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4-Oxo-α-amino acids: a caution when determining absolute configurations by ^{1}H NMR using MPA derivatization and Ba^{2+} complexation

Marion A. Earle and Philip G. Hultin*

Department of Chemistry, University of Manitoba, Winnipeg, MB, Canada R3T 2N2

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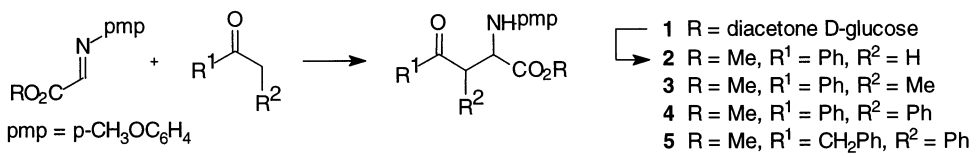
Abstract

A method for determining the absolute configurations of chiral amines based on changes in the ^{1}H NMR spectra of their (*R*)-MPA amides on addition of Ba^{2+} was applied to both enantiomers of a series of γ-oxo-α-amino acid methyl esters. The chemical shift changes $\Delta\delta^{Ba}$ observed for these compounds were inconsistent with the recently proposed model relating them to the absolute configuration of the amino group. These results suggest that care must be taken when using this technique. © 2000 Published by Elsevier Science Ltd.

The asymmetric synthesis of γ-oxo-α-amino acids has attracted considerable recent attention.[1] Our interest in carbohydrate chiral auxiliaries[2] led us to study the aldol-like condensations of some ketone enolates with a diacetone-D-glucose derived glyoxylimine, as a means of preparing such compounds. The *relative* configurations (*syn* versus *anti*) of our products were readily identified by converting them to the methyl esters **2**–**5** (Scheme 1). These were compared with the corresponding racemic esters whose structures were known from X-ray crystallography. Difficulties arose, however, in determining the *absolute* configurations of the glucose-linked adducts.[3]



Scheme 1.

* Corresponding author.

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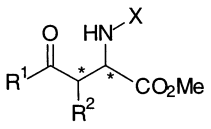
Our first attempts using MTPA amides[4,5] failed. Mosher's model[6] for such compounds predicts trends in $\Delta\delta^{SR}$ in terms of three conformers, defined by the CF_3–C–C=O dihedral. The synperiplanar (sp) conformer[7] is thought to control the differences between the NMR spectra of (*R*)- and (*S*)-MTPA amides. The spectra of *anti* diastereomers **6a**/**b** prepared from **3** (Fig. 1) displayed the expected trends in $\Delta\delta^{SR}$. However, for *syn* compounds **7a**/**b**, both the ester and β-H signals shifted downfield ($\Delta\delta^{SR}>0$). This suggested that a simple conformational model might not apply to our compounds.



X	R^1	R^2	Config.	
MTPA	Ph	Me	*anti*	**6a/b**
MTPA	Ph	Me	*syn*	**7a/b**
(*R*)-MPA	Ph	H	2*S*	**8a**
(*R*)-MPA	Ph	H	2*R*	**8b**
(*R*)-MPA	Ph	Ph	*anti*	**9a/b**
(*R*)-MPA	Ph	Ph	*syn*	**10a/b**
(*R*)-MPA	CH_2Ph	Ph	*anti*	**11a/b**

Figure 1.

Our attention was drawn to a promising new technique based on α-methoxyphenylacetic acid (MPA) amides, reported by Riguera et al.[8] The MPA amides have only two important conformers, the ap and the sp (Fig. 2),[9] with the former being more stable. The method uses Ba^{2+} complexation to stabilize the sp conformer. The authors reported consistent changes in the shielding effects of the MPA phenyl group on protons in L_1 and L_2, and developed empirical rules linking these with the amine stereochemistry. The signs of $\Delta\delta^{Ba}$ for corresponding protons in MPA amides of enantiomeric amines were opposed, as well as the signs of $\Delta\delta^{Ba}$ for protons in L_1 and L_2. The reported examples included amines containing aromatic moieties or groups that might compete for coordination with Ba^{2+}.

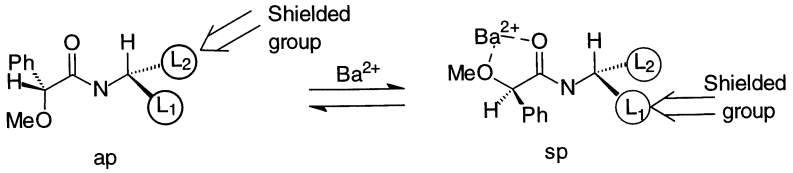


Figure 2.

We prepared (*R*)-MPA derivatives **8**–**11** from racemic *syn* and *anti* γ-oxo-α-amino acid methyl esters **2**, **4** and **5**. The diastereomeric amides were separated whenever possible. We also synthesized authentic (2*S*)-**8a** from (*S*)-**2** obtained using our chiral auxiliary.[10] The 300 MHz ^{1}H NMR spectra of **8**–**11** in CD_3CN were acquired before and after the addition of two equivalents of $BaClO_4$. Table 1 shows the $\Delta\delta^{Ba}$ values for signals expected to be diagnostic.

For **8a**, the ester –OMe signal shifted upfield (L_1, $\Delta\delta^{Ba}<0$) and the signals of the other substituents shifted downfield (L_2, $\Delta\delta^{Ba}>0$) in the presence of Ba^{2+}, in accord with Riguera et al.'s observations for the *S* configuration. However, for **8b** the method failed. Shielding of the ester –OMe group decreased on addition of Ba^{2+} (i.e. L_2, $\Delta\delta^{Ba}>0$), but the signals from the β-CH_2 and the phenyl groups also moved downfield. The other amides showed similar inconsistencies. The *anti* compounds **9a**/**b** and **11a**/**b** all exhibited increased shielding of their ester groups *and* their β-hydrogens ($\Delta\delta^{Ba}<0$). The γ-CH_2 protons of **11a** displayed an increase, and **11b** a decrease in shielding. For *syn* compounds **10a**/**b** both esters were deshielded ($\Delta\delta^{Ba}>0$). The α-H and β-H signals in this pair were not resolved.

Table 1
^{1}H NMR chemical shift changes for the (*R*)-MPA amides **8**–**11** in CD_3CN at 300 K

Compound	$\Delta\delta^{Ba}$ (CO_2Me)[a]	$\Delta\delta^{Ba}$ (β-H)[a]	$\Delta\delta^{Ba}$ (γ-R^1)[a,c]
8a	−0.001	+0.027 (+0.018)	+0.007 (+0.010)
8b	+0.027	+0.067 (+0.053)	+0.029
9a	−0.025	−0.035	+0.010 (+0.007)
9b	−0.017	−0.014	+0.003 (+0.003)
10a[b]	+0.013	–	–
10b[b]	+0.011	–	–
11a	−0.006	−0.022	−0.012 (−0.008)
11b	−0.007	−0.006	+0.002 (+0.003)

[a] $\Delta\delta^{Ba}$ = (δ in the presence of Ba^{2+}) − (δ in the absence of Ba^{2+}).
[b] Compounds were not separable. NMR data were obtained from the mixture of diastereomers.
[c] Data are for phenyl-*ortho* (*meta*), or for **11a**/**b**-CH_2.

In summary, we observed two inconsistencies with Riguera et al.'s report. First, except in the case of **8a**/**b**, in each pair of diastereomeric amides the ester resonances shifted in the same direction on addition of Ba^{2+}. Second, in a given compound the signs of $\Delta\delta^{Ba}$ for L_1 and L_2 were often the same. Two factors could explain these inconsistencies. The model considers the proximity of either L_1 or L_2 to the MPA phenyl ring to cause the shielding/deshielding influences in each amide rotamer. A mobile side chain containing another aromatic ring could create additional shielding influences that the model neglects. The failure of the MTPA method as well as the MPA/Ba^{2+} method is consistent with this explanation. The γ-oxo functionality in **8**–**11** may also provide competing modes of Ba^{2+} complexation (although the ^{1}H spectra did not show evidence for this). This could perturb the conformations of the L_1/L_2 side chains instead of the ap/sp population. Since the method rationalizes the $\Delta\delta^{Ba}$s only in terms of an ap/sp shift, it might not give consistent results in such cases.

In conclusion, we recommend caution when applying the MPA/Ba^{2+} technique to more complex amines. Neither the MPA/Ba^{2+} nor the MTPA methods permitted us to assign absolute configurations to the α-centers of the γ-oxo-α-amino acids **2**–**5**. While the MPA/Ba^{2+} technique probably can successfully assign the configurations of amines closely related to those tested by Riguera et al.,[8] our observations suggest that the method as currently implemented may not be fully general.

Acknowledgements

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