# Synthesis of Triethyl *N*-Formyl-*N*-phosphonomethylglycinate and Diethyl *N*-Formyl-*N*-phosphonomethylglycine and Studies of Their Rotational Conformers by Dynamic NMR

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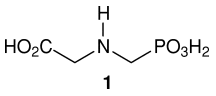
Reaction of ethyl *N*-phosphonomethylglycinate with triethyl orthoformate gave a mixture of triethyl *N*-formyl-*N*-phosphonomthylglycinate (**3**) and diethyl *N*-formyl-*N*-phosphonomethylglycine (**4**), the rotational barriers of which have been investigated theoretically and experimentally.

The disclosure of herbicidal activity of *N*-phosphonomethylglycine (**1**, *glyphosate*) in 1971, instituted a milestone in biochemistry of aminophosphonic acids.[1]

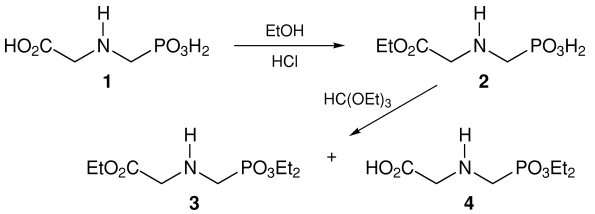


**1**

**Fig. 1**

Despite inhibiting 5-*enol*-pyruvylshikimate-3-phosphate synthase, an important plant and bacterial enzyme, and thus blocking aromatic amino acids biosynthesis, *N*-phosphonomethylglycine does not exhibit antibacterial activity.[1] This may result from its inability to permeate through bacterial cytoplasmic membrane. Attachment of additional amino acids to *N*-phosphonomethylglycine should result in phosphono peptides that should overcome this limitation and might be promising antibacterials. The first step of phosphono peptide synthesis is the preparation of aminophosphonate esters which are suitable substrates for further syntheses.

Ethyl *N*-phosphonomethylglycinate **2** readily underwent reaction with ethyl orthoformate yielding triethyl *N*-phosphonomethylglycinate **3** (Scheme 1). In some cases, however, the product was accompanied by a side-product, diethyl *N*-phosphonomethylglycine **4**. We have found that the composition of the product was strongly dependent on the quality of ethyl orthoformate, namely on the presence of trace amounts of water which causes de-esterification of the carboxylic moiety.



**Scheme 1**

Examination of the NMR spectra of compounds **3** and **4** in $(CD_3)_2SO$, $D_2O$ and $CDCl_3$ clearly show the presence of two conformers in each case. This was additionally supported by the presence of coalescence of doubled signals, at temperatures above 370 K, in $^1H$ and $^{31}P$ NMR spectra, taken in $(CD_3)_2SO$. Because of good separation of the peaks and lack of overlapping signals, $^{31}P$ NMR spectra and the formyl region of the $^1H$ NMR spectra were chosen to determine free energies of activation, $\Delta G^{\ddagger}$, of restricted rotation around the partially double formyl C–N bond. Although phosphorus spectra seemed to be ideal for dynamic NMR studies we were unable to use them successfully because the $^{31}P$ chemical shifts appeared to be significantly dependent on temperature. Thus, phosphorous decoupled $^1H\{^{31}P\}$ spectra were used for further analysis and the obtained activation parameters are given in Table 3.

Activation parameters found for compounds **3** and **4** are similar to values in the literature for rotation about C–N bonds in *N*,*N*-disubstituted amides.[13]

We have also applied several types of theoretical approaches to study rotational barriers in compounds **3** and **4**. In each case, calculations provided two values of the activation enthalpy ($\Delta H^{\ddagger}$) which derive from the fact that the ground states for both isomers have different energies. A considerable dispersion of $\Delta H^{\ddagger}$ values were observed which appeared to be strongly dependent on the applied computation method. *Ab initio* methods, although requiring considerable computer capacity, gave quite reasonable agreement with experimental data when considering that the calculations provide rotational barriers in the gas phase. Very good results were obtained when calculations were carried out using the HF/6-31*/MP2/6-31* method which afforded barriers of rotation consistent with experimental values to within $\pm 3$ kcal mol$^{-1}$ (1 cal = 4.184 J). Much less accurate results were obtained when using less time-consuming and more restrictive semi-empirical methods (AM1 and PM3).

Calculations using molecular mechanics were performed using CVFF, AMBER and CFF91 force fields which were parameterized to reproduce peptide and protein properties. Our results alongside with those which describe the use of

**Table 3** Activation parameters for internal rotation in compounds **3** and **4** in $(CD_3)_2SO$

| Compound | $\Delta\nu$/Hz | Coalescence temperature/K | $\Delta H^{\ddagger}$/kcal mol$^{-1}$ | $\Delta S^{\ddagger}$/J cal mol$^{-1}$ | $\Delta G^{\ddagger}$/kcal mol$^{-1}$ | $E_a$/kcal mol$^{-1}$ |
|---|---|---|---|---|---|---|
| **3** | 14.6 | 375 | 23.6 | 6.9 | 20.7 | 24.3 |
| **4** | 14.0 | 376 | 22.2 | 10.5 | 19.6 | 22.9 |

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the MM3 force field in similar calculations[13c] show that empirical methods could be also successfully used for prediction of rotational barriers in amides. The obtained values are, however, strongly dependent on the type of the applied force field.

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References: 24

Table 1: $^{31}P$, $^{1}H$, and $^{13}C$ NMR data for compound **3** in $CDCl_3$

Table 2: $^{31}P$, $^{1}H$, and $^{13}C$ NMR data for compound **4** in $D_2O$

Table 4: Calculations of the rotational barriers (kcal $mol^{-1}$) in compounds **3** and **4** using quantum mechanics.

Table 5: Calculations of the rotational barriers (kcal $mol^{-1}$) in compounds **3** and **4** using molecular mechanics.

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