Table 1.

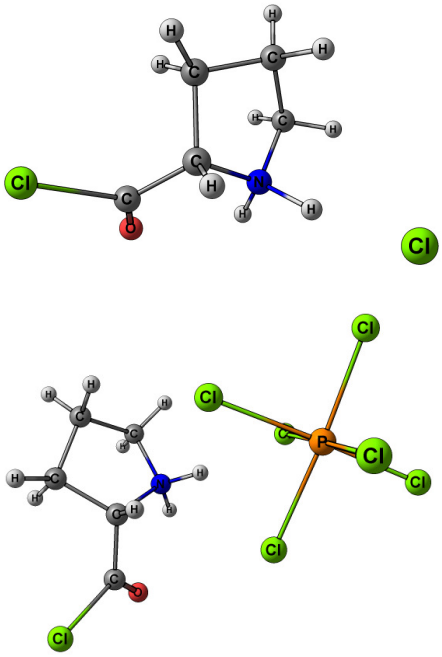


Figure 1. DFT M06/C-PCM calculated structures of $[NH_2(CH_2)_3CHC(O)Cl]Cl$, **1**, and $[NH_2(CH_2)_3CHC(O)Cl][PCl_6]$, **2**, with implicit solvation.

Table 1. Selected computed bond distances (Å) for **1** and **2** (M06/C-PCM calculations).

	1	**2**
C=O	1.177	1.191
C–Cl	1.789	1.176
ClC–C	1.503	1.503
N–CH_2	1.497	1.518
N–CH	1.497	1.509
CH–CH_2	1.550	1.531
$CHCH_2$–CH_2	1.527	1.524
NCH_2–CH_2	1.511	1.517
P–Cl		2.148
		2.149
		2.152
		2.204
		2.206
		2.218
CO···N	2.771	2.225
Cl^-···N	3.001	
PCl···N (*shortest*)		3.313

According to Table 1, negligible differences are observable with reference to the geometric parameters of the pyrrolidinium-2-carbonylchloride skeleton. In **1** and **2**, respectively, the $Cl^{-}\cdots N$ (3.001 Å) and the shortest $PCl\cdots N$ (3.313 Å) distances are shorter than the sum of the van der Waals radii of Cl and N,[11] thus suggesting that **1** and **2** exist in solution as tight ion pairs. This outcome is coherent with the experimental NMR features (see above). In particular, the electron density surface predicted for **2** (Figure 2) may provide an explanation for the broad, downfield shifted ^{31}P NMR resonance of $[PCl_6]^{-}$ observed at room temperature (see above).[9]

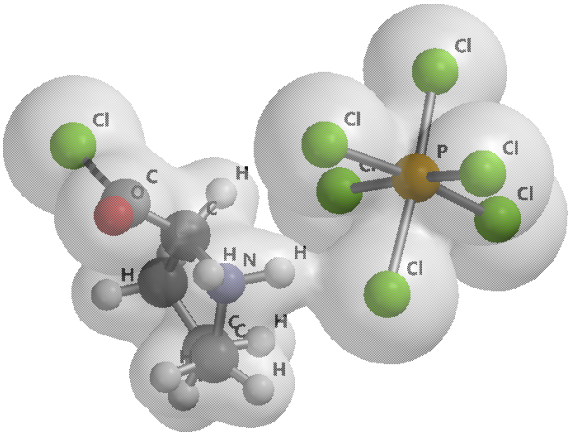


Figure 2. DFT-calculated electron density of $[\overline{NH_2(CH_2)_3CHC(O)Cl}][PCl_6]$, **2**, (surface isovalue = 0.02 a.u.).

In accordance with the literature reports, **1** and **2** underwent degradation at 20 °C with evolution of HCl when stored under inert atmosphere, both in the solid state and in CD_2Cl_2 solution (see Experimental for details). Notwithstanding, the degradation process is significantly faster for **1** respect to **2**, thus indicating some stabilizing effect of the $[PCl_6]^{-}$ anion when compared to Cl^{-}. This is reasonable since the formation of HCl from **2** requires the breaking of a P–Cl bond. NMR experiments carried out on solutions contained in sealed tubes revealed the formation of several decomposition products whose identity could not be ascertained (see Experimental). On the other hand, a different outcome was achieved when CH_2Cl_2 solutions of **1** or **2** were allowed to stir at room temperature for several days with

periodic flow of nitrogen gas, in order to remove hydrogen chloride from the reaction system. The treatment of the final mixtures with an aqueous solution of $KHCO_3$, followed by chromatography on silica, led to the isolation of dkp (see Scheme 1). The process appeared much more efficient by using **2** as starting material: in these conditions, dkp was finally recovered in *ca.* 60% yield (Scheme 1). To the best of our knowledge, this simple procedure has never been described in the literature so far. Dkp was identified by IR [12] and NMR [6b,13] spectroscopy and GC-MS analysis, moreover optical rotation measurement indicated the retention of configuration respect to the precursor *L*-proline.

The present investigation was extended to a selection of zwitterionic α-aminoacids bearing a primary ammonium group (Scheme 1). Thus we carried out the reactions of glycine, *L*-alanine, *L*-phenylalanine and *L*-leucine with PCl_5 by using strictly 1:1 molar ratio. The products precipitated from the respective reaction mixtures (in CCl_4 or CH_2Cl_2) and, once isolated, resulted almost insoluble in inert solvents. Their characterization relied on elemental analysis and IR spectroscopy, which suggested the clean formation of $[RCH(NH_3)C(O)Cl][Cl]$ (R = H, **3**; R = CH_3, **4**; R = CH_2Ph, **5**; R = CH_2CHMe_2, **6**) in very good yields (Eqn. 2).

$$[RCH(NH_3)COO] + PCl_5 \rightarrow [RCH(NH_3)C(O)Cl][Cl] + POCl_3 \quad (2)$$

R =		
	H	**3**
	CH_3	**4**
	CH_2Ph	**5**
	CH_2CHMe_2	**6**

The IR spectra of **3-6** display an intense, diagnostic absorption at *ca.* 1790 cm^{-1}, closely to what detected for **1**. The IR spectra of **3-6** did not change after storing the compounds at room temperature for 24-48 h, in the solid state under nitrogen atmosphere. This points suggests that, for the α-amino acids reported in Eqn. 2, the employment of one equivalent of PCl_5 is sufficient to yield a handleable chlorinated product. We optimized also the structures of **3-6** by DFT calculations. Views of the structures are provided as

Supporting Information (Figures S1-S4), together with the relevant calculated bonding parameters (Tables S1-S4). The structures of **3-6** resemble that of the homologous salt **1**, in that tight $Cl^{-}\cdots N$ interactions occur between each cation and the chloride anion in the respective cases. Indeed the Cl–N distances are all comparable, falling in the range 2.976 to 3.019 Å; likewise the thermodynamics for HCl elimination in dichloromethane do not significantly vary along the series including **1** and **3-6** (ΔG = *ca.* 0 kcal mol^{-1}).

Therefore, in order to give an explanation for the higher stability exhibited by **3-6** in comparison with **1**, we computed the model reactions of the α-amino-acylchloride compounds, derived from **1,3-6** by HCl release, with acetylchloride [$CH_3C(O)Cl$]. The calculated ΔG values are quite similar, except for the *L*-proline-derived compound showing a more favourable process by about 6 kcal mol^{-1}. According to these outcomes, it may be outlined that **1** possesses higher tendency to give self-condensation products with respect to **3-6**; this is presumably a consequence of the higher degree of substitution at the *N*-center, conferring better nucleophilicity in the condensation step.

Conclusions

Acylchloride derivatives of α-aminoacids have been known as reactive species in synthetic chemistry, and they have been generally claimed to be prepared as *hydrochloride salts* by treatment of the precursors with variable, relative amounts of PCl_5. No spectroscopic characterization was reported in the literature. In this paper, we have demonstrated that different anion-based salts may be selectively obtained, by modulating the ratio between the reactants. In the case of *L*-proline, the use of a two-fold excess of PCl_5 allows the isolation of the relatively inert $[PCl_6]^{-}$ salt and is strongly preferable in this respect to the 1:1 molar reaction. On the other hand, the 1:1 molar reactions of PCl_5 with glycine, *L*-alanine, *L*-phenylalanine and *L*-leucine lead to $[Cl]^{-}$ salts showing satisfying stability at room

temperature. In agreement with NMR evidences and DFT calculations, the main degradation pathway of the acylchloride products is strictly associated with the occurrence of N–H···Cl cation-anion interactions. However, the self-condensation reaction appears significantly more favoured in the case of the *L*-proline-derived species respect to the other cases, presumably due to the higher nucleophilicity of the amino function. The slow degradation reaction of the pyrrolidinium-2-carbonylchloride $[PCl_6]^-$ salt may represent a new, simple and gentle procedure to obtain the *L*-proline-derived 2,5-dieketopiperazine.

Experimental.

1) General. The reaction vessels were oven dried at 140°C prior to use, evacuated (10^{-2} mmHg) and then filled with nitrogen. PCl_5 (98+%), *L*-proline (>99%), glycine (ultrapure), *L*-alanine, *L*-phenylalanine (>99.5%) and *L*-leucine (>99.0%) were purchased from Apollo Sci. and stored under nitrogen atmosphere as received. Once isolated, the reaction products were conserved in sealed glass tubes under nitrogen. Solvents (Sigma Aldrich) were distilled from CaH_2 under argon atmosphere before use. Infrared spectra were recorded at 298 K on a FT IR-Perkin Elmer Spectrometer, equipped with UATR sampling accessory and working in the 650-4000 cm^{-1} range. NMR spectra were recorded on a Bruker Avance DRX400 instrument equipped with BBFO broadband probe. The chemical shifts for ^{1}H and ^{13}C were referenced to the non-deuterated aliquot of the solvent. The chemical shifts for ^{31}P were referenced to external H_3PO_4. The ^{1}H and ^{13}C NMR spectra were fully assigned *via* ^{1}H,^{13}C correlation measured through *gs*-HSQC and *gs*-HMBC experiments.[14] Optical rotation measurement was performed with a Perkin–Elmer 141 polarimeter (Na lamp, 589 nm). Carbon, hydrogen and nitrogen analyses were performed on Carlo Erba mod. 1106 instrument. The chloride content was determined by the Mohr method [15] on solutions prepared by dissolution of the solid in aqueous KOH at boiling temperature, followed by cooling to room temperature and addition of HNO_3 up to neutralization.

2) Synthesis, isolation and solid state characterization of $[\overline{NH_2(CH_2)_3CHC(O)Cl}][X]$ (X = Cl, 1; X = PCl_6, 2). *General procedure*: A suspension of PCl_5 in CH_2Cl_2 (15 mL) in a Schlenk tube was cooled with an ice bath, then *L*-proline was added. The cooled mixture was stirred over 1 hour thus obtaining a colourless solution. Then the volatiles were removed *in vacuo* affording a colourless residue, which was washed with hexane (2 x 20 mL) and dried *in vacuo*.

2A) $[\overline{NH_2(CH_2)_3CHC(O)Cl}][Cl]$, 1. From PCl_5 (0.250 g, 1.20 mmol) and *L*-proline (0.137 g, 1.19 mmol). Yield 0.162 g, 80%. The solid product was maintained at 0-5 °C before the analyses; it almost completely decomposed after being stored at room temperature under inert atmosphere for one hour. Anal. Calcd. for $C_5H_9Cl_2NO$: C, 35.32; H, 5.34; N, 8.24; Cl, 41.70. Found: C, 35.22; H, 5.20; N, 8.37; Cl, 41.45. IR (solid state): $\tilde{\upsilon}$ = 3093w-sh, 2975w, 2880w, 2666w, 1790vs (C=O), 1540m, 1447w-m, 1405m, 1358w, 1332m, 1302m, 1247w, 1167w, 1084m, 993vs, 952vs, 907m, 872vs, 818w, 779w, 739w cm^{-1}.

2B) $[\overline{NH_2(CH_2)_3CHC(O)Cl}][PCl_6]$, 2. From PCl_5 (0.320 g, 1.54 mmol) and *L*-proline (0.088 g, 0.764 mmol). Yield 0.246 g, 85%. The solid product resulted unchanged after 1 h room temperature under inert atmosphere, but it underwent prevalent decomposition after 24 hours. Anal. Calcd. for $C_5H_9Cl_7NOP$: C, 15.88; H, 2.40; N, 3.70; Cl, 65.61. Found: C, 15.59; H, 2.37; N, 3.65; Cl, 65.34. IR (solid state): $\tilde{\upsilon}$ = 3184w (N–H), 2963w, 2879w, 2689w, 1778vs (C=O), 1584w, 1566w-m, 1449w, 1396w-m, 1369w-m, 1291m, 1274m-sh, 1206w, 1070m, 1048w, 1002s, 950m, 903w, 868s, 849m, 801w, 760w cm^{-1}.

3) Synthesis, isolation and solid state characterization of $[RCH(NH_3)C(O)Cl][Cl]$ (R = H, 3; R = CH_3, 4; R = CH_2Ph, 5; R = CH_2CHMe_2, 6). *General procedure*: A Schlenk tube, containing a

suspension of PCl_5 in CH_2Cl_2 or CCl_4, was cooled with an ice bath, then the appropriate α-aminoacid was added. The resulting mixture was stirred for 15 minutes, then the ice bath was removed and the stirring was prolonged for further 4 h. The colourless precipitates were isolated, washed with hexane (2 x 20 mL) and dried *in vacuo*.

3A) [$CH_2(NH_3)C(O)Cl$][Cl], 3. From PCl_5 (0.250 g, 1.20 mmol) and glycine (0.089 g, 1.19 mmol) in CCl_4 (20 mL). Yield 0.126 g, 82%. Anal. Calcd. for $C_2H_5Cl_2NO$: C, 18.48; H, 3.88; N, 10.77; Cl, 54.55. Found: C, 18.36; H, 3.95; N, 10.64; Cl, 54.33. IR (solid state): $\tilde{\upsilon}$ = 2987m, 2941m, 2856m, 2595w-m, 1784vs (C=O), 1568m, 1494m-s, 1435w, 1418w, 1367m, 1296w, 1225m, 1113m, 1057s, 963vs, 892s, 860w, 745vs cm^{-1}.

3B) [$CH(CH_3)(NH_3)C(O)Cl$][Cl], 4. From PCl_5 (0.220 g, 1.06 mmol) and *L*-alanine (0.094 g, 1.06 mmol) in CCl_4 (20 mL). Yield 0.131 g, 86%. Anal. Calcd. for $C_3H_7Cl_2NO$: C, 25.02; H, 4.90; N, 9.73; Cl, 49.24. Found: C, 24.79; H, 4.81; N, 9.82; Cl, 49.03. IR (solid state): $\tilde{\upsilon}$ = 2993w-m, 2940m, 2845m, 2527w, 1780vs (C=O), 1573w-m, 1526m, 1497m, 1455w, 1386w, 1348w, 1234w, 1200w-m, 1131w, 1113m, 1014w, 1005w, 962s, 882m, 868m, 798w, 720s cm^{-1}.

3C) [$CH(CH_2Ph)(NH_3)C(O)Cl$][Cl], 5. From PCl_5 (0.280 g, 1.34 mmol) and *L*-phenylalanine (0.220 g, 1.33 mmol) in CH_2Cl_2 (20 mL). Yield 0.234 g, 79%. Anal. Calcd. for $C_9H_{11}Cl_2NO$: C, 49.11; H, 5.04; N, 6.36; Cl, 32.22. Found: C, 49.02; H, 4.90; N, 6.47; Cl, 31.96. IR (solid state): $\tilde{\upsilon}$ = 2983w, 2895w-m, 2817m, 2699w, 2626w-m, 1785s (C=O), 1600w-m, 1495vs, 1454w-m, 1439w-m, 1347w, 1260w, 1225w, 1210w, 1148m, 1109m, 1084w, 1052w, 991vs, 889m-s, 880m, 824m, 758s, 734s, 700vs, 664m cm^{-1}.

3D) [$CH(CH_2CHMe_2)(NH_3)C(O)Cl$][Cl], 6. From PCl_5 (0.250 g, 1.20 mmol) and *L*-leucine (0.155 g, 1.18 mmol) in CCl_4 (20 mL). Yield 0.182 g, 83%. Anal. Calcd. for $C_6H_{13}Cl_2NO$: C, 38.73; H, 7.04; N, 7.53; Cl, 38.11. Found: C, 38.44; H, 7.16; N, 7.44; Cl, 38.02. IR (solid state): $\tilde{\upsilon}$ = 3130w-br, 3080w,

959m, 2870m-s, 2845m-s, 2613w, 1792vs (C=O), 1586m, 1513vs, 1469w, 1436w, 1390w, 1369w, 1341w, 1247w, 1173w, 1106w, 1052w, 975vs, 945vs, 831w-m, 752vs, 668w cm^{-1}.

4) NMR studies.

General procedure: PCl_5, CD_2Cl_2 (0.65 mL) and *L*-proline were introduced into a NMR tube in the order given. The tube was sealed, briefly shaken in order to homogenize the mixture and maintained at *ca.* 5 °C. After 30 minutes, the content of the tube appeared as a colourless solution, which was promptly analyzed. The solution turned red after 24 hours at room temperature; subsequent NMR spectra showed the presence of a complicated mixture of products.

4A) From PCl_5 (0.200 g, 0.960 mmol) and *L*-proline (0.111 g, 0.964 mmol). ^1H NMR (CD_2Cl_2, 278 K): δ = 10.45, 9.42 (br, 2 H, NH_2); 4.99 (br, 1 H, CH); 3.58 (br, 2 H, NCH_2); 2.61, 2.39 (m, 2 H, CH_2); 2.17, 2.11 ppm (m, 2 H, CH_2). $^{13}C\{^1H\}$ NMR (CD_2Cl_2, 278 K): δ = 171.8 (C=O); 67.6 (CH); 46.5 (NCH_2); 29.1, 23.1 ppm (CH_2). ^{31}P NMR (CD_2Cl_2, 278 K): δ = 4.6 ppm (s, $POCl_3$).

4B) From PCl_5 (0.250 g, 1.20 mmol) and *L*-proline (0.069 g, 0.600 mmol). ^1H NMR (CD_2Cl_2, 298 K): δ = 9.85, 8.73 (br, 2 H, NH_2); 4.95 (br, 1 H, CH); 3.58 (br, 2 H, NCH_2); 2.64, 2.37 (m, 2 H, CH_2); 2.12 ppm (br, 2 H, CH_2). $^{13}C\{^1H\}$ NMR (CD_2Cl_2, 298 K): δ = 172.4 (C=O); 67.8 (CH); 47.4 (NCH_2); 29.3, 23.4 ppm (CH_2). ^{31}P NMR (CD_2Cl_2, 298 K): δ = 4.7 (s, $POCl_3$); −190 ppm (br, $\Delta\nu_{1/2} = 1.4 \cdot 10^3$ Hz). ^{31}P NMR (CD_2Cl_2, 198 K): δ = 8.7 (s, $POCl_3$); −294.6 ppm (br, $\Delta\nu_{1/2}$ = 15 Hz, PCl_6^-).

5) Synthesis and isolation of (*S*,*S*)-octahydrodipyrrolo[1,2-*a*:1',2'-*d*]pyrazine-5,10-dione (dkp). A suspension of PCl_5 (1.10 g, 5.28 mmol) in CH_2Cl_2 (20 mL) was treated with *L*-proline (0.300 g, 2.61 mmol). The mixture was stirred at room temperature for 11 days. During this period of time, the system was purged with nitrogen in order to remove the released gas (HCl). Bubbling the latter into an aqueous

solution of $AgNO_3$ determined the precipitation of a white solid (AgCl). Then a 0.2 M aqueous solution of $KHCO_3$ (25 mL) was added. The organic phase was separated and charged on a silica pad. The use of a mixture (1:1 *v*/*v*) of diethyl ether and acetone as eluent allowed to isolate a fraction corresponding to dkp. The product was afforded as a light-yellow solid upon removal of the volatile materials *in vacuo*. Yield 0.154 g, 61%. Anal. Calcd. for $C_{10}H_{14}N_2O_2$: C, 61.84; H, 7.27; N, 14.42. Found: C, 61.67; H, 7.25; N, 14.21. IR (solid state): $\tilde{\upsilon}$ = 2973w, 2956w, 2883w, 1654vs (C=O),[12] 1512w, 1428s, 1336m, 1292w-m, 1279m, 1259m, 1235w-m, 1202w, 1160m, 1069w, 1020w, 1001w, 920w-m, 802m, 749s, 664m cm^{-1}. ^1H NMR ($CDCl_3$): δ = 4.18 (m, 1 H, CH); 3.52 (m, 2 H, NCH_2); 2.29, 2.17 (m, 2 H, CH_2); 2.01, 1.91 ppm (m, 2 H, CH_2). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ = 166.4 (C=O); 60.4 (CH); 45.2 (NCH_2); 27.7, 23.3 ppm (CH_2). GC-MS: 195 ($[M+1]^+$). $[\alpha]_D^{25}$ = –67 (*c* 1, CH_3OH).[12]

6) Computational studies. The computational geometry optimization of the complexes was carried out without symmetry constrains, using the hybrid DFT EDF2 functional [16] in combination with the 6-31G(d,p) basis set.[17] Further geometry optimization was performed using the hyper-GGA functional M06 [18] in combination with the C-PCM implicit solvation model (ε = 9.08) [19] and the 6-311G(d,p) basis set.[20] In all of the cases the stationary points were characterized by IR simulations.[21] DFT-simulated IR data, obtained with harmonic approximation, assisted the interpretation of experimental IR spectra.

Supporting information. The structures of **3-6** are provided as Supporting Information (Figures S1-S4), together with relevant calculated bonding parameters (Tables S1-S4). The Cartesian coordinates of all the optimized structures are collected in a separated .xyz file.

References and Notes

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