

Short Communication

Selective formation of glycylglycine by dehydration of glycine adsorbed on silica gel

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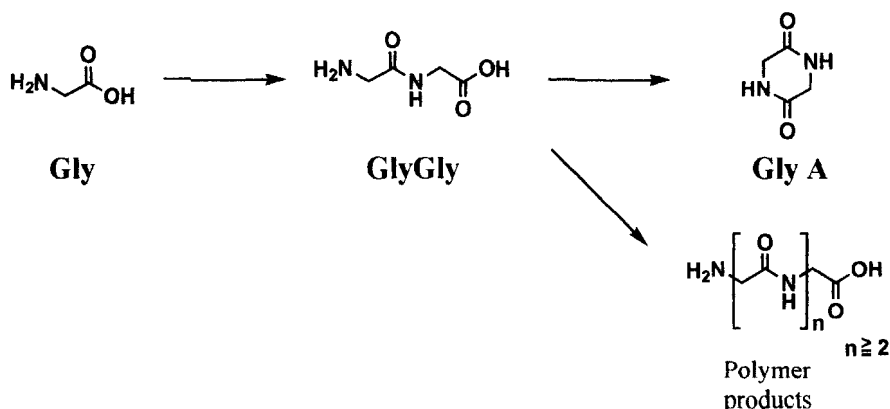
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ABSTRACT: Silica gel promotes the selective dehydration of glycine to form intermediate glycylglycine, with inhibition of the formation of stable glycine anhydride and polymer products. IR measurements indicate that glycine adsorbed on silica gel results in the formation of neutral species having C=O and NH₂ groups. The species is considered to stimulate dehydration, leading to the reported selective dehydration. Copyright © 1999 John Wiley & Sons, Ltd.

KEYWORDS: glycylglycine; glycine; dehydration; silica gel



Scheme 1

The application of solid adsorbents such as silica gel and alumina as solid supports in organic synthesis affords a new procedure for selective reactions, where substrates are adsorbed and oriented on the surface of adsorbents with suppression of translational movement.¹ The significant potential of adsorbents is highlighted in selective organic transformations involving oxidation,² alkylation,³ condensation,⁴ acetylation,⁵ monoetherification⁶ and monomethyl esterification.⁷ Generally, dehydration of amino acids proceeds both consecutively and simultaneously, and consequently affords lactam and polymer products. We have reported the selective formation of ϵ -caprolactam from 6-aminocaproic acid using silica gel to suppress the formation of polymer

products.⁸ Generally, direct synthesis of intermediate glycylglycine (GlyGly) from glycine (Gly) is not readily achieved because of the subsequent ease of intramolecular or intermolecular dehydration from intermediate GlyGly, consequently forming glycine anhydride (Gly A) or the polymer products, respectively. It has been reported that Gly A is formed from Gly in a solution using metal alkoxides such as titanium isopropoxide.⁹ We report here the selective formation of intermediate GlyGly from Gly using silica gel as the solid support.

Dehydration of Gly adsorbed on silica gel was achieved using the following method (adsorption method): silica gel (C-200, Wako, 10 g) was added to an *N,N*-dimethylformamide (DMF) or water solution containing a predetermined amount of Gly, and the solvent was subsequently removed under reduced pressure. The solid obtained (adsorption sample) was

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Table 1. Selective dehydration of Gly to GlyGly^a

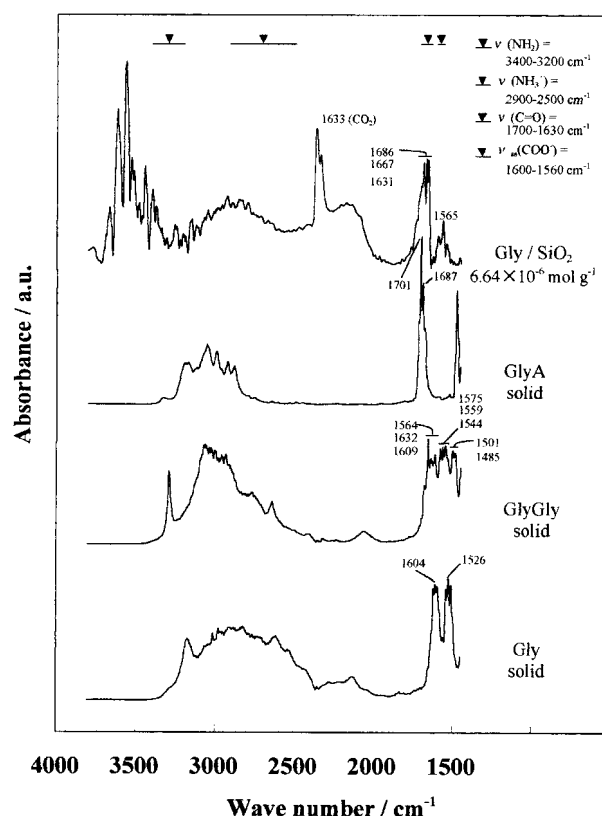
Method	Amount of Gly (10 ⁻⁴ mol g ⁻¹ SiO ₂)	Intact Gly (%)	Yield (%)		Selectivity ^b (%)
			GlyGly	Gly A	
Adsorption	0.066	0.0	92.4	0.0	92.4
Adsorption ^c	0.066	63.9	29.2	0.0	80.7
Adsorption ^d	0.066	17.9	15.9	0.0	19.4
Adsorption	0.21	0.0	29.2	35.2	29.2
Adsorption	0.66	0.0	10.7	44.3	10.7
Adsorption	2.7	0.0	2.3	34.6	2.3
Homogeneous ^e	—	0.0	2.4	3.6	2.4
Homogeneous ^f	—	0.0	0.0	22.6	0.0

^a Each experiment was carried out under reflux in toluene for 20 h.^b The value of [yield of the GlyGly/(100 – intact Gly)] × 100.^c In the absence of toluene solvent at room temperature.^d In the absence of toluene solvent at 100 °C.^e 0.022 M solution of Gly in ethylene glycol under reflux.^f 0.20 M solution of Gly in ethylene glycol under reflux.

added to toluene (10–50 ml) and heated under reflux for 20 h using a Dean–Stark trap to collect the water formed in the reaction. A reaction period of 20 h was sufficient for completion of the reaction. After the reaction the mixture was filtered and the solid was thoroughly washed with distilled water and DMF. The combined washings and filtrate were evaporated to low volume (*in vacuo*) and the products were analyzed by gas–liquid chromatography with a Yanagimoto Model G2800F gas chromatograph equipped with Unisol 30T column (0.5 m) and high-performance liquid chromatography with a Tokyo-Rikakikai EYELA PLC-10 system equipped with a TR-35-415F(ODS) column (15 cm) using water as the eluent. Butane-1,4-diol or higher alkanes were used as standards for quantitative analysis.

The results of the dehydration are given in Table 1. According to the adsorption method, the product GlyGly was readily obtained in 92.4% yield with the adsorption sample (6.6×10^{-6} mol g⁻¹, $\theta = 0.0025$). The selectivity for the formation of GlyGly increases with decrease in the amount of adsorbed Gly, suppressing the formation of Gly A and polymer products. Significant yields of Gly A were attained with higher loadings. In the absence of toluene as solvent at room temperature, 80.7% of the selectivity was achieved, but the reactivity of Gly was suppressed, as illustrated by the remains of significant quantities of unreacted Gly (63.9%). When the reaction temperature was at 100 °C, the reactivity increased with intact Gly (17.9%), but the selectivity decreased drastically, and only a 15.9% yield of GlyGly was obtained. Under homogeneous conditions, lower selectivities were recorded, and a 22.6% yield of Gly A was obtained in a 0.20 M solution of Gly. In a 0.022 M solution, only a 2.4% yield of GlyGly was obtained.

The IR absorption of Gly adsorbed on silica gel was measured by Fourier transform IR spectrometry with a JASCO FT/IR-7000 infrared spectrometer by the diffuse reflection technique. Spectra including the absorption of

**Figure 1.** IR absorption of Gly on silica gel

authentic samples are illustrated in Fig. 1. Authentic samples of Gly, GlyGly and Gly A were all guaranteed grade from Tokyo-Kasei. The spectrum of authentic Gly in the solid state was very complicated, but it exhibited the characteristic bands at *ca* 1600–1560 cm⁻¹ due to the stretching vibration of carboxylate anion [$\nu_{as}\text{CO}_2^-$ (as = asymmetric vibration)] and at *ca* 2900–2500 cm⁻¹ due to νNH_3^+ .¹⁰ Similarly, the spectrum of Gly adsorbed on silica gel was also complicated, but notable differ-

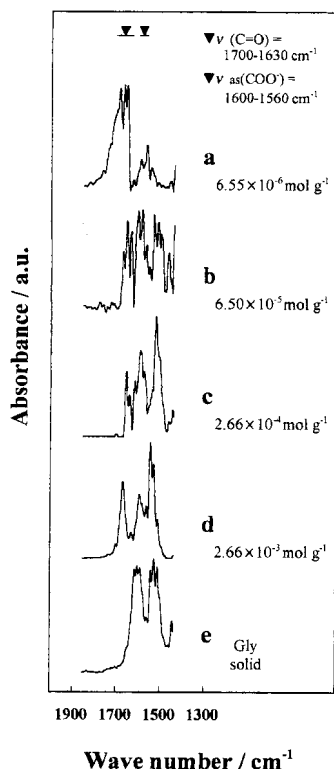


Figure 2. IR absorption of Gly at various loadings

ences existed, including new bands at $1700\text{--}1630\text{ cm}^{-1}$ due to the $\nu\text{C=O}$ stretching vibration together with the disappearance of the characteristic CO_2^- absorption as seen with Gly in the solid state. Slight differences also existed in the absorption intensities of the bands at $ca\ 3400\text{--}3200$ and $ca\ 2900\text{--}2500\text{ cm}^{-1}$ due to νNH_2 and νNH_3^+ , respectively, *i.e.* an increase in intensity of νNH_2 was observed with a decrease in that of νNH_3^+ .

IR spectra of Gly on various loadings are illustrated in Fig. 2. Changes in the spectra were observed with a decrease in the amount of Gly, where the intensity of the absorption of $\nu\text{C=O}$ increased with a simultaneous decrease in that of $\nu_{\text{as}}\text{CO}_2^-$ (spectra d–a, Fig. 2). This indicates that Gly at lower loadings is adsorbed mainly as species having a C=O group. At fairly high loadings (more than $2.7 \times 10^{-3}\text{ mol g}^{-1}\text{ SiO}_2$, $\theta > 1.0$), the spectra were similar to that of Gly in the solid state. The

amount required for complete surface coverage could be estimated as $2.7 \times 10^{-3}\text{ mol g}^{-1}$ on the basis of the cross-sectional area of Gly ($ca\ 0.23\text{ nm}^2\text{ molecule}^{-1}$ by molecular modelling) and the specific surface area of silica gel ($371\text{ m}^2\text{ g}^{-1}$) by BET measurement. These data imply that a decrease in the amount of Gly on silica gel allows easier dispersion of Gly molecules on the silica gel surface, thus suppressing intermolecular interactions between Gly molecules. This resulted in Gly being adsorbed predominantly as neutral species having C=O and NH_2 groups. This species is considered to promote the dehydration of Gly readily, and the selective formation of intermediate GlyGly is believed to be achieved with the suppression of intermolecular interactions between GlyGly molecules.

REFERENCES

1. J. H. Clark, A. P. Kybett and D. J. Macquarrie, *Supported Reagents: Preparation, Analysis, and Applications*. VCH, New York (1992); K. Smith (Ed.), *Solid Supports and Catalysis in Organic Synthesis*. Prentice Hall, Englewood Cliffs, NJ (1992); P. Laszlo (Ed.), *Preparative Chemistry Using Supported Reagents*. Academic Press, San Diego (1987); A. McKillop and D. W. Young, *Synthesis* 401 (1979); G. H. Posner, *Angew. Chem., Int. Ed. Engl.* **17**, 487 (1978); A. Cornelis and P. Laszlo, *Synthesis* 909; (1985); H. Ogawa, M. Kodomari and T. Chihara, *PETROTECH* **19**, 404 (1996).
2. Z. Cohen, E. Keinan, Y. Mazur and T. H. Varkony, *J. Org. Chem.* **40**, 2141 (1975); E. Keinan and Y. Mazur, *J. Org. Chem.* **42**, 844 (1977), and references cited therein.
3. G. Bram and T. Fillebeen-Khan, *J. Chem. Soc., Chem. Commun.* 522 (1979).
4. E. Keinan and Y. Mazur, *J. Am. Chem. Soc.* **99**, 3861 (1977); J. Muzard, *Synthesis* 60 (1982).
5. T. Chihara, S. Teratani and H. Ogawa, *J. Chem. Soc., Chem. Commun.* 1120 (1981); T. Chihara, Y. Takagi, S. Teratani and H. Ogawa, *Chem. Lett.* 1451 (1982).
6. T. Nishiguchi, K. Kawamine and T. Ohtsuka, *J. Chem. Soc., Perkin Trans. 1* 153; (1992) T. Nishiguchi and K. Kawamine, *J. Chem. Soc., Chem. Commun.* 1766, (1990).
7. H. Ogawa, T. Chihara and K. Taya, *J. Am. Chem. Soc.* **107**, 1365 (1985); H. Ogawa, *J. Phys. Org. Chem.* **4**, 346 (1991); H. Ogawa, T. Chihara, S. Teratani and K. Taya, *J. Chem. Soc., Chem. Commun.* 1337 (1986).
8. H. Ogawa, K. Nozawa and P. Ahn, *J. Chem. Soc., Chem. Commun.* 1393 (1993).
9. N. Yoshino and T. Yoshino, *Bull. Chem. Soc. Jpn.* **46**, 2899 (1973).
10. R. M. Silverstein, G. C. Bassler and T. C. Morrill, *Spectrometric Identification of Organic Compounds*, 4th ed., p. 126. J Wiley, New York (1981); S. Sternhell and J. R. Kalman, *Organic Structures from Spectra*, p. 13. J Wiley, New York (1987).