(d, 2 H, J = 9.0, ArH), 4.57 (ddd, 1 H, J = 6.8, 6.8, and 3.0, -C(O)HCH$_a$H$_b$O), 4.18 (d, 1 H, J = 2.3, NCHCHR*), 4.11 (dd, 1 H, J = 8.4 and 6.8, -C(O)HCH$_a$H$_b$O), 3.90 (dd, 1 H, J = 3.0 and 2.3, NCHCHR*), 3.83 (dd, 1 H, J = 8.4 and 6.8, -C(O)HCH$_a$H$_b$O), 3.77 (s, 3 H, OCH$_3$), 2.08 (br s, 2 H, NH$_2$), 1.38, 1.30 (s, 3 H, C(CH$_3$)$_2$). ^{13}C NMR ($CDCl_3$): δ 167.25 (C=O), 156.66, 130.17, 119.83, 114.39 (ArC), 110.02 (C(CH$_3$)$_2$), 72.64 (-C(O)HCH$_2$O), 65.83 (NCHCHR*), 63.46 (NCHCHR*), 60.60 (-C(O)HCH$_2$O), 55.49 (OCH$_3$), 26.06, 24.79 (C(CH$_3$)$_2$). This product was converted without purification to 2-azetidinone **11** for comparison of the optical rotation (vide supra).

***cis*-(3*S*,4*S*)-3-Amino-4-[(1′*S*)-1′,2′-*O*-isopropylideneethyl]-2-azetidinone (10d).** Following the same procedure as described above for **10a**, crude **9d** was deprotected to afford 1.47 g (93%) of **10d** as a pale yellow oil. ^{1}H NMR ($CDCl_3$): δ 5.77 (br s, 1 H, NH), 4.23 (m, 3 H, NCHCHR*, -C(O)HCH$_a$H$_b$O, and C(O)HCH$_a$H$_b$O), 3.75 (dd, 1 H, J = 7.9 and 4.6, NCHCHR*), 3.68 (m, 1 H, -C(O)HCH$_a$H$_b$O), 2.15 (br s, 2 H, NH$_2$), 1.42, 1.33 (s, 3 H, C(CH$_3$)$_2$). ^{13}C NMR ($CDCl_3$): δ 172.60 (C=O), 109.94 (C(CH$_3$)$_2$), 74.93 (-C(O)HCH$_2$O), 66.70 (NCHCHR*), 62.35 (NCHCHR*), 56.71 (-C(O)HCH$_2$O), 26.21, 25.24 (C(CH$_3$)$_2$).

***trans*-(3*R*,4*S*)-1-(4-Methoxyphenyl)-3-phthalimido-4-[(1′*S*)-1′,2′-*O*-isopropylideneethyl]-2-azetidinone (11).** To a solution of 0.88 g (3.0 mmol) of pure *trans*-**10a** in 50 mL of THF was added 10 mL of a saturated aqueous Na_2CO_3 solution and subsequently 1.10 g (5.0 mmol) of Nefkens reagent.[33] The mixture was stirred vigorously for 1 h at room temperature and then extracted three times with 30 mL of EtOAc. The organic extracts were dried over Na_2SO_4 and concentrated in vacuo affording 1.6 g of an off-white solid. This was washed twice with 20 mL of cold (0 °C) Et_2O and dried in vacuo, yielding 1.17 g (92%) of pure **11** as a white solid, mp 154 °C, dec. $[\alpha]^{20}_D$ +5.97 (c 0.7, methanol). ^{1}H NMR ($CDCl_3$): δ 7.87-7.81, 7.78-7.72 (m, 2 H, ArH of phthalim), 7.39 (d, 2 H, J = 8.9, ArH of anisyl), 6.91 (d, 2 H, J = 8.9, ArH of anisyl), 5.58 (d, 1 H, J = 2.6 NCHCHR*), 4.64 (ddd, 1 H, J = 7.0, 6.5, and 2.3, -C(O)HCH$_a$H$_b$O), 4.50 (dd, 1 H, J = 2.6 and 2.3, NCHCHR*), 4.13 (dd, 1 H, J = 8.4 and 6.5, -C(O)HCH$_a$H$_b$O), 3.80 (s, 3 H, OCH$_3$), 3.64 (dd, 1 H, J = 8.4 and 7.0, -C(O)HCH$_a$H$_b$O), 1.54, 1.36 (s, 3 H, C(CH$_3$)$_2$). ^{13}C NMR ($CDCl_3$): δ 166.87, 161.55 (C=O), 157.19, 134.53, 131.72, 123.74, 120.73, 114.55 (ArC), 110.63 (C(CH$_3$)$_2$), 71.96 (-C(O)HCH$_2$O), 66.15 (NCHCHR*), 59.37 (-C(O)HCH$_2$O), 55.52 (OCH$_3$), 54.16 (NCHCHR*), 26.11, 25.43 (C(CH$_3$)$_2$). Anal. Calcd for $C_{23}H_{22}N_2O_6$: C, 65.39; H, 5.25; N, 6.63. Found: C, 64.84; H, 5.45; N, 6.53.

(33) Nefkens, G. H. L.; Tesser, G. I.; Nivard, R. J. F. *Recl. Trav. Chim. Pays-Bas* **1960**, *79*, 688.

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Registry No. **1a**, 81983-63-3; **1b**, 141039-95-4; **1c**, 78605-23-9; **2a**, 622-29-7; **2b**, 17599-61-0; **2c**, 129171-89-7; **2d**, 125875-26-5; **2e**, 141039-96-5; (*E*)-**2f**, 141039-97-6; (*Z*)-**2f**, 141039-98-7; **2g**, 141039-99-8; **2h**, 104973-19-5; **2i**, 103239-04-9; **2j**, 86299-28-7; **2k**, 140874-23-3; **2l**, 140874-24-4; **3a**, 113830-78-7; **3b**, 140874-25-5; *trans*-(3*R*,4*S*)-**4a**, 129086-49-3; *trans*-(3*S*,4*R*)-**4a**, 141040-00-8; *trans*-(3*R*,4*S*)-**4b**, 129086-50-6; *trans*-(3*S*,4*R*)-**4b**, 141040-01-9; *cis*-(3*R*,4*R*)-**4c**, 141040-03-1; *trans*-(3*S*,4*R*)-**4c**, 141040-02-0; *trans*-(3*R*,4*S*)-**4c**, 140874-26-6; *cis*-(3*R*,4*S*)-**5a**, 140874-27-7; *cis*-(3*S*,4*R*)-**5a**, 141040-04-2; *trans*-(3*R*,4*R*)-**5a**, 141040-05-3; *trans*-(3*S*,4*S*)-**5a**, 141040-06-4; *cis*-(3*R*,4*S*)-**5b**, 133774-21-7; *cis*-(3*S*,4*R*)-**5b**, 141040-07-5; *trans*-(3*R*,4*R*)-**5b**, 133693-71-7; *trans*-(3*S*,4*S*)-**5b**, 141040-08-6; *cis*-(3*R*,4*S*)-**5c**, 141040-09-7; *cis*-(3*S*,4*R*)-**5c**, 133774-22-8; *trans*-(3*S*,4*S*)-**5c**, 133693-73-9; *cis*-(3*R*,4*S*)-**6b**, 133774-25-1; *cis*-(3*S*,4*R*)-**6b**, 141040-10-0; *trans*-(3*R*,4*R*)-**6b**, 133693-72-8; *trans*-(3*S*,4*S*)-**6b**, 141040-11-1; *cis*-(3*R*,4*S*)-**6c**, 141040-12-2; *cis*-(3*S*,4*R*)-**6c**, 141040-13-3; *trans*-(3*S*,4*S*)-**6c**, 133693-76-2; *cis*-(3*R*,4*S*)-**7b**, 133774-23-9; *cis*-(3*S*,4*R*)-**7b**, 141040-14-4; *trans*-(3*R*,4*R*)-**7b**, 133693-74-0; *trans*-(3*S*,4*S*)-**7b**, 141040-15-5; *cis*-(3*R*,4*S*)-**7c**, 141040-16-6; *cis*-(3*S*,4*R*)-**7c**, 141040-17-7; *trans*-(3*S*,4*S*)-**7c**, 133693-77-3; *cis*-(3*R*,4*S*)-**8b**, 133774-24-0; *trans*-(3*R*,4*R*)-**8b**, 133693-75-1; *trans*-(3*S*,4*S*)-**8b**, 141040-18-8; *cis*-(3*S*,4*R*)-**8c**, 141040-19-9; *trans*-(3*S*,4*S*)-**8c**, 133693-78-4; *cis*-(3*S*,4*S*)-**9a**, 141040-20-2; *cis*-(3*R*,4*R*)-**9a**, 141040-21-3; *trans*-(3*R*,4*S*)-**9a**, 133693-70-6; *cis*-(3*S*,4*S*)-**9d**, 140874-28-8; *trans*-(3*R*,4*S*)-**10a**, 141040-22-4; *cis*-(3*S*,4*S*)-**10d**, 140874-29-9; **11**, 141040-23-5; 2-pyridylcarbaldehyde, 1121-60-4; (+)-*R*-α-methylbenzylamine, 3886-69-9; 2-furancarboxaldehyde, 98-01-1; 3-(trimethylsilyl)-2-propynal, 2975-46-4.

Supplementary Material Available: ^{1}H and ^{13}C NMR spectra of some of the new compounds (42 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

The Reaction of Glyoxylic Acid with Ammonia Revisited

Anthonius J. Hoefnagel,* Herman van Bekkum, and Joop A. Peters

Laboratory of Organic Chemistry and Catalysis, Delft University of Technology, Julianalaan 136, 2628 BL Delft, The Netherlands

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Upon addition of ammonia or an alkylamine to glyoxylic acid an ammonium derivative of glyoxylic acid precipitates quantitatively. With the use of solid-state ^{13}C and ^{15}N NMR spectroscopy, it is shown that adducts of glyoxylic acid and ammonia or the alkylamine are obtained. These compounds are not stable in aqueous solution. The compositions of the aqueous solutions have been investigated by ^{1}H, ^{13}C, ^{15}N, and ^{17}O NMR. Under basic conditions hexahydro-*s*-triazine-2,4,6-tricarboxylate is the predominant species in a solution of the adduct of ammonia and glyoxylic acid, whereas upon acidification (pH < 6) glyoxylate is the only organic species. In a basic solution of the adduct of ethylamine and glyoxylic acid *N*-ethyliminoacetate is the only species. The *N*-methyl adduct shows an intermediate behavior: both the hexahydrotriazine and the imine are observed. Under acidic conditions deamination to glyoxylate always occurs. Intermediates in the reaction of glyoxylic acid and ammonia could be detected with ^{1}H NMR, when the reaction was performed with an excess of ammonia. The mechanism of these reactions is discussed.

Introduction

Glycine and hydroxyglycine units are occurring in various pharmacologically important compounds, such as amoxicillin- and cephalosporin-type antibiotics. Ammonium derivatives of glyoxylic acid have been proposed as intumescent fire-retarding and heat-insulating materials.[1] Furthermore, iminoacetic acid is thought to be an inter-

(1) Masciantonio, P. X.; Mihelic, E. L. *U.S. Pat.* 3 668 121; *Chem. Abstr.* **1972**, *77*, 76845.

0022-3263/92/1957-3916$03.00/0

Table I. ^{13}C Chemical Shifts of the Compounds Studied in the Solid State (ppm)[a]

compd	COOH	CH	alkyl
3a	175.1	75.0	
3b	173.7	79.3	26.3
3c	175.6	76.8	34.5; 11.3
3d	176.3	91.5	27.9; 53.0
3e	171.2	85.0	36.8; 39.9
1, Na salt	180.9	88.8	
1, Na salt[b]	176.6	88.1	
Na glycolate	182.1	62.1	
NH_4 glycolate	180.5; 179.3	60.3	

[a] With respect to adamantane as standard (tertiary carbon at δ = 38.3 ppm), see Experimental Section. [b] 0.5 M solution in D_2O; chemical shifts with respect to dioxane (δ = 66.6 ppm) as internal standard.

mediate in the biosynthesis and biodegradation of glycine.[2]

Hydroxyglycine can be considered as an adduct of ammonia and glyoxylic acid. The structure of the product of reaction of equimolar amounts of ammonia and glyoxylic acid has been the subject of a long-lasting polemic between Perkin[3] and Debus.[4] According to Perkin the adduct is hydroxyglycine,[3] whereas Debus assumed that the ammonium salt of nonhydrated glyoxylic acid is formed.[4] This question has never been settled satisfactorily. Yanagawa et al. have obtained *N*-oxalylglycine from a reaction of glyoxylic acid with ammonium sulfate in water followed by lyophilization and hydrolysis in 6 N HCl,[2] but that compound was not identical with that described by Perkin and Debus.

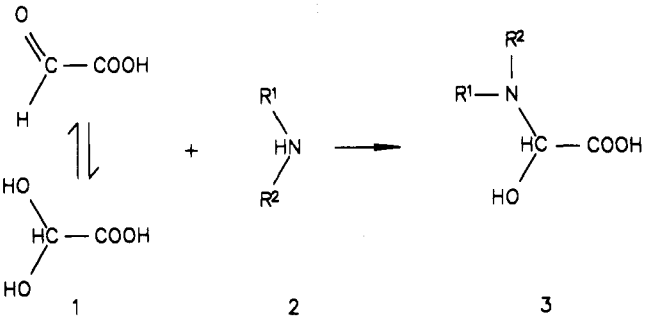
In this paper, we describe a facile preparation of the adducts of glyoxylic acid with ammonia and with some alkylamines. The structures of these adducts have been investigated with solid-state ^{13}C and ^{15}N NMR spectroscopy, whereas the behavior of these compounds in aqueous solution has been studied with the use of multinuclear NMR spectroscopy.

Results and Discussion

Synthesis. Upon addition of aqueous solutions of glyoxylic acid (1) and ammonium acetate in a molar ratio of 1:2 at 0 °C, a white precipitate (**3a**) was obtained. The elemental analysis is in agreement with that of the compound described by Perkin[3] and Debus.[4] The corresponding *N*-methyl (**3b**), *N*-ethyl (**3c**), *N*-*tert*-butyl (**3d**), *N*,*N*-dimethyl (**3e**), as well as the *N*-propyl, and *N*-decyl compounds were prepared from glyoxylic acid and the appropriate alkylamines **2**.

Solid-State ^{13}C and ^{15}N NMR Spectroscopy. In Table I the solid-state ^{13}C NMR spectra of the precipitates obtained are compared with ^{13}C NMR spectra of solid sodium glyoxylate and of its aqueous solution. The spectra of solid sodium glyoxylate have a signal at 88 ppm, whereas no aldehyde ^{13}C signal could be observed, which demonstrates that this compound occurs almost exclusively in the hydrated form both in aqueous solution and in the solid state. Earlier we reported on ^1H NMR spectra of glyoxylic acid in water showing, at 21 and 85 °C, 9 and 15% of aldehyde form to be present, respectively.[5] The large differences among the chemical shifts of compounds **3**, and particularly the fact that the chemical shift of the *C*H signal of **3a** is substantially lower than that of glyoxylate, demonstrates that hydroxyglycines **3a–e** are obtained rather than ammonium glyoxylates (see Scheme I). The chemical shift difference between ammonium and sodium glyoxylate is expected to be smaller; for the corresponding salts of glycolic acid, we observed indeed a difference of only 1.8 ppm. No signals in the region 150–170 ppm were observed for compounds **3a–e** in the solid state, so no dehydration toward imines has occurred.

Scheme I



a R^1 = H R^2 = H
b R^1 = Me R^2 = H
c R^1 = Et R^2 = H
d R^1 = t-Bu R^2 = H
e R^1 = Me R^2 = Me

Further support for these conclusions was obtained from a solid-state ^{15}N spectrum of ^{15}N-labeled **3a**, which displayed a peak at 16.7 ppm with respect to solid $^{15}NH_4Cl$ as external standard.

Compositions of Aqueous Solutions of 3a–e. The NMR spectra of aqueous solutions of the compounds **3a–e** were strongly dependent upon the pH. Up to pH 6 almost identical ^1H and ^{13}C NMR spectra were obtained: the only differences were found in the signals due to the alkyl group R. The identity of the other signals was confirmed by measuring spectra of mixtures. Upon addition of glyoxylic acid (1) to the sample of **3a** no new ^{13}C NMR signals were observed at pH < 6. Therefore, it can be concluded that below pH 6 (alkyl)ammonium glyoxylate is the predominant species. Plotting the ^{13}C chemical shifts of, for instance, **3a** versus pH resulted in sigmoidal curves with an inflection point at pH 2.5 (see Figure 1), which corresponds with the pK_a of glyoxylic acid, taking into account the partially deuterated medium and the relatively high concentration in the sample used for the NMR measurements.

Upon increasing the pH (pH > 6), the intensity of the glyoxylate signals decreased, whereas new signals showed up. For **3a** two new ^{13}C signals were observed, with chemical shifts significantly lower than that of glyoxylate (see Figure 1). Apparently at pH > 6, an addition of ammonia to glyoxylate occurs. The ^{13}C NMR signals of this adduct show a pH jump at about pH 8, which is, most likely, related to dissociation of an ammonium group. Splitting could be discerned in the ^{13}C NMR signals of the ^{15}N labeled compound at pH 12; both signals were triplets (splitting *C*H 2.5 Hz, *C*OO 1.5 Hz), indicating that the concerning species contains at least two nitrogen atoms. No splitting was observed in the signals, which were present at low pH and which were assigned to glyoxylate. It is well known that primary imines are highly reactive and have a tendency to oligomerize.[6] Therefore, we as-

(2) Yanagawa, H.; Makino, Y.; Sato, K.; Nishizawa, M.; Egami, F. *Origins Life* **1984**, *14*, 163.
(3) Perkin, W. H. *J. Chem. Soc.* **1877**, *32*, 90.
(4) Debus, H. *J. Chem. Soc.* **1904**, *85*, 1382.
(5) Hoefnagel, A. J.; Peters, J. A.; van Bekkum, H. *Recl. Trav. Chim. Pays-Bas* **1988**, *107*, 242.
(6) Reeves, R. L. In *The Chemistry of the Carbonyl Group*; Patai, S., Ed.; Interscience: London, 1966; p 608.

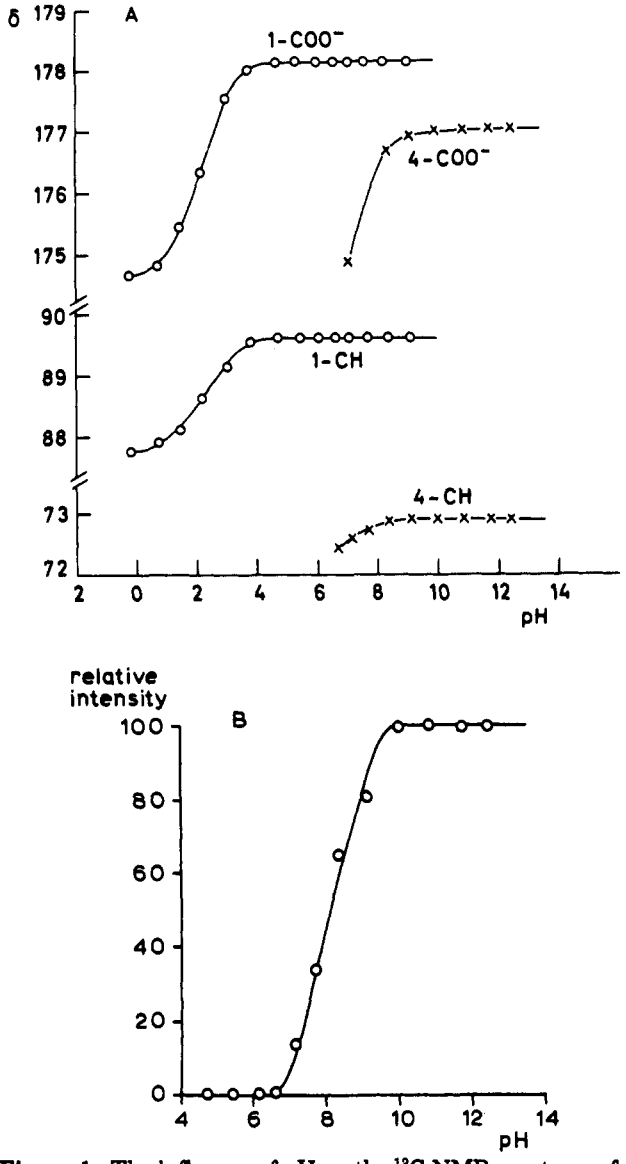


Figure 1. The influence of pH on the ^{13}C NMR spectrum of a 0.5 M solution of **3a** in D_2O at 25 °C: (A) chemical shifts; (B) relative intensity of **4a**, the remainder is glyoxylate **1**.

sume that such an oligomerization occurs at high pH (> 6), which is also in line with the absence of signals for iminoacetate (**5a**) in the ^{13}C NMR spectra. A similar reaction between formaldehyde and ammonia leads quantitatively to hexamethylenetetramine.[7] The simplicity of the NMR spectra of **3a** indicates that the condensation product is highly symmetric; a hexamethylenetetramine derivative formed from **3a** could not have a symmetry that is consistent with the observations. Probably, in the present case the oligomerization terminates at the six-membered ring (**4a**), most likely the all-cis isomer. Imino compounds seem logical intermediates for such a cyclotrimerization.

Upon acidification of the sample the original ^{13}C NMR spectrum with exclusively glyoxylate signals was obtained once again, showing that these reactions are reversible.

In the ^1H NMR spectra analogous phenomena were observed: at low pH (<6) only a peak for glyoxylate (**1**, δ = 5.03 ppm) was observed, whereas at higher pH values a new peak at δ = 4.18 ppm appeared. In the ^{15}N-labeled compound the latter signal was a triplet with a splitting

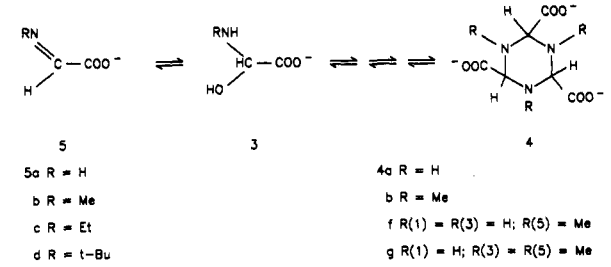
(7) Smolin, E. M.; Rapoport, L. *s-Triazines and Derivatives*; Interscience: New York, 1959; Chapter 10.

Table II. ^{13}C and ^1H Chemical Shifts (ppm) of 0.5 M Solutions of 3a–e in D_2O at 25 °C

species	pH	*C*OO	*C*H/*C*=N	alkyl (^{13}C)	C*H*	alkyl (^1H)
1	5.0	178.13	89.60		5.03	
4a	7.2	174.90	72.58		4.33	
	12.4	177.04	72.93		4.18	
4b	8.6	178.06	90.38	38.41	2.78	2.04
4f[a]	12.4	177.19	72.16	35.72	4.04	2.03
		177.65	81.00		3.76	
4g[a]	12.4	177.59	80.94	37.79	3.41	2.02
		177.12	91.02		3.01	
5b	12.5	172.29	163.14	47.28	7.69[b]	3.32[b]
5c	11.1	172.55	161.22	55.18	*c*	*c*
				16.29		
5d	11.2	173.59	156.83	59.00	*c*	*c*
				29.84		
3e	9.9	177.17	89.90	38.34	*c*	*c*
	12.3	177.55	88.80	39.66	*c*	*c*

[a] Measured in solutions of mixtures of **3a** and **3b** in D_2O. [b] $J(CH,CH_3)$ = 2.0 Hz. [c] Not measured.

Scheme II



of about 2.5 Hz. In addition at high pH a very small peak (<0.5%) was observed at 8.74 ppm, which may be ascribed to monomeric iminoacetate **5a**.

The ^{15}N NMR spectrum of the ^{15}N-labeled compound once again gave a single signal for ammonium glyoxylate (δ = −359.0 ppm) at low pH, whereas at high pH a major signal at −320 ppm showed up, which can be assigned to the oligomer **4a**. In addition a small signal for NH_3 (δ = −320.3 ppm) and some small unidentified other signals could be observed. The signals of NH_3 and **4a** were exchange broadened, as witnessed by the decrease of the line widths upon raising the temperature.

The ^{17}O NMR spectra of a sample of 5% ^{17}O-enriched **3a** in ^{17}O-depleted water at pH 9 showed only a sharp water signal at about 0 ppm ($\Delta\nu_{1/2}$ = 49 Hz) and a broad carboxylate signal at 263 ppm ($\Delta\nu_{1/2}$ = 425 Hz). Apparently the labeled hydroxyl oxygen exchanges rapidly with the bulk water oxygens.

The NMR spectra of the product from methylamine and glyoxylic acid (**3b**) were more complex at pH > 6. The ^{13}C NMR spectrum showed signals at 47.3, 163.1, and 172.3 ppm, which can be assigned to imine **5b**. This was confirmed by the presence of a quartet at 7.7 ppm and a doublet at 3.3 ppm (J = 2.0 Hz) in the ^1H NMR spectrum. The ^{13}C and ^1H spectra displayed, in addition, a set of signals at 38.4, 90.4, and 178.1 ppm and at 2.78 and 2.04 ppm, respectively, which are assigned to the oligomerization product **4b**. The *C*H nucleus has a chemical shift that is 17.5 ppm higher than that of the corresponding parent (N-unsubstituted) compound, which is about twice the β-substituent effect of a methyl group. Therefore, each CHCOO function should have two neighboring NCH_3 groups. The chemical shifts of **4b** were independent of the pH, in contrast to what was observed for **4a** and the carbinol **3e**. Apparently, the protonated form persists up to at least pH 12. The distribution of the various species of the *N*-methyl adduct as function of the pH is depicted in Figure 2.

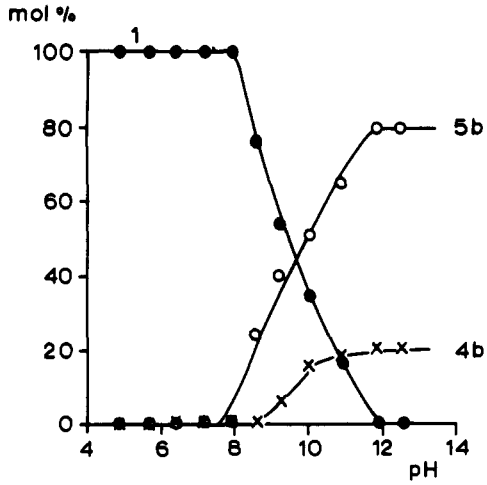


Figure 2. Distribution of species in a 0.5 M solution of **3b** in D_2O as a function of pH at 25 °C.

The structures of the hexahydrotriazines **4a** and **b** are confirmed by NMR spectra obtained of samples prepared from mixtures of **3b** and the unsubstituted adduct **3a**. Up to pH 7, only signals for glyoxylic acid (1) and methylamine (**2b**) were observed. Upon further increase of the pH, first signals for **4a** and a set of signals for a mixed compound with one methyl group (**4f**) emerged, and at somewhat higher pH also signals for a species with two N-methyl groups (**4g**, see Table II). Furthermore, signals for imine **5b** and various small unidentified signals were observed. Species **4b**, however, was not detected.

In the ^{13}C NMR spectrum of the *N*-ethyl compound up to pH 8 only the signals for ethylamine (**2c**) and glyoxylate 1 could be observed. At higher pH additional signals for the imine (**5c**) appeared at 16.3, 55.2, 161.2, and 172.6 ppm. Here, steric hindrance probably destabilizes the hexahydrotriazine **4c**.

An analogous behavior was shown by the *N*-*tert*-butyl compound **3d**. Here, the imine signals were present at pH > 10. Obviously, the addition of an alkylamine to glyoxylic acid is favorable above the pK_a of the concerning ammonium salt.

The *N*,*N*-dimethyl compound is not able to form either an imine or a dimer. Above pH 9, the intensity of the glyoxylate signals decreased, whereas new signals emerged, which have to be ascribed to the carbinol **3e** (see Table II). The chemical shifts of these signals showed a pH jump between pH 8 and 9, which can be associated with deprotonation of the ammonium function. The chemical shift difference between the *CH* signal in this sample and that in the solid state (see Table I), which is the corresponding zwitterionic form, is an agreement with the substituent effect for deprotonation of an ammonium group.

Mechanism of the Reaction between Glyoxylic Acid and Ammonia. The reactions described above were all performed with about 0.5 M solutions of **3**. Then the equilibria were established before a NMR spectrum could be measured. In the presence of an excess of ammonia the reactions slowed down, which allowed following the reaction with ^1H NMR spectroscopy.

Upon dissolution of hydroxyglycine (**3a**, 0.3 mol/L) in 20% ND_3 in D_2O (molar ratio ND_3/**3a** = 34.5), initially a peak at 4.58 ppm was observed in the ^1H NMR spectrum, which was assigned to hydroxyglycine (**3a**). This was confirmed by the ^{13}C spectrum, which showed initially a *CH* peak at 79.39 ppm. The increase in chemical shift upon going from the solid-state spectrum (see Table I) to this one is an agreement with the effect, which is generally

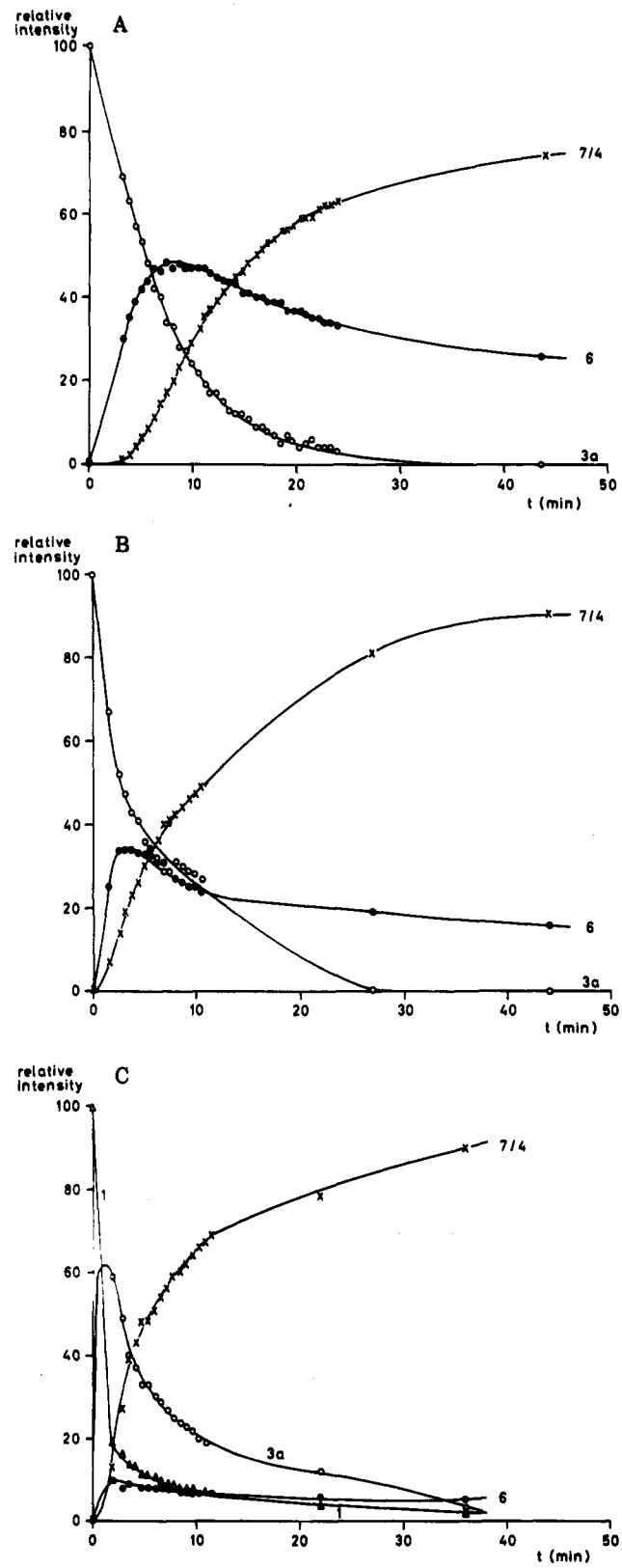
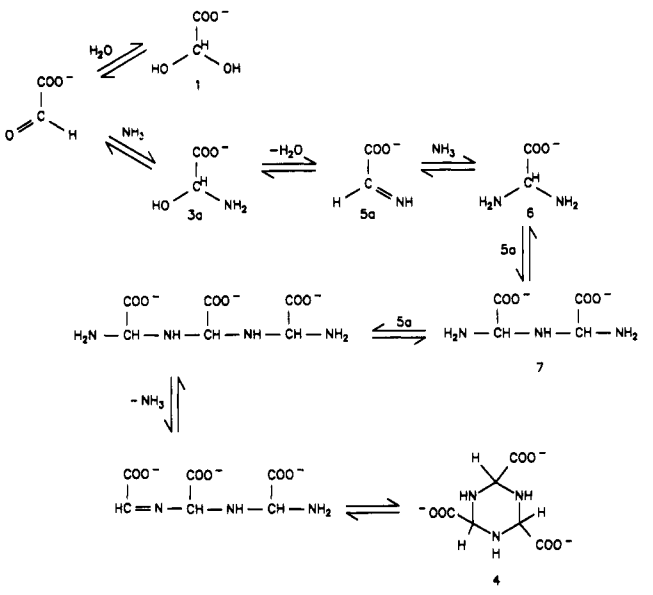


Figure 3. Plots of relative signal intensities in ^1H NMR spectra of hydroxyglycine (**3a**) or glyoxylic acid (1) and ND_3 in D_2O at 25 °C: (A) 0.31 M **3a**, 10.8 M ND_3; (B) 0.24 M 1, 6.9 M ND_3; (C) 0.19 M 1, 2.3 M ND_3.

observed upon deprotonation of the ammonium group of a zwitterion. This species was converted into another one with a ^1H signal at 4.02 ppm and a *CH* ^{13}C chemical shift of 69.24 ppm (see Figure 3A). On the basis of the relatively low values of these shifts compared to those of **3a** and **4a**, these signals were assigned to diaminoacetic acid

Scheme III



(6). In a consecutive step this compound gave species with chemical shifts identical to those of the hexahydrotriazine **4a**. The ^1H spectrum, however, showed in this case two hardly resolved signals at 4.17 ppm, after 60 h a small third peak at this position was observed. So probably the dimer **7** (see Scheme III), which has two diastereomeric forms, has about the same chemical shift as **4a**, and its conversion into the latter is relatively slow at this high ammonia concentration. The course of this reaction as a function of time is depicted in Figure 3A.[8] Analogous phenomena were observed when glyoxylic acid (1) was dissolved in 20% ND_3 in D_2O.

At lower ammonia concentrations the concentration of the intermediate diaminoacetate **6** was lower (see Figure 3B), and at molar ratios $ND_3/\mathbf{3a} \leq 12$ glyoxylate **1** was also present during the firt minutes of the reaction (see Figure 3C). During the course of the latter reactions, the molar ratio of glyoxylate and hydroxyglycine was about constant, indicating that the equilibrium between these species is established relatively fast. From these reactions the equilibrium constant K (=[1][NH_3]/[**3a**]) has been estimated to be about 1 mol/L.

From these phenomena it can be concluded that at high pH glyoxylate is converted into the hexahydrotriazine derivative **4a** via the pathway depicted in Scheme III. The preparations of the solid hydroxyglycines **3** were performed at about the isoelectric point at 0 °C. Under these conditions the zwitterion **3** precipitates selectively from the reaction mixture.

When an excess of glyoxylate was applied,[9] the ^1H NMR spectrum of the reaction mixture became very complex: at least 10 peaks between 3.6 and 5.2 ppm and peaks at 7.8 and 7.9 ppm were observed. Probably under these conditions pathways starting with a condensation between iminoacetate and hydroxyglycine occur, leading to less symmetric species. It cannot be excluded that these pathways also play a role during the formation of **4** upon dissolution of **3** in water.

Conclusions

The present study shows that the view of Perkin that glyoxylic acid forms hydroxyglycine upon neutralization with ammonia[3] is correct, as far as the precipitate is concerned. In aqueous solution, however, the situation is more complicated: at low pH (<6) glyoxylate is the only species, whereas at high pH (>6) the highly reactive iminoacetate is produced, which cyclotrimerizes to *all-cis*-hexahydro-*s*-triazine-2,4,6-tricarboxylate. N-alkyl-substituted hydroxyglycines show a similar behavior, but for alkyl groups larger than methyl self-condensation does not occur. It may be expected that the hydroxyglycines are versatile reagents in organic synthesis. Work on their use in the synthesis of dihydroquinazolinecarboxylic acids is in progress.[10]

Experimental Section

Materials. ^{17}O water (10% labeled) was purchased from Icon Services, Inc., Summit, NJ, and ammonium-^{15}N chloride (99% isotopically pure) from MSD Isotopes, Montreal, Canada.

NMR Measurements. The solid-state NMR spectra were recorded with a Varian VXR-400 S spectrometer equipped with a Doty V153 multinuclear solid-state probe. A 5-mm Kel-F rotor was used, and the spinning rate was 6 kHz. For ^{13}C NMR, cross-polarization with contact times of 0.4–1.4 ms was used. ^{15}N NMR spectra were measured both undecoupled and with gated decoupling. For ^{13}C measurements, the sample was spun inside the probe for some minutes. Then the rotor was opened and the cylindrical hole in the center of the sample was filled with adamantane, which was used as reference (tertiary C at δ = 38.3 ppm). The ^{15}N chemical shifts were measured with respect to solid $^{15}NH_4Cl$ as external reference.

The ^{13}C and ^{17}O NMR spectra were recorded with a Nicolet NT-200 WB or a Varian VXR-400 S spectrometer at 25 °C. The quantitative ^{13}C NMR spectra were measured with the use of a gated decoupling technique (decoupler on during acquisition only), a 60° flip angle, and a waiting time of 30 s. The ^1H NMR spectra were measured with the Varian VXR-400 S apparatus. ^{13}C chemical shifts (in the liquid state) were measured with respect to the ^{13}C CH_3 signal of *tert*-butyl alcohol at δ = 31.2 ppm as internal standard. The ^1H chemical shifts were referenced with respect to its ^1H CH_3 signal at 1.20 ppm, and the ^{17}O chemical shifts were measured with respect to tap water as external standard. The liquid-state ^{15}N spectra were measured with a saturated solution of $^{15}NH_4Cl$ in a coaxial capillary as standard (δ = −359 ppm).

The kinetic ^1H NMR measurements were performed by mixing the appropriate amounts of glyoxylic acid or hydroxyglycine and ND_3 in D_2O, and then after the sample was inserted into the NMR, spectra of four acquisitions with a flip angle of 20° and an acquisition delay of 5 s were run continuously. The first spectrum could be started 2–3 min after mixing the reactants. The peak areas were determined via simulation using Lorenzian line shapes and the deconvolution program of Varian.

Other Analyses. Attempts to measure EI mass spectra failed because of explosive decomposition of the sample upon heating, whereas application of the FAB method failed due to chemical reactions between the sample and the matrix.

Hydroxyglycine (3a). To an ice-cold solution of 4.60 g (0.05 mol) of glyoxylic acid monohydrate in 10 mL of water was added an ice-cold solution of 9.50 g (0.1 mol) of ammonium acetate monohydrate in 10 mL of water. Within 2 min a cloudy reaction mixture was obtained. After 45 min of stirring and 2 h of standing at 0 °C the precipitation was complete. Filtration and washing with water and methanol yielded 4.11 g (90.3%) of white crystals, dec 105–106 °C. Anal. Calcd for $C_2H_5NO_3$: C, 26.36; H, 5.54; N, 15.39. Found: C, 26.13; H, 5.63; N, 15.11.

^{15}N-Labeled Hydroxyglycine. This compound was prepared analogously starting from ^{15}N-labeled ammonium chloride.

^{17}O-Labeled Hydroxyglycine. This compound was synthesized by heating glyoxylic acid in 10% ^{17}O-enriched water at 80–90 °C for 8 h, followed by evaporation of the solvent. The compound obtained was converted into ^{17}O-labeled **3a** according

(8) In addition to the signals mentioned, some tiny other ones were observed at 3.87, 4.38, and 7.1 ppm. The intensities of these signals were almost constant during the course of the reactions.

(9) The pH was adjusted to 12 by addition of diluted NaOD in D_2O.

(10) Hoefnagel, A. J.; Peters, J. A.; Sinnema, A.; van Bekkum, H. To be published.

to the procedure described above.

Hydroxysarcosine (3b). Through an ice-cold solution of 4.60 g (0.05 mol) of glyoxylic acid monohydrate in 10 mL of water was bubbled methylamine gas, by which the pH of the solution in 1 h rose from 2.60 to 6.30. Filtration, after two days of standing at 0 °C and subsequent washing with water and methanol, yielded 2.94 g (56.0%) of white crystals, dec 100–101 °C. Anal. Calcd for C_3H_7NO3: C, 34.26; H, 6.72; N, 13.33. Found: C, 34.19; H, 6.56; N, 13.49.

***N*-Ethylhydroxyglycine (3c).** The above procedure yielded with ethylamine gas 2.00 g (33.6%) of white crystals, dec 92.5–93.5 °C. Anal. Calcd for $C_4H_9NO_3$: C, 40.31; H, 7.62; N, 11.76. Found: C, 39.99; H, 7.30; N, 11.81.

***N*-*tert*-Butylhydroxyglycine (3d).** This compound was prepared using the same procedure as described for **3c**, dec 120–121 °C. Anal. Calcd for $C_6H_{13}NO_3 \cdot 0.5H_2O$: C, 46.12; H, 9.04; N, 8.97. Found: C, 46.09; H, 8.61; N, 8.98.

***N*,*N*-Dimethylhydroxyglycine (3e).** This compound was prepared using the same procedure as described for **3c**, dec 126–127 °C. Anal. Calcd for $C_4H_9NO_3$: C, 40.31; H, 7.62; N, 11.76. Found: C, 40.26; H, 7.45; N, 11.64.

Acknowledgment. Thanks are due to A. Sinnema and A. van Estrik for measuring some of the NMR spectra and for helpful discussions.

Registry No. **2a**, 7664-41-7; **2b**, 74-89-5; **2c**, 75-04-7; **2d**, 75-64-9; **2e**, 124-40-3; **3a**, 4746-62-7; **3b**, 141555-52-4; **3c**, 141555-53-5; **3d**, 141555-54-6; **3e**, 141555-55-7; **4a**, 141555-56-8; **4b**, 141555-57-9; **4f**, 141555-58-0; **4g**, 141555-59-1; **5a**, 141555-60-4; **5b**, 141555-61-5; **5c**, 141555-62-6; **5d**, 141555-63-7; **6**, 103711-21-3; (*R**,*R**)-**7**, 141555-64-8; (*R**,*S**)-**7**, 141555-65-9; glyoxylic acid, 298-12-4; ammonium acetate, 631-61-8; ammonium glyoxylate, 51276-19-8; oxygen, 7782-44-7.

A Method for Synthesis of Fluorine Compounds Using Abnormal Grignard Reaction of Halothane

Toshiyuki Takagi, Atsushi Takesue, Mayumi Koyama, Akira Ando, Takuichi Miki, and Itsumaro Kumadaki*

Faculty of Pharmaceutical Sciences, Setsunan University, Nagaotoge-cho, Hirakata, Osaka 573-01, Japan

Tomohiro Sato

Shionogi Research Laboratories, Sagisu, Fukushima-ku, Osaka 553, Japan

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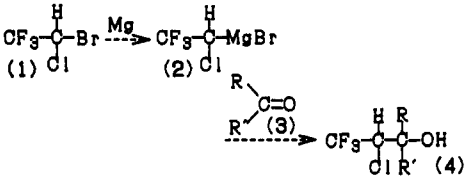
The reaction of 2-bromo-2-chloro-1,1,1-trifluoroethane (1) with 2-octanone (**3a**) in the presence of magnesium did not give 2-chloro-1,1,1-trifluoro-3-methyl-3-nonanol (**4a**) but 2-bromo-2-chloro-1,1,1-trifluoro-3-methyl-3-nonanol (**5a**) and 2-chloro-1,1-difluoro-3-methyl-1-nonen-3-ol (**6a**). This suggested that the primary Grignard reagent, 1-chloro-2,2,2-trifluoroethylmagnesium bromide (2), reacted with excess 1 rather than with the ketone **3a** to give 1-bromo-1-chloro-2,2,2-trifluoroethylmagnesium bromide (8), which added to the ketone to give **5a**. Detection of 1,1,1-trifluoro-2-chloroethane supported this mechanism. Compound **5a** was formed preferentially at −53 °C, and as the reaction mixture was warmed to 0 °C, the amount of **5a** decreased, while that of **6a** increased. Therefore, compound **6a** must be formed by reduction of **5a** with excess magnesium. Treatment of **6a** with hydrogen fluoride gave 2-chloro-1,1,1-trifluoro-3-methyl-2-nonene (**9a**). Cyclohexanone and acetophenone reacted similarly to give corresponding products.

Introduction

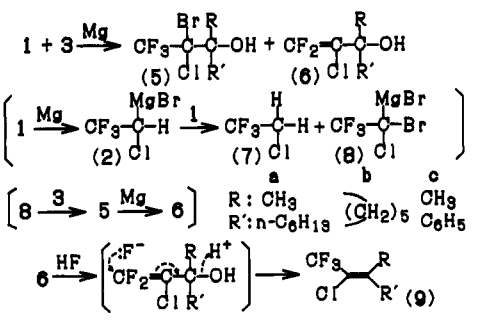
We are developing new methods for syntheses of fluorine compounds. We have reported trifluoromethylation of halogen compounds with trifluoromethyl iodide and copper powder[1] and ene reaction of trifluoromethyl carbonyl compounds.[2] As an extension of this research, we planned to use halothane, 2-bromo-2-chloro-1,1,1-trifluoroethane (1), as a building block and examined its reaction with a ketone in the presence of magnesium. We expected that the bromine of 1 would react with magnesium to form a Grignard reagent **2** and that **2** would add to a carbonyl group of the ketone **3** to give 2-chloro-1,1,1-(trifluoroethyl)carbinol **4**. This product is a polyfunctional trifluoromethyl compound and was expected to be a good precursor for various types of fluorine compounds (Scheme I).

Hemer et al. reported reaction of polyhalogenoethanes with a Grignard reagent in the presence of carbonyl compounds, where exchange of the Grignard reagent occurred and polyhalogenated alcohols were obtained.[3] Thus, treatment of 1,1,1-trichloro-2,2,2-trifluoroethane (Freon 113) with isopropylmagnesium bromide gave 1,1-dichloro-2,2,2-trifluoroethylmagnesium bromide, which reacted with carbonyl compounds to give some (1,1-dichloro-2,2,2-trifluoroethyl)carbinols. However, they re-

Scheme I



Scheme II



* Correspondence should be addressed to this author.

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