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On the solvolysis kinetics of amidoesters derived from β-aminoalcohols

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ABSTRACT

To better understand reactivity in such systems, fifteen amidoesters derived from β-aminoalcohols were solvolyzed at the ester group in mildly basic methanol-d_4. All trials showed pseudo-first-order kinetics by ^{1}H NMR. The rate constants are about 2 to 140-fold larger than those found with simple alkyl esters. The least bulky *N*-acyl groups generally sponsor the largest rate constants, and strongly so in two cases, but apparently not as a result of lesser steric crowding between the amide and ester groups. Rate constants are also greater for those amidoesters favoring an *anti* conformation at the amide linkage.

Introduction

We reported previously on the base-promoted solvolysis of *N*-acyl amino acid esters (Eq. 1; AA = prolyl, *N*-methylglycyl, or *N*-(*t*-butyl)glycyl; *N*-acyl = formyl, acetyl, propionyl, isobutyryl, or trimethylacetyl).[1] Some such esters solvolyze unusually easily, with rate constants up to 100 times greater than those of comparable simple esters. It is also striking that the specific identity of the *N*-acyl group can affect the rate constant strongly (Table 1). We found no evidence of conventional neighboring-group participation, but we did note the general variation of the rate constant with the C=O stretching frequency of the *N*-acyl group. This made sense if we viewed the NC=O moiety as an electron-withdrawing group (EWG) and/or a transient charge sink. Any capacity of that moiety to absorb electron density from the ester group and thus perhaps enhance ester reactivity would depend on its own specific electronic character, and NC=O character does plainly vary with the identity of the *N*-acyl group, as seen in the IR data.

$$N-\text{Acyl}-\text{AA}-\text{OEt}+\text{MeOD}\rightarrow N-\text{Acyl}-\text{AA}-\text{OMe}+\text{EtOD} \quad (1)$$

We also reported previously on the solvolysis of di- and tripeptide esters.[2] For such compounds, differences in amide structure several bonds distant from the ester group had a strong impact on the ester half-life. In those compounds and in the amino acid esters, the amide groups are formally part of the acyl portion of the ester group. In the present work, we wanted to assess whether an amide group present within an ester's alkoxy portion would likewise influence the ester solvolysis kinetics. Such a structural arrangement occurs in accepted acyl-enzyme intermediates of serine protease and serine esterase systems.[3,4] Some influence should be expected if the amide group can truly act as an EWG and/or an electron sink. To address the question in a simple way, we have carried out the base-promoted methanolysis of fifteen amidoesters derived from β-aminoalcohols. The measured rate constants do in fact indicate a general activation as compared with simple alkyl esters. The data also indicate a dependence on structural detail at the amide linkage.

Results and discussion

Rate constants. Each compound in Figure 1 was converted to its respective alcohol plus methyl acetate under mild conditions (0.1 M ester and 1.03 M *i*-Pr_2NEt in methanol-d_4, 21.5 ± 1 °C; see Eq. 2).[5,6] The reactions were monitored directly by ^{1}H NMR. The pseudo-first-order rate constant was calculated from successive integrations of the diminishing –CH_2OAc or *CH*OAc signal of the reactant or the growing –CH_2OD or *CH*OD signal of the product.[7] The results are given in Table 2.

Table 1
Pseudo-first-order rate constants for formylated, acetylated, and trimethylacetylated proline esters and ethyl cyclopentane carboxylate undergoing base-promoted methanolysis (0.1 M ester and 1.03 M *i*-Pr_2NEt in methanol-d_4 at 21.5 ± 1 °C).[1] Ac = acetyl, Piv = pivaloyl (trimethylacetyl), and Cp = cyclopentyl

Ester	k (10^{-5} s^{-1})	$\nu_{NC=O}$ (cm^{-1})
OHC-Pro-OEt	3.3	1663
Ac-Pro-OEt	0.099	1644
Piv-Pro-OEt	0.00053	1622
$CpCO_2Et$	0.031	—

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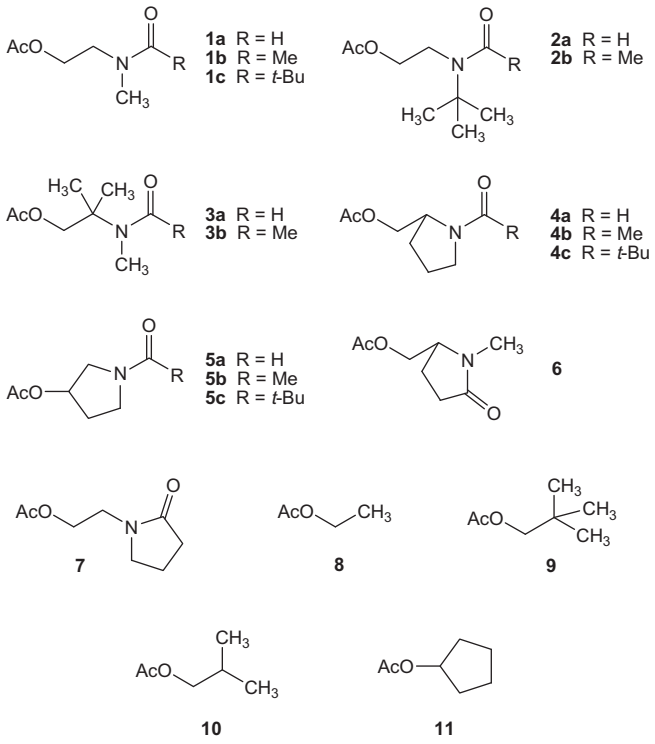

Figure 1. Amidoesters and alkyl esters used in the present study.

Table 2
Pseudo-first-order rate constants for ester solvolysis, IR stretching frequencies of the NC=O carbonyl, and ^{13}C NMR chemical shifts of the ester carbonyl

Compd	R	k (10^{-5} s^{-1})	$\nu_{NC=O}$ (cm^{-1})[a]	$\delta_{OC=O}$ (ppm)[b,c]
1a	H	4.4	1663	170.7, 170.8
1b	Me	3.5	1639	170.7, 170.8
1c	*t*-Bu	2.0	1625	170.8
2a	H	2.2	1651	170.8, 171.0
2b	Me	5.6	1645	170.8
3a	H	3.3	1647	170.6, 170.8
3b	Me	0.13	1640	170.9
4a	H	5.5	1658	170.6, 170.9
4b	Me	2.1	1636	170.5, 170.7
4c	*t*-Bu	0.42	1619	171.1
5a	H	2.7	1653	170.4, 170.6
5b	Me	2.5	1630	170.4, 170.6
5c	*t*-Bu	2.1	1602	170.6
6	—	3.8	1672	170.8
7	—	1.9	1677	171.0
8	—	0.27	—	171.3
9	—	0.023	—	171.5
10	—	0.23	—	171.5
11	—	0.086	—	171.2

[a] Obtained for neat compounds.
[b] Obtained for $CDCl_3$ solutions.
[c] Values are given for both amide conformations, *syn* and *anti*, if observed.

$$ROAc + MeOD \rightarrow ROD + MeOAc \quad (2)$$

The results show the amidoesters to be generally activated in comparison to simple alkyl esters. For example, amidoesters **1a–c** are about 7 to 16-fold more reactive than ethyl acetate (**8**). Likewise, amidoesters **5a–c** are 24 to 31-fold more reactive than cyclopentyl acetate (**11**). Amidoester **3a** shows an unusually large degree of activation compared to a sterically similar alkyl analog (neopentyl acetate, **9**; $k_{3a} \approx 140 \times k_{9}$). Only **4c** shows a relatively small activation compared to an alkyl analog (isobutyl acetate, **10**; $k_{4c} \approx 1.7 \times k_{10}$).

Within each amidoester series, the rate constant varies with the specific identity of the *N*-acyl group. In general, a smaller *N*-acyl group affords higher reactivity. The exception is series **2**, with compound **2b** yielding a larger rate constant than **2a**. The rate constant is more sensitive to details of structure within series **3** and **4** than it is within series **1** or **5**.

On the basic mechanism of the reaction. In analogy with studies by Schowen et al. on ester solvolysis, we expected solvolysis under our conditions to involve a direct, base-assisted pyramidalization of the ester group by the solvent (Fig. 2, pathway **a**).[8,9] This mechanism is consistent with our observed pseudo-first-order kinetics and with our finding that each amidoester in Figure 1 shows little or no reactivity when the base is omitted from the reaction. A possible alternative mechanism involving neighboring-group participation by the amide group (pathway **b**) is unlikely for at least some of the amidoesters. Specifically, amidoesters **5a–c** and **6** would require highly strained bridged bicyclic intermediates in such a mechanism, yet these amidoesters do not in fact exhibit low reactivity. Furthermore, amidoester **2b** should adopt the necessary *syn* amide geometry for a neighboring-group interaction only with relative difficulty (vide infra), yet it is more reactive than its less constrained analog **2a**. Barring future evidence to the contrary, we will suppose that pathway **a** is generally valid for the compounds in this study.

It is noteworthy that **3b**, the least reactive amidoester in the presence of the base, is the most reactive compound when the base is omitted ($k = 7.4 \times 10^{-8}$ s^{-1}). This suggests that **3b** may follow an alternative solvolysis mechanism under neutral conditions. Neighboring-group participation is one possibility.[10,11] The structure of **3b** is distinctive in having a predominantly *syn* amide geometry (vide infra) and containing a geminal dimethyl moiety. By virtue of a *gem*-dialkyl effect, it may populate a relatively large proportion of conformations in which a neighboring group interaction is possible (e.g., *syn*-**3b**-II in Fig. 3).[12–14]

On the nature of the ester activation. In our previous study of the solvolysis of *N*-acyl amino acid esters, a dependence of rate constant on the presence and specific identity of the acylamino group was plainly evident, as is the case here.[1] In the previous study, we interpreted the acylamino moiety as an activating EWG and/or an electron sink, and the dependence of k on the specific *N*-acyl group

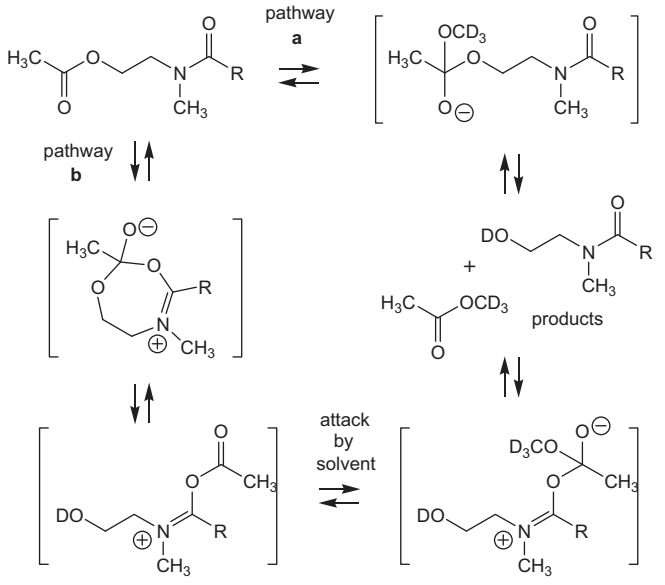

Figure 2. Simple pathways for base-promoted solvolysis of amidoesters from Figure 1.

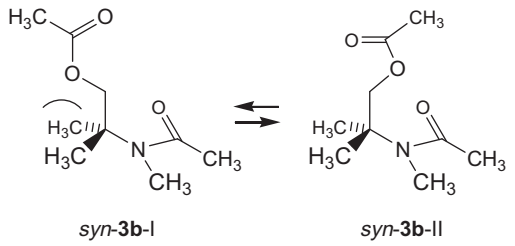

Figure 3. A *gem*-dimethyl effect in **3b** should enhance the proportion of conformations that have the ester and amide groups close to one another, for example, *syn*-**3b**-II.

as the result of differences in the various acylamino groups' electron-withdrawing capacities. The IR stretching frequency of the *N*-acylcarbonyl group was noted to generally decrease as the bulk of the *N*-acyl group was increased (Table 1). This observation suggested that variations in local crowding by the *N*-acyl group (e.g., Fig. 4) affect the electronic character of the N–C═O moiety and, in turn, its capacity as an EWG or sink.

To assess whether the acylamino group in the present study acts as an EWG, the ^{13}C shift of the ester carbonyl was examined. Maciel et al. found that in esters of structure $AcOCH_2CH_2X$, typical EWGs (X = Br, Cl, Ph, OCH_3, and NMe_3^+) deshield the C═O carbon by 0.1–0.8 ppm relative to that of ethyl or propyl acetate.[15,16] The acylamino group in the present study, however, has a mild shielding effect on the ester carbonyl. The ester C═O signal for each amidoester, **1**–**7**, falls between 170.4 and 171.1 ppm while that for the alkyl esters **8**–**11** falls between 171.2 and 171.5 ppm (Table 2). Thus while ground-state electron-withdrawing character for the acylamino group cannot be ruled out on this simple basis, the ^{13}C data do not seem to indicate such character.

Does the specific identity of the *N*-acyl group affect the electronic character of the N–C═O moiety? A dependence is clearly evident in Table 2. Within each set of compounds, **1** through **5**, as the bulk of the *N*-acyl group is increased, the stretching frequency of the N–C═O carbonyl decreases by as much as 51 cm^{-1}. At the same time, the value of *k* also decreases (except for ester **2b**). Therefore, if the acylamino and ester groups interact electronically in some fashion, as seems inevitable from their mutual proximity, the *N*-acyl group may be influencing ester reactivity through an impact on N–C═O character. We currently suppose that the degree of such impact depends on the specific degree of crowding within each amide group, as we argued previously for the amino acid esters.[1]

On the influence of amide conformation. Table 2 shows that within each of the amidoester series **1**, **3**, **4**, and **5**, bulkier *N*-acyl groups always afford lower values of *k*. The reactivity of **3b** is conspicuous within this trend since it is particularly low as compared with its analog **3a**. It is also conspicuous that amidoesters **2a** and **2b** do not fit the general trend since **2b** is more reactive than **2a**. Both of these results make sense if we infer a dependence of ester reactivity on amide conformation as follows.

Each of the compounds in sets **1**–**5** can in principle populate two different conformations at the amide linkage, *syn* and *anti*. Steric interactions within compounds **2a** and **3b** were expected, a priori, to favor the *syn* conformation, while steric interactions within **2b** and **3a** were expected to favor *anti* (Fig. 5). The simple $CDCl_3$ and CD_3OD NMR spectra are consistent with these expectations. For example, the ^1H spectra of all other *N*-formyl and *N*-acetyl compounds in the study show two sets of signals each, corresponding to *syn* and *anti* conformations. The spectra for **2b** and **3b**, however, each show a single set of signals at temperatures as low as −77 °C. The spectra for **2a** and **3a** each show two sets of signals at 21 °C. By integration of the ^1H signals, the population ratio of conformations in **3a** is 20:1. The ratio in **2a** is solvent-dependent, being about 26:1 in $CDCl_3$ and about 18:1 in CD_3OD, but favoring the same conformation in each solvent. Comparison of the ^{13}C spectra for **2a** versus **2b** suggests that the sole amide conformation in **2b** is the minor conformation in **2a**, as expected. In particular, the *N*-CH_2 carbon in **2a** shows ^{13}C resonances at 44.93 ppm (minor conformer) and 39.99 ppm (major conformer), while the corresponding carbon in **2b** shows a resonance at 44.39 ppm only. Comparison of the^{13} C spectra of **3a** versus **3b** likewise suggests that the sole amide conformation in **3b** is the minor conformation in **3a**, as expected. In particular, the *N*-Me carbon in **3a** shows resonances at 33.75 ppm (minor conformer) and 26.26 ppm (major conformer), while the corresponding carbon in **3b** shows a resonance at 34.06 ppm only. All of these observations are consistent with an assignment of *syn*-**2a**, *anti*-**2b**, *anti*-**3a**, and *syn*-**3b** as the most stable conformations in their respective ground-state conformational equilibria.

Now, if *anti* and *syn* amide conformations activate the ester group to different degrees, and if *anti* were generally more activating than *syn*, then the greater reactivity of **2b** compared to **2a** can be explained. That is, the intrinsic steric bias in **2b** favors a more reactive conformation. Such a conformational factor would be superimposed on the crowding factor proposed above that would

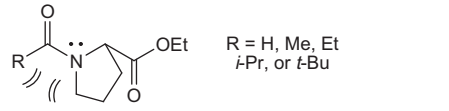

Figure 4. Crowding within the amide group of *N*-acyl amino acid esters that correlates with the IR stretching frequency of the *N*-acyl carbonyl (from Ref. 1). Larger R groups sponsor a lower frequency and a lower rate constant for solvolysis at the ester group.

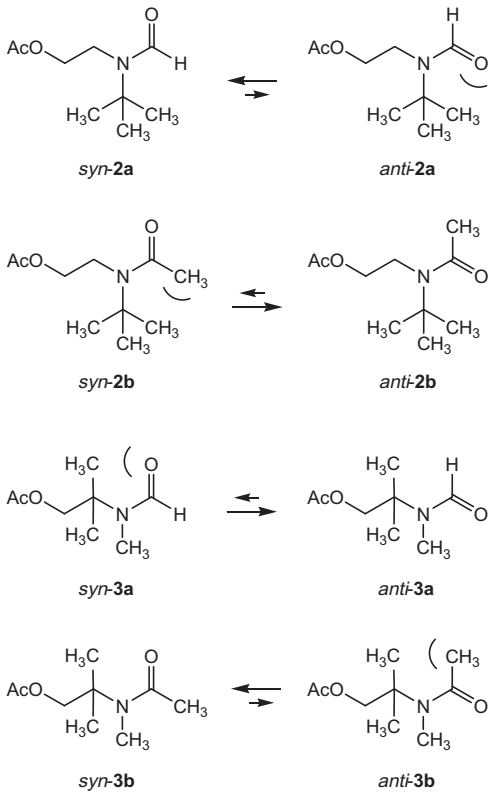

Figure 5. Differential steric interactions that favor the *syn* amide conformation in compounds **2a** and **3b** and the *anti* amide conformation in **2b** and **3a**.

tend to make **2b** less reactive than **2a**. If these two factors truly operate as the main determinants of relative reactivity, the conformational factor must outweigh the crowding factor in these two compounds since **2b** is in fact more reactive than **2a**.

The especially low reactivity of **3b** also makes sense by this model since the crowding and conformational factors should both act to depress reactivity in **3b**. That is, **3b** has greater crowding in its amide group than **3a**, and the intrinsic steric bias in **3b** favors a less reactive (*syn*) conformation.

Esters **2a**, **2b**, **3a**, and **3b** were selected for this study to test for a conformational factor after such a factor became evident in our amino acid study.[1] As a further test in the present context, lactam-esters **6** and **7** were also prepared and solvolyzed. The lactam rings in these two compounds lock the amide moiety into *anti* and *syn* conformations, respectively. The observation that **6** is indeed more reactive than **7** (Table 2) lends further support to the idea that the *anti* conformation is more activating.

Conclusion

The amidoesters used in this study are generally activated for base-promoted solvolysis in comparison to simple alkyl esters. In most cases, the smallest *N*-acyl groups afford the greatest degrees of activation. Within each of the series **1**–**5**, the IR stretching frequency of the NC═O carbonyl decreases as the size of the *N*-acyl group is increased (Table 2). This impact is likely due to greater crowding within the bulkier amide groups, as we discussed in detail in our previous paper.[1] Because the amide and ester groups in these molecules are intimate neighbors, this impact on NC═O character is suspected to be a direct factor behind the measured solvolysis rate constants. For example, NC═O may serve as an inductive or hyperconjugative electron sink during ester solvolysis, and its precise capacity to do so may be modulated by the identity of its *N*-acyl group. Finally, three of the pairs of amidoesters in this study were used to gauge the impact of amide conformation on ester reactivity. The results with all three pairs indicate that an *anti* conformation is more activating than *syn*.

It is an open question as to how amide conformation is able to influence the solvolytic reactivity of the present compounds, as is the question of whether that influence is actually separate from the fundamental mechanism of ester activation. Further studies are in progress.

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5. Except for **6** and **7**, all amidoesters in Figure 1 were prepared from the corresponding aminoalcohols by bis-acetylation or by sequential *N*-acylation and *O*-acetylation. Lactam-esters **6** and **7** were prepared by acetylation of the corresponding lactam-alcohols, which were prepared by reduction of the corresponding ethyl esters with $NaBH_4$/MeOH.[1]
6. Each amidoester in Figure 1 gave satisfactory ^1H NMR, ^{13}C NMR, IR, and high-resolution mass spectral data.
7. For each kinetics trial, 1.00 mL of a 1.03 M $(i\text{-Pr})_2$NEt/MeOH-d_4 solution was added to a measured amount of ester so that the initial concentration of ester was about 0.1 M. Kinetics data were collected as a series of signal integrations with a Bruker Avance DPX-300 NMR spectrometer. Each rate constant was calculated by the least-squares method for the simple linear regression equation $ln\ (\%ROAc) = -kt + C$. Each value in Table 2 is the average of at least two determinations.
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