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Structure of *N*,*N*′-Bis(amino acids) in the Solid State and in Solution. A ^{13}C and ^{15}N CPMAS NMR Study

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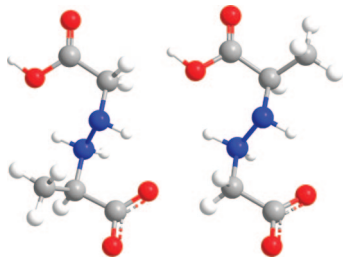
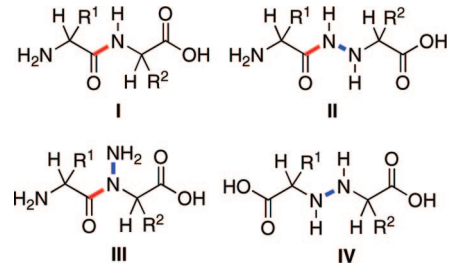


Three bis(amino acids) linked by the amino groups have been prepared and structurally characterized. We have named them Gly-Gly, Ala-Ala and Gly-Ala (or Ala-Gly). These compounds have been characterized by NMR both in solution and in the solid state. They exist as zwitterions with the ammonium group proximal to the carboxylate anion. In the case of Gly-Ala, a dynamic situation is observed by CPMAS NMR (^{13}C and ^{15}N) corresponding to a double proton migration between two proximal tautomers.

α-Amino acids and their corresponding peptides have been modified in any imaginable way: conformationally restricted, pseudo, non-natural, C,C′-linked, etc.[1] The peptide bond in **I** has been modified to yield two well-known derivatives having a N−N bond: the hydrazinopeptides **II**[2] and the *N*-amino peptides **III**.[3]



Surprisingly, a third possibility (**IV**) has almost never been explored (no compound with the connectivity present in **IV** is reported in the CSD).[4] We describe here the synthesis of the three simplest *N*,*N*′-bis(amino acids) and their structural study by NMR supported by theoretical calculations. Scheme 1 presents the compounds **1**−**5** studied in this work, including the three *N*,*N*′-bis(amino acids) Gly-Gly, Ala-Ala, and Gly-Ala (or Ala-Gly). It should be noted that in the bis(amino acids), Ala stands for racemic alanine. In the case of the Ala-Ala derivative, only the *meso* compound was synthesized and studied. Besides the structures of Scheme 1, we have calculated the neutral forms [H_2N-CH(R)-CO_2H, HO_2C-CH(R)-NH-NH-CH(R)-CO_2H] as well as the double zwitterions [^-O_2C-CH(R)-NH_2^+-NH_2^+-CH(R)-CO_2^-] of Gly-Gly, Ala-Ala and Ala-Gly, but since they are not observed, we report the results in Supporting Information.

More than 100 years ago, Thiele and Bailey[5] prepared Ala-Ala as a mixture of diastereoisomers through an intermediate hydrazinopropionic acid derivative. The unsubstituted counterpart Gly-Gly was synthesized by Gisin and Brenner[6] starting from glyoxylic acid and later by Arakawa et al.[7] through a hetero Diels−Alder reaction. Gly-Gly has important applications in photography and ∼50 of Fuji's patents deal with this compound.[8,9] To our knowledge, the preparation of Ala-Gly has not been reported before. In the present work, the synthesis of the bis(amino acids) Gly-Gly (**3**), Ala-Ala (**4**), and Ala-Gly (**5**) was carried out following a common route resulting from modification of the procedure described by Arakawa et al.[7] for **3**. After condensation of di-*tert*-butyl azodicarboxylate with the corre-

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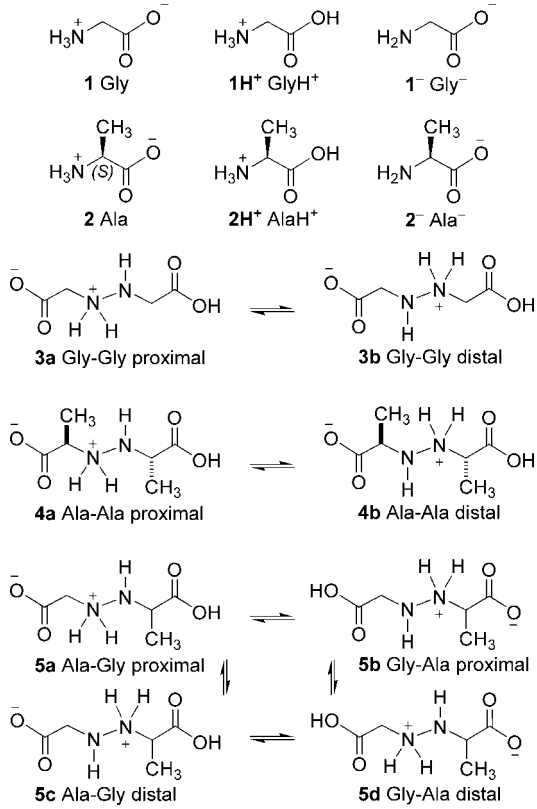
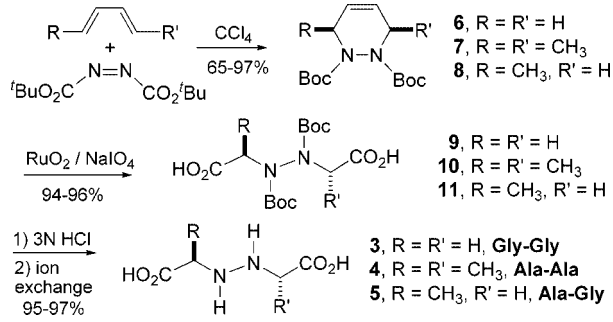
SCHEME 1. Molecules under Study



SCHEME 2. Synthetic Procedure



sponding diene (Scheme 2), the C=C double bond in the resulting adduct (**6**−**8**) was subjected to oxidative cleavage by treatment with ruthenium(IV) oxide to yield the diacids **9**−**11**. Removal of the Boc protecting groups in 3 N HCl at room temperature followed by treatment with an ion-exchange resin afforded the desired compounds **3**−**5** in 60−88% global yield. In the original protocol,[7] the diacid **9** was transformed into the methyl diester prior to hydrolysis. We found no advantage in carrying out this additional step. On the contrary, hydrolysis of the diester required harsher conditions (heating in 6 N HCl), which could result in cleavage of the N−N bond.[7]

We have gathered in Table 1 the NMR results concerning compounds **1**−**5** and represented in Figure 1 the ^{13}C and ^{15}N CPMAS spectra corresponding to Gly-Gly, Ala-Ala, and Ala-Gly (or Gly-Ala).

All structures represented in Scheme 1 have been calculated at the B3LYP/6-31G* level[12,13] using the solvation model of Tomasi (PCM) with water as solvent and Pauling's van der Waals radii.[14] Without solvent, in all cases the only minima

TABLE 1. NMR Results (δ ppm)

compd/conditions	CH(R)	CH_3	CO	N	ref
1 Gly					
water neutral	42.8		173.6	−347.3	^{13}C,[10] ^{15}N[11]
CPMAS	43.3		176.1	−344.8	this work
1H$^+$ GlyH$^+$					
water acid	41.5		171.2	−345.4	^{13}C,[10] ^{15}N[11]
1$^-$ Gly$^-$					
water basic	46.0		182.7	−354.7	^{13}C,[10] ^{15}N[11]
2 Ala					
water neutral	51.9	17.5	177.0	−331.1	^{13}C,[10] ^{15}N[11]
CPMAS	50.5	20.0	177.4	−334.6	this work
2H$^+$ AlaH$^+$					
water acid	50.1	16.5	174.0	−331.3	^{13}C,[10] ^{15}N[11]
2$^-$ Ala$^-$					
water basic	52.7	21.7	185.7		^{13}C[10]
3 Gly-Gly					
CD_3OD[a]	51.7		173.0	−306.6	this work
CPMAS	50.0		177.8	−292.3	this work
	54.0		173.6	−305.6	
4 Ala-Ala					
CD_3OD[b]	59.2[c]	15.9[d]	176.0	−297.3	this work
CPMAS	55.3	17.7	177.5	−281.5	this work
	61.0	16.7	176.6	−282.6	
		15.1	175.7	−292.0	
				−293.8	
5 Gly-Ala					
CD_3OD[e]	51.5[f,g]		172.6[g]	−308.1	this work
	58.8[h,i]	15.4[d]	175.0[i]	−296.4	
CD_3CN[j]	52.1[g]		173.9[g]	not obsd	this work
	58.9[i]	16.1	176.3[i]	not obsd	
CPMAS[k]	51.1[g]		175.1	−297	this work
	57.9[i]	15.3			

[a] <3.6 mg/0.75 mL. [b] 4 mg/0.75 mL. [c] ^1J = 144.7 Hz. [d] ^1J = 129.0 Hz. [e] <4.3 mg/0.75 mL. [f] ^1J = 140.3 Hz. [g] Gly. [h] ^1J = 143.8 Hz. [i] Ala. [j] <5.6 mg/0.75 mL. [k] See spectra (Figure 1).

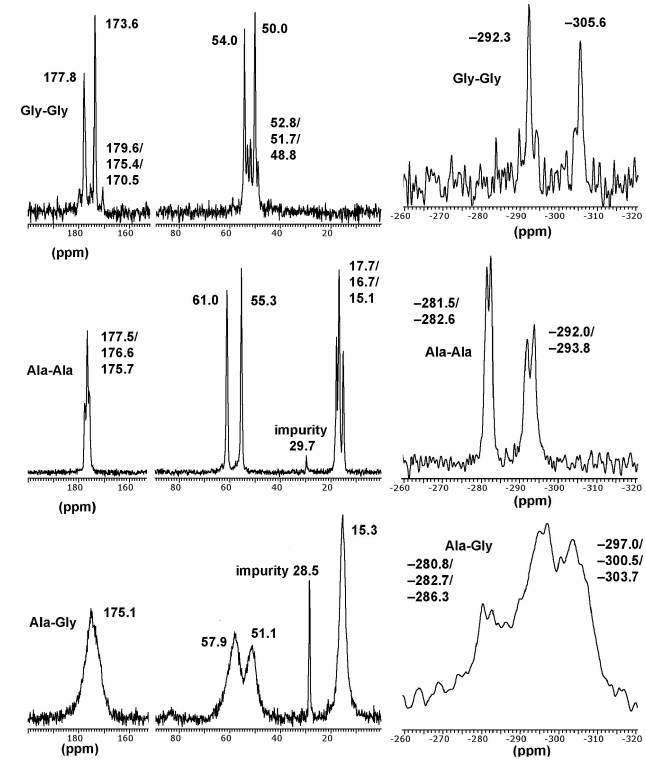


FIGURE 1. ^{13}C (left) and ^{15}N (right) CPMAS NMR spectra recorded at 100.73 and 40.60 MHz, respectively.

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correspond to neutral molecules (no proton transfer between the carboxylic acid and the amino group occurs). Over the optimized geometries, absolute shieldings σ were calculated with the GIAO approximation.[15]

Concerning the energies including solvation, the following values have been obtained: Gly-Gly, distal 3.18 kJ mol^{-1} higher than proximal; Ala-Ala, distal 8.49 kJ mol^{-1} higher than proximal. Thus, although proximal zwitterions are always preferred, the difference is higher for *N*,*N*′-bis(alanine) than for *N*,*N*′-bis(glycine). In the case of the *N*-glycine-*N*′-alanine derivative, the most stable tautomer is the Ala-Gly **5a**, followed by the Gly-Ala **5b** (+0.89 kJ mol^{-1}) [at 25 °C, this corresponds to 59% of **5a** and 41% of **5b**]. Considering the three equilibria, this may indicate that the neutral -NH-CH(R)-CO_2H group is more stable for R = CH_3 than for R = H. The distal tautomers are less stable, **5c** +3.65 [at 25 °C, this corresponds to 82% of **5a** and 18% of **5c**] and **5d** +5.58 kJ mol^{-1}.

The σ values are given in Supporting Information. In Table 2 are reported the corresponding chemical shifts. To transform the absolute shieldings into chemical shifts in solution (CD_3OD and CD_3CN) and in the solid state (CPMAS), the four following equations have been used:

$$\text{Solution: } \delta^{13}\text{C} = 203.3 - 1.094\sigma^{13}\text{C},\ n = 20,\ r^2 = 1.000$$

$$\text{Solution: } \delta^{15}\text{N} = -188.9 - 0.69\sigma^{15}\text{N},\ n = 7,\ r^2 = 0.971$$

$$\text{Solid: } \delta^{13}\text{C} = 204.5 - 1.098\sigma^{13}\text{C},\ n = 15,\ r^2 = 1.999$$

$$\text{Solid: } \delta^{15}\text{N} = -150.8 - 0.876\sigma^{15}\text{N},\ n = 6,\ r^2 = 0.992$$

The average values were calculated for 50:50 mixtures in the cases of Gly-Gly and Ala-Ala, i.e., assuming a rapid equilibrium between two identical tautomers, **3a/3a**, **3b/3b**, **4a/4a**, or **4b/4b**. In the case of the mixed *N*,*N*′-bis(amino acid), we have used the theoretically calculated 59:41 mixture.

It is well-known that protonation effects on the amino and hydrazino groups are weak or very weak both in ^{13}C and in ^{15}N NMR.[16] Therefore, no great differences are expected among the different structures of the *N*,*N*′-bis(amino acids) under study.

In solution and using the ^{13}C chemical shifts, it is difficult to assign the structure to the proximal (fitted values) or to the distal (predicted values) situations because in both cases the correlation coefficient is $r^2 = 1.000$. However, the intercept is closer to 0 (0.6 vs 2.4) and the slope is closer to 1 (0.99 vs 0.97) for the proximal structure than for the distal structure. The situation becomes clearer using the ^{15}N chemical shifts (adding the five data of **1**, **1H**$^+$, **1**$^-$, **2**, and **2H**$^+$). For the proximal, the intercept is 0 and the slope is 1, whereas for the distal, the intercept is 38.4 and the slope is 1.1.

TABLE 2. Calculated NMR Chemical Shifts[a]

compd/phase[b]	near	CH(R)	CH_3	CO	N
1 Gly					
solution		41.9		173.4	−342.2
solid		42.5		174.5	−345.3
1H$^+$ GlyH$^+$					
solution		42.7		170.2	−345.6
1$^-$ Gly$^-$					
solution		45.8		184.3	−352.4
2 Ala					
solution		52.8	15.7	176.4	−334.2
solid		53.3	16.2	177.5	−335.1
2H$^+$ AlaH$^+$					
solution		53.6	16.7	172.9	−337.4
2$^-$ Ala$^-$					
solution		51.2	21.6	185.0	*−348.2*
3a Gly-Gly prox					
solution	average[c]	50.8		174.6	−304.8
solid	CO_2H	51.4		175.6	−301.5[d]
	CO_2^-	53.3		173.4	−294.2[e]
3b Gly-Gly dist					
solution	average[c]	*50.0*		*175.5*	*−307.5*
solid	CO_2H	51.6		171.8	*−312.1*[d]
	CO_2^-	49.7		180.9	*−290.4*[e]
4a Ala-Ala prox					
solution	average[c]	61.4	14.4	175.6	−297.1
solid	CO_2H	58.6	15.2	177.3	−291.9[d]
	CO_2^-	65.3	14.4	175.9	−284.2[e]
4b Ala-Ala dist					
solution	average[c]	*59.6*	*13.6*	*178.3*	*−303.1*
solid	CO_2H	62.9	13.9	174.3	*−312.1*[d]
	CO_2^-	57.6	14.5	183.9	*−290.4*[e]
5a/5b					
solution	av[f] Gly	*51.7*		*173.5*	*−307.4*
	av[f] Ala	*60.1*	*13.5*	*176.1*	*−295.4*
5a Ala-Gly prox					
solid	Gly	*53.3*		*173.6*	*−301.1*
	Ala	*58.9*	*14.8*	*177.7*	*−286.0*
5b Gly-Ala prox					
solid	Gly	*51.0*		*175.7*	*−303.0*
	Ala	*63.2*	*12.6*	*176.5*	*−294.1*
5c Ala-Gly dist					
solid	Gly	*49.5*		*180.9*	*−289.3*
	Ala	*63.2*	*13.6*	*174.1*	*−303.5*
5d Gly-Ala dist					
solid	Gly	*51.7*		*171.7*	*−319.1*
	Ala	*57.6*	*14.4*	*184.2*	*−281.7*
5a/5b					
solid	av[c] Gly	*52.2*		*174.6*	*−302.0*
	av[c] Ala	*61.0*	*13.7*	*177.1*	*−290.0*
5c/5d					
solid	av[c] Gly	*50.6*		*176.3*	*−304.2*
	av[c] Ala	*60.4*	*14.0*	*179.1*	*−292.6*

[a] δ ppm; roman = fitted; italic = predicted. [b] "Solution" means the average situation found in methanol or acetonitrile, and "solid" represents the unique tautomer found in the solid state with the exception of compound **5**. [c] 50:50. [d] NH_2^+. [e] NH. [f] 59:41.

For the proximal Ala-Gly (Gly-Ala) derivative, **5a/5b**, in CD_3OD the calculations predict values very close to the experimental ones: experimental (Table 1)/calculated (Table 2): 51.5/51.7, 172.6/173.5, −308.1/−307.4, 58.8/60.1, 15.4/13.5, 175.0/176.1 and −296.4/−295.4 ppm.

In the solid state, there are two different cases: Gly-Gly and Ala-Ala present narrow signals in both ^{13}C and ^{15}N CPMAS NMR spectra. The calculations (Table 2) reproduce well the positions of all signals, but mainly in Ala-Ala there is a clear splitting of several signals, e.g., the methyl group (three signals instead of two), the carboxylic group (three signals instead of

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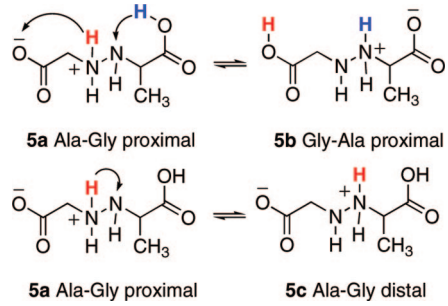
SCHEME 3. Possible Solid-State Intramolecular Double Proton Transfers



two), and both nitrogen atoms (two signals instead of one). Since the distal isomer **4b** can be excluded (no signal at −312 ppm in ^{15}N NMR), the multiplicity must be related to the existence of two independent molecules in the unit cell, probably two different conformers. In the Gly-Gly derivative, there are some small signals in the ^{13}C NMR spectrum (Figure 1) that could correspond to a minor conformer.

The Ala-Gly (Gly-Ala) derivative behaves differently. In both spectra (Figure 1) the signals are broad (the narrowness of the impurity at 28.5 ppm proves that this is not due to a lack of resolution). We assign this broadening to a rapid equilibrium between **5a** and **5b** that we assumed are present in a 50:50 mixture in the solid state (Scheme 3). The calculated average signals (Table 2) agree reasonably well with the broad signals: 13.7/15.3, 52.2/51.1, 61.0/57.9, 174.6−177.1/175.1 ppm (^{13}C) and −290 and −302 ppm with the large signal between −281 and −304 ppm (Figure 1, ^{15}N). Note that this signal can be described as the sum of two signals at −282.7 and −303.7 ppm (slow proton transfer) plus a central signal at −297.0 ppm (fast proton exchange, calculated at −296.0 ppm).

The other possibility, a rapid equilibrium in the solid state between two Ala-Gly tautomers **5a** and **5c** should be rejected for the two following reasons. Solid state proton transfer (SSPT) occurs only between tautomers of identical or very similar energies;[17] the difference being 0.89 kJ mol^{-1} for the **5a/5b** pair but 3.65 kJ mol^{-1} for the **5a/5c** pair. Another reason is that 1,2-proton transfers in hydrazine derivatives (**5a/5c** pair) are generally forbidden.[18]

In summary, the study of the molecules described in this paper has resulted in the observation of interesting solid state properties, including a new example of the rare phenomenon of SSPT. Further studies will be needed to finish this work, including X-ray structure determinations (for the moment, it has been impossible to grow convenient crystals) and ^{15}N-labeled molecules for CPMAS low-temperature NMR studies.

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Experimental Section

Characterization of compounds **3**−**11** is given in Supporting Information.

General Procedure for the Hetero Diels−**Alder Reaction.** To a solution of di-*tert*-butyl azodicarboxylate (4.0 g, 17.39 mmol) in CCl_4 (40 mL) cooled at −40 °C was added the corresponding diene (1.5−5.0 equiv) dissolved in CCl_4 (20 mL). The reaction mixture was stirred at this temperature for 2 h and then at room temperature for 7 days. After removal of the solvent, the remaining residue was purified by column chromatography on silica gel (eluent, hexanes/EtOAc 9:1) to afford **6**−**8**.

General Procedure for Double Bond Cleavage. A solution of **6**−**8** (7.74 mmol) in EtOAc (40 mL) was cooled to 0 °C, and a 10% aqueous solution of sodium periodate (70 mL) containing ruthenium(IV) oxide (30 mg, 0.23 mmol) was added. The resulting biphasic system was vigorously stirred at 0 °C for 2 h and then at room temperature overnight. The organic layer was separated, and the remaining aqueous layer was extracted with EtOAc (3 × 30 mL). The combined organic extracts were dried over anhydrous $MgSO_4$ and filtered. Evaporation of the solvent yielded a black oil, which was purified by column chromatography on silica gel (eluent, Et_2O) to afford **9**−**11**.

General Procedure for *N*-Boc Deprotection and Isolation of the Final Bis(amino acid). A 3 N solution of HCl in anhydrous EtOAc (5 mL) was added to **9**−**11** (1.67 mmol), and the reaction mixture was stirred at room temperature for 1 h. After evaporation of the solvent, the residue was taken up in water and lyophilized. It was then redissolved in water (10 mL) and Amberlyst A26 (hydroxyde form) (950 mg, wet wt) was added. The mixture was stirred manually occasionally until the resin color completely turned from pink to pale yellow (about 2 h). The resin was removed by filtration and washed thoroughly with water. Concentration of the aqueous solution followed by lyophilization afforded **3**−**5**.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra and characterization of all compounds synthesized. Details on NMR structural studies and theoretical calculations. Total energy, nuclear shieldings and Cartesian coordinates of the molecules calculated at the B3LYP/6-31G(d,p) computational level. This material is available free of charge via the Internet at http://pubs.acs.org.

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