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NMR Studies of Substituted 2,3-Diaminopropenoates

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The orientation of substituted amino groups around the double bond in 2,3-diaminopropenoates, versatile agents in the syntheses of heterocyclic systems, was determined in solution by NMR techniques. Nuclear Overhauser enhancement and long-range ^{13}C–^{1}H coupling constants were measured by NOESY or ROESY and HMBC experiments, respectively. © **1997 by John Wiley & Sons, Ltd.**

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INTRODUCTION

Recently, the synthesis of various derivatives of pyran-2-one and fused pyran-2-one has attracted great interest, since many of them have been found as nonpeptide HIV protease inhibitors.[1,2]

2-Amino-substituted 3-dimethylaminopropenoates are versatile synthons for the preparation of 2*H*-pyran-2-ones and other heterocyclic systems with an amino acid structural element incorporated or partially incorporated into the cyclic systems.[3,4] In this connection, the following compounds have been prepared recently: methyl (*Z*)-2-benzoylamino-3-dimethylaminopropenoate (**1**),[5] methyl (*Z*)-2-acetylamino-3-dimethylaminopropenoate (**2**) and methyl (*Z*)-2-acetylamino-3-(2-methyl-3-nitrophenyl)aminopropenoate (**3**),[6] ethyl (*Z*)-2-[2,2-bis(ethoxycarbonyl)vinyl]amino-3-dimethylaminopropenoate (**4**)[7] and ethyl 2-(2-benzoyl-2-ethoxycarbonyl-1-ethenyl)amino-3-dimethylaminopropenoate (**5**) (Fig. 1).[8] X-ray analyses have been carried out for compound **1** and some of its derivatives, including dipeptides,[9] and for compound **5**,[7] showing that in the solid state the orientation of both substituted amino groups around the double bond in both compounds is *Z*. However, in solution, the presence of another isomer and/or rotamer has been observed in some instances.[8]

Recently, it has been shown that ^{13}C–^{1}H long-range coupling constants may be used in the configuration assignment of some trisubstituted alkenes. It has been successfully applied as a criterion for the *E*–*Z* differentiation of ethyl 2-acyloxy-2-alkenoates even if only one isomer is available.[10]

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RESULTS AND DISCUSSION

The orientation of groups around the C=C double bond in compounds **1**–**5** was studied by NOESY, ROESY and HMBC techniques in DMSO-d_6 and $CDCl_3$. The proton chemical shifts (Table 1) were assigned using the 1D ^{1}H spectra and confirmed by the analysis of NOESY and ROESY spectra.

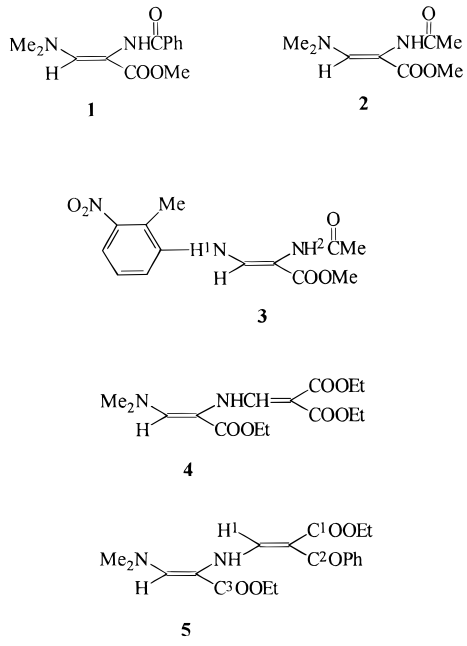

Figure 1. Structures of compounds **1**–**5**.

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Table 1. ^{1}H chemical shifts for compounds 1–5 in DMSO-d_6 and $CDCl_3$

	1		2				3[a]		4		5[a,b]		
			Isomer 1		Isomer 2						Isomer 1		Isomer 2
	DMSO	$CDCl_3$	DMSO	$CDCl_3$	DMSO	$CDCl_3$	DMSO	$CDCl_3$	DMSO	$CDCl_3$	DMSO	$CDCl_3$	DMSO
Me_2N	2.96	3.02	2.92	2.99	3.00	3.06			2.97	2.99	3.01	3.01	3.01
H	7.35	7.46	7.22	7.35	7.26	7.31	7.58	7.53	7.26	7.22	7.30	7.25	7.27
H^1											7.80	7.98	7.46
CH									7.69	7.88			
NH	8.98	6.95	8.38	6.26	7.83	6.03	8.15	9.17	9.49	9.70	10.74	11.09	9.51
NH^2							9.06	7.55					
COOMe	3.52	3.66	3.50	3.64	3.55	3.69	3.67	3.80					
Ph	7.46^m	7.43^m					7.36–7.44^{m,p}, 7.48^o	7.18^m, 7.28^p, 7.35^o			7.30–7.47	7.36^m, 7.39^p, 7.49^o	7.30–7.47
	7.53^p	7.50^p											
	7.89^o	7.82^o											
COMe			1.85	2.07	1.69	1.89	2.02	2.21					
Me							2.26	2.38					
Et-CH_3									1.17, 1.18, 1.21	1.23, 1.26, 1.35	0.88^{Et1}	0.94^{Et1}	0.86^{Et1}
											1.19^{Et3}	1.24^{Et3}	1.18^{Et3}
Et-CH_2									4.03, 4.04, 4.13	4.16, 4.19, 4.26	3.87^{Et1}	3.97^{Et1}	3.95^{Et1}
											4.08^{Et3}	4.17^{Et3}	4.07^{Et3}

[a] ^{o,m,p} indicates the *ortho*, *meta* and *para* protons of the phenyl proton resonances.
[b] ^{Et1} indicates the protons of the C^1OOEt group and ^{Et3} indicates the protons of the C^3OOEt group of **5**.

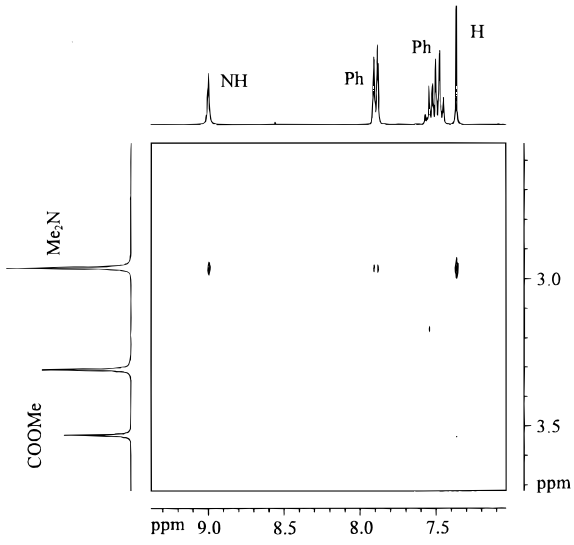

Figure 2. Partial NOESY spectrum of **1** measured in DMSO-d_6 at 302 K.

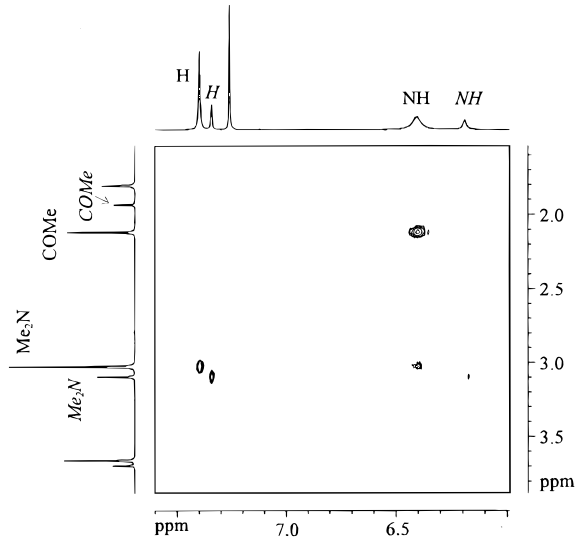

Figure 3. Partial ROESY spectrum of **2** measured in $CDCl_3$ at 275 K. Both isomers possess the NOE between the NH and NMe_2 protons characteristic of the *Z* form but only one has the NOE between the NH and COMe protons, indicating the *cis–trans* isomerism of the amide bond.

Compounds **1**, **3** and **4** exist as a single isomer in both solvents. For the compound **2** two sets of signals are found in the ratio 10:1 and 10:3 in DMSO-d_6 and $CDCl_3$, respectively. Compound **5** also exists as two isomers in DMSO-d_6 in the ratio 5:3, while one isomer is present to the extent of >95% in $CDCl_3$. All compounds have the same type of cross peaks in NOESY or ROESY spectra in both solvents (Table 2), indicating that the orientation of groups around the double bond is not influenced by the type of solvent.

The orientation of groups around the double bond for a compound of the type **1** can be easily determined by the analysis of NOEs. The NOE between the NH proton and the Me protons can only be seen in the case of *Z* orientation. Indeed, compounds **1**, **2**, **4** and **5** possess the NOE between the NH proton and the NMe_2 protons, indicating that all of them exist in the *Z* form (Table 2, Fig. 2) concerning the orientation around the double bond to which both amino groups are attached.

In the case of compound **3**, NOE between NH protons is expected when the orientation around the double bond is *Z*. This NOE could not be observed in DMSO-d_6 owing to the strong exchange peak between NH protons or in $CDCl_3$ at 275 K owing to overlap between the H and NH^2 resonances. However, the observation of weak NOE between H and COOMe protons in both solvents indicates that **3** also exists in the *Z* form.

The isomerization of compound **2** does not arise from the different orientations of the groups around the double bond, which is in the *Z* form for both isomers, but from the *cis–trans* configuration around the amide bond. The major isomer has the NOE between NH and COMe protons in both solvents (Table 2, Fig. 3), which is possible only with the *trans* orientation of the amide bond. This NOE is lacking for the minor isomer, indicating that the amide bond of this isomer adopts the *cis* configuration.

Table 2. Results of the NOESY or ROESY measurements of the compounds 1–5 in DMSO-d_6 and $CDCl_3$

Compound	Solvent	Cross peaks			
1	DMSO[a]	Me_2N–NH	Me_2N–Ph	Me_2N–H	
	$CDCl_3$ [a]	Me_2N–NH	Me_2N–Ph	Me_2N–H	
2	DMSO[a]	Me_2N–NH	Me_2N–H	NH–COMe	
	Isomer 2	Me_2N–NH	Me_2N–H		
	$CDCl_3$ [b]	Me_2N–NH	Me_2N–H	NH–COMe	
	Isomer 2	Me_2N–NH	Me_2N–H		
3	DMSO[a]	H–COOMe	NH^1–H	NH^1–Me	NH_2–COMe
	$CDCl_3$ [b]	H-COOMe	NH^1–H	NH^1–Me	NH^2–COMe
4	DMSO[a]	Me_2N–NH	Me_2N–H	Me_2N–CH	
	$CDCl_3$ [a]	Me_2N–NH	Me_2N–H		
5	DMSO[a]	Me_2N–NH	Me_2N–H	Me_2N–H^1	
	Isomer 2	Me_2N–NH	Me_2N–H		
	$CDCl_3$ [b]	Me_2N–NH	Me_2N–H	Me_2N–H^1	

[a] Data from the NOESY spectra measured at 302 K.
[b] Data from the ROESY spectra measured at 275 K.

Both isomers of **5** possess the NOE between the NH proton and the NMe_2 protons, indicating that isomerization of **5** in DMSO-d_6 arises from the orientation around the other double bond, to which COPh and COOEt groups are attached. No NOEs between the NH or H^1 proton with the Ph or Et protons, which could determine the orientation around this double bond, were observed. Therefore, the long-range ^{13}CO–^1H coupling constants were evaluated from the antiphase splitting of cross peaks in the HMBC spectrum (Fig. 4). The small value of 3.7 Hz for $^3J(C^1O,H^1)$ of the major isomer is characteristic of the *cis* orientation of the H^1 proton with respect to the C^1O carbonyl, i.e. for the *E* orientation around this double bond. The minor isomer has a large $^3J(C^1O,H^1)$ of 10.0 Hz, pointing to the *trans* orientation of the H^1 proton with respect to the C^1O carbonyl, i.e. to the *Z* form. The value of 3.8 Hz for $^3J(C^1O,H^1)$ in $CDCl_3$ indicates the *E* form. Thus **5** exists in DMSO in *E,Z* and *Z,Z* forms in the ratio 5:3, whereas in $CDCl_3$ the *E,Z* isomer is present to the extent of >95%. The values of $^3J(CO,H)$ for the *E* and *Z* forms of **5** compare well with $^3J(CO,H)$ for ethyl 2-acyloxy-2-alkenoates, which are 2.9–3.8 Hz for the *Z* and 9.5–10.1 Hz for the *E* isomers.[10]

For the 3-amino-substituted 2-benzoylpropenoates, characteristic differences in chemical shifts between the CH and NH protons for the *Z* and *E* isomers were observed: $\Delta\delta(Z) = 2.52$–2.97 ppm and $\Delta\delta(E) = 3.00$–4.67 ppm in $CDCl_3$.[11] Compounds **3** and **5** contain the same structural element, HNCH, with differences in chemical shifts between the two protons of 0.57, 1.64, 2.94, 3.11 and 2.05 ppm for **3** in DMSO and $CDCl_3$, for isomer 1 of **5** in DMSO and $CDCl_3$ and for isomer 2 of **5** in DMSO, respectively. The difference between the chemical shifts of the two protons is smaller for the *Z* than for the *E* isomer also for **3** and **5**, but in comparison with the 3-amino-substituted 2-benzoylpropenoates the absolute differences are smaller, especially for the *Z* isomer. This result indicates that chemical shift difference between the CH and NH protons of the HNCH structural element cannot be used for the differentiation between *E* and *Z* isomers in an absolute manner.

X-ray analysis of **1** and **5** showed the same orientation of both substituted amino groups around the double bond as found in solution, i.e. the *Z* form,[7,9] whereas for the **2**, **3** and **4** no suitable crystals could be grown.

EXPERIMENTAL

NMR spectra were measured at a constant temperature of 302 K on a Bruker DPX-300 spectrometer, with a 5 mm indirect detection probe, operating at 300.13 MHz. The ROESY spectra of compounds **2**, **3** and **5** in $CDCl_3$ were measured at 275 K. The sample concentrations in DMSO-d_6 and $CDCl_3$ were 30 mM, except for the measurement of the HMBC spectrum of **5** where a 100 mM concentration was used. ^1H NMR spectra were referenced to the solvent ($\delta CDCl_3 = 7.24$ ppm, δDMSO-$d_6 = 2.495$ ppm).

NOESY[12] spectra were acquired in the phase-sensitive mode using States–TPPI quadrature detection in F_1.[13] Spectra were recorded with 4096 data points in the t_2 dimension, 512 t_1 increments, spectral widths of 3.5 kHz, 16 to 32 scans, a mixing time of 150 or 300 ms and a relaxation delay of 1 s.

The phase-sensitive ROESY[14–16] spectra were recorded with 4096 data points in the t_2 dimension, 512 t_1 increments, spectral widths of 3.5 kHz, 16 to 32 scans, continuous spin-lock field, a mixing time of 150 or 300 ms and a relaxation delay of 1 s. Quadrature detection in F_1 was provided by time-proportional phase incrementation (TPPI).[17]

Data were zero-filled twice and apodizied with a squared sine-bell function shifted by $\pi/2$ in both dimensions.

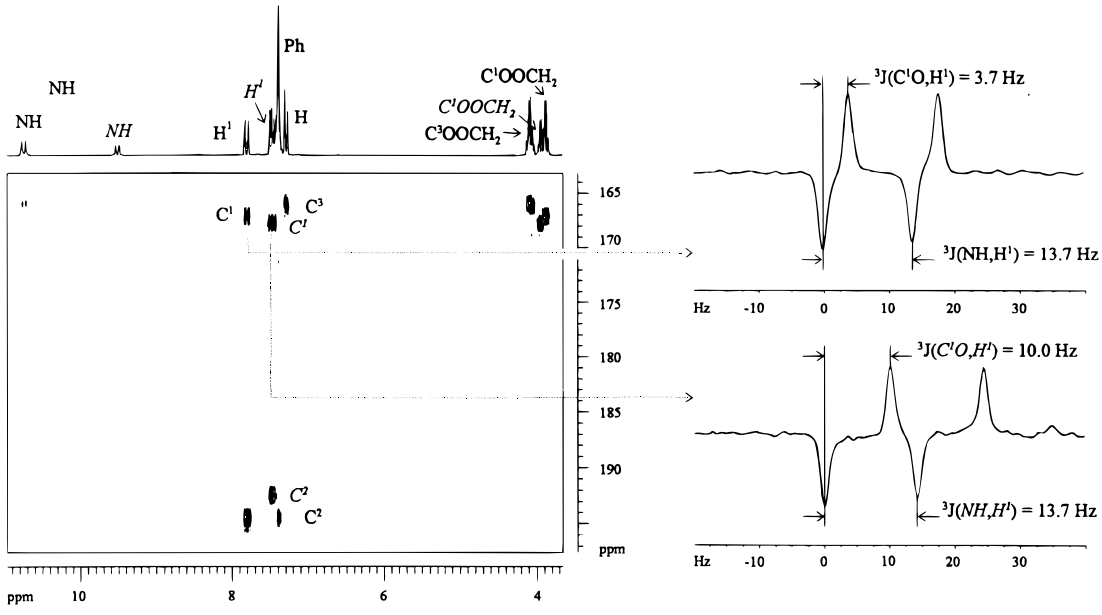

Figure 4. Carbonyl part of the HMBC spectrum of **5** in DMSO-d_6 with traces containing the $^3J(C^1O,H^1)$ couplings of both isomers. The cross peaks of the minor conformer are indicated in italics.

The phase-sensitive HMBC[18,19] spectra were recorded with 8192 data points in the t_2 dimension, 64 scans, 312 t_1 increments, a spectral width of 3.5 kHz in the t_2 and 11 kHz in the t_1 dimension and a relaxation delay of 1 s. Quadrature detection in F_1 was provided by TPPI.[17]

Data were zero-filled twice and apodizied with a squared sine-bell function shifted by $\pi/2$ in both dimensions. The slices containing coupling information were extracted from the 2D spectra, inverse Fourier transformed, zero-filled and processed with a squared sine-bell function shifted by $\pi/2$.

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