Effect of the amino acid substituents on amide bond cleavage in *N*-acyl-α,α-dialkylglycine derivatives

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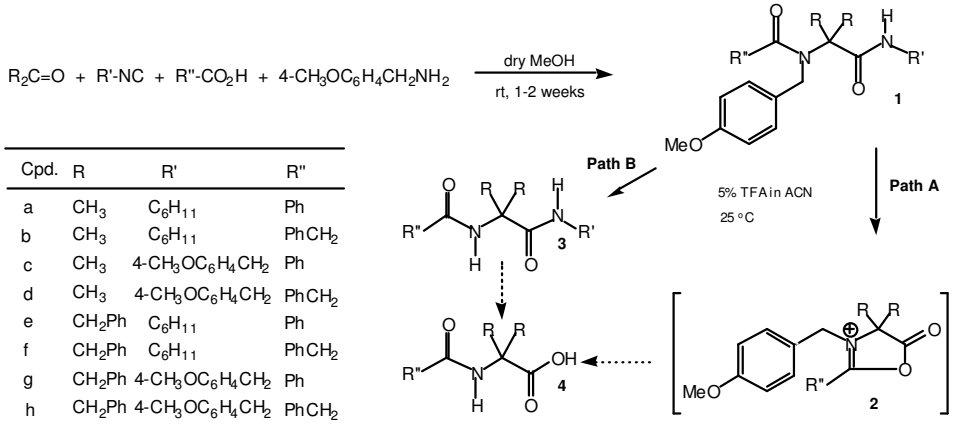
Introduction

α,α-Dialkylglycines and their peptides have attracted considerable attention, as they show unique biological activities and very stable secondary structures. In previous work, we have reported that the amide bond at the C-terminus of a series of α,α-dialkylglycine derivatives such as Deg, Dpg, $D_i$bg and Db_zg is labile to acid; cleavage was achieved by reaction with neat TFA, the products being obtained by aqueous work-up [1]. We believe that an oxazolinonium-type intermediate (**2**) is involved in these reactions, as proposed by other authors [2]. Now, we report the synthesis of a set of derivatives of Aib and Db_zg (**1a-h**) and preliminary results of accurate kinetic studies concerning their cleavage, having in mind to establish structure-reactivity relationships to evaluate the role of the various substituents on the reactivity of these compounds.

Results and Discussion

Compounds **1a-h** were obtained in moderate to good yields (45-80%) by Ugi four-component condensation reactions, as shown in the scheme below. They were then reacted under controlled temperature (25 °C) with a 5% solution of TFA in acetonitrile and samples collected at intervals for HPLC monitoring (flow, 1 cm^3 min^{-1}; eluent, ACN/H_2O 3:1; detection, 260 nm). The reagent peak areas were measured until they faded out and plotted against time, showing first order behaviour on a logarithmic scale. At least three different kinetic experiments were performed for each reagent and the mean values of the rate constants (k) are presented in Table 1.



Cpd.	R	R'	R"
a	CH_3	C_6H_{11}	Ph
b	CH_3	C_6H_{11}	$PhCH_2$
c	CH_3	4-$CH_3OC_6H_4CH_2$	Ph
d	CH_3	4-$CH_3OC_6H_4CH_2$	$PhCH_2$
e	CH_2Ph	C_6H_{11}	Ph
f	CH_2Ph	C_6H_{11}	$PhCH_2$
g	CH_2Ph	4-$CH_3OC_6H_4CH_2$	Ph
h	CH_2Ph	4-$CH_3OC_6H_4CH_2$	$PhCH_2$

Table 1. *Rate constants for cleavage of N,α,α-trialkylglycine derivatives* ***1a-h***

Cpd.	**1a**	**1b**	**1c**	**1d**	**1e**	**1f**	**1g**	**1h**
10^4 ***k*** **(s^{-1})**	1.97	11.3	4.85	23.1	1.95	1.96	2.91	3.38

From NMR data concerning the reaction products it was found that when R" is benzyl (compounds **1b**, **1d**, **1f** and **1h**) cleavage follows Path A predominantly while Path B predominates when R" is phenyl (compounds **1a**, **1c**, **1e** and **1g**). The kinetic results (Table 1) show that for the former set of compounds (*set A*), the reactions are always faster than those corresponding to the latter (*set B*). It can also be seen that, in the case *set A*, when R is methyl (compounds **1b** and **1d**) the reactions are faster than when it is benzyl (compounds **1f** and **1h**). Again in *set A*, when R' is methoxybenzyl (compounds **1d** and **1h**) the reactions are faster than when it is cyclohexyl (compounds **1b** and **1f**). These differences can also be observed in *set B* but at a smaller extent.

In conclusion, this not only reflects a correlation between the size of the substituents and the reaction rate constants, but also shows that cleavage of the *N*-methoxybenzyl group is less sensitive to steric hindrance than cleavage of the amide bond. Our results would also suggest that a phenyl group conjugated with the amide bond at the N-terminus (*set B*) hinders formation of the *5*(*4*H)-oxazolonium intermediate **2** required for cleavage at the C-terminus, possibly by lowering the nucleophlicity of the oxygen atom of the former.

We are now collecting data to measure (*i*) reaction rates for the formation of products **2a-h** and **3a-h** (Paths A and B) and also (*ii*) thermodynamic functions from temperature effects in order to improve our knowledge concerning structure-reactivity relationships within these compounds.

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