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Structure dependence in the solvolysis kinetics of amino acid esters

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ABSTRACT

To better understand acyl transfer reactions of oligopeptides, seventeen *N*-acyl amino acid esters were solvolyzed in mildly basic methanol-d_4. All show pseudo-first-order kinetics by ^{1}H NMR. The rate constant varies up to 400-fold with the identity of the amino acid and up to 6200-fold with the identity of the *N*-acyl group. The impact of the *N*-acyl group on the rate constant is discussed in terms of crowding, amide conformation, and amide C=O bond character.

1. Introduction

We reported previously that under mildly basic solvolysis conditions, some closely related amino acid and oligopeptide esters have strikingly varied half-lives (Eqn. 1 and Table 1).[1] Each compound suffers a clean acyl transfer, yielding the corresponding methyl ester plus ethanol. The hypothesis under consideration was that oligopeptides of different lengths would show different degrees of acyl transfer reactivity. The data show an impact of structural differences that are four to seven bonds distant from the ester group. One would like to understand this impact well given that it is similar to rate/length dependences seen in the proteolysis of oligopeptides. Rate/length dependences in proteolysis are usually rationalized in terms of enzyme/substrate interactions. We have suggested, however, that substrate structure itself plays a larger and more consequential role than formerly suspected.[1]

Table 1
Half-life values for ethyl esters undergoing solvolysis to their respective methyl esters in 2.06 M *i*-Pr_2NEt/MeOH at ambient temperature (from Ref. 1)

Compound	$t_{1/2}$ (d)
Piv-Pro-OEt	1700
Piv-Pro-Pro-OEt	220
Ac-Pro-Pro-OEt	30
Piv-Sar-Pro-Pro-OEt	15
Ac-Pro-OEt	2.4

Piv = pivaloyl, Pro = prolyl, Ac = acetyl, Sar = sarcosyl.

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X-Pro-OEt → X-Pro-OMe (1)

As a next step in our project, we proceeded to inspect the simplest esters more closely. This Letter compares *N*-acyl amino acid esters undergoing acyl transfer. Even in such small compounds, the variation of reactivity with structure is pronounced and intriguing.

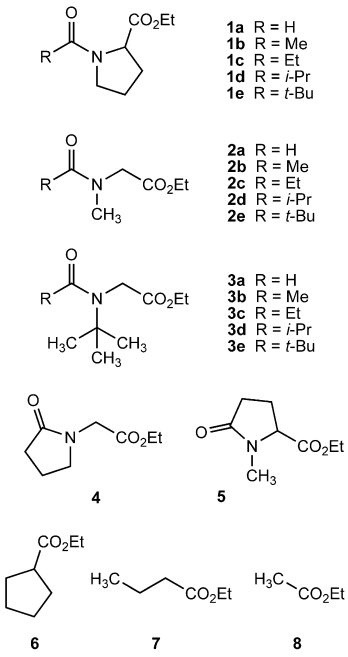

Figure 1. *N*-Acyl amino acid esters subjected to base-promoted solvolysis.

2. Results and discussion

Each of the esters in Figure 1 converts cleanly to its respective methyl ester plus ethanol under mild conditions (0.1 M ester and 1.03 M *i*-Pr_2NEt in methanol-d_4, 21.5 ± 1 °C).[2–6] The reactions were monitored directly by ^1H NMR. The pseudo-first-order rate constant was calculated from successive integrations of the diminishing $-CO_2CH_2CH_3$ signal of the reactant or the growing $DOCH_2CH_3$ quartet.[7] The results are listed in Table 2.

Series **1**–**3** differ in their absolute reactivity and in their rate constant patterns. Comparisons with control compounds show that the amide group can boost ester reactivity significantly. The rate constants for **1a** and **2a** are about 100-fold and 85-fold greater than those for the similar simple esters ethyl cyclopentanecarboxylate (**6**) and ethyl butanoate (**7**). The rate constant varies significantly with the identity of the *N*-acyl group, and most strongly in series **1**.

The acyl transfer mechanism probably involves a base-assisted pyramidalization of the ester group by the solvent.[8,9] Neighboring-group participations are unlikely. Deuteration next to the amide carbonyl was not evident in any of the kinetics trials. Also, when the base was omitted from the reaction, the rate constants were greatly reduced. This control experiment was run for all amide-esters except **1e** and **3e**. Conventional neighboring-group participations should show atleast one of two consequences. They should show deuteration if amide enolization is occurring (not expected under our mild conditions). Alternatively, if the neutral amide group were the nucleophile, *k* should be largely unaffected by omitting the base. For most compounds in the study, deuteration next to the ester carbonyl was also either not evident or its rate constant was less than one-half that for acyl transfer. Enolization of the ester group and/or ketene formation is therefore not likely a part of the acyl transfer mechanism for those compounds.[10] As for the remaining compounds, kinetic isotope data suggest that the ester group is not deprotonated as a part of acyl transfer events.

One possible explanation for the variation of *k* within each ester series is that the ester group is directly crowded to different extents by the different *N*-acyl groups. This explanation is most credible for series **3** since the bulky *N*-*t*-butyl group should generally favor conformations that have the *N*-acyl R group and the ester group close to each other (Fig. 2). The largest R groups might then interfere the most with ester pyramidalization and sponsor the lowest rate constants.

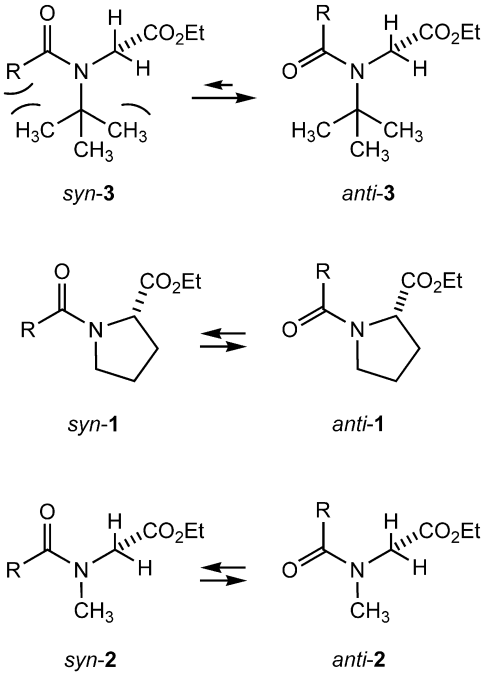

Figure 2. Amide conformation in series **1**–**3** according to NMR data and ab initio calculations.

The explanation does not apply as neatly to series **1** and **2**, however, since those series do not favor an amide conformation in which the *N*-acyl R group and the ester group are close to each other. Proton NMR integrations and carbon chemical shifts indicate the alternative amide conformation to be slightly favored for most of series **1** and **2** (*syn*-**1** and *syn*-**2** in Fig. 2). Therefore, for mutual crowding of the *N*-acyl and ester groups to be the main source of variation in *k*, the anti conformation would need to be the more reactive conformation for most of each series, and substantially more reactive than the syn conformation. The possibility is not ruled out. Note that ester **3a** has a smaller rate constant than **3b**–**d**. This is interesting because esters **1a** and **2a**, also bearing the smallest *N*-acyl group, each show the largest rate constants in their series. The predominant amide conformation in **3a** is evidently *syn*-**3a**, with NOE measurements supporting a prediction from ab initio modeling (gas phase; 6-31G* level). Therefore, the anti conformation may indeed have more of an activating effect on ester reactivity.

To test the importance of amide conformation more plainly, esters **4** and **5** were prepared and solvolyzed. The lactam rings in **4** and **5** lock the amide linkage into syn and anti conformations, respectively. The rate constants are shown in Table 2. Ester **5** is slightly more reactive than **4**, despite having more branching next to its ester carbonyl. The impact of this branching should be mild. The rate constants for esters **6**–**8** imply that each alkyl substituent next to the ester carbonyl in that control series lowers *k* by a factor of about 3. Thus the data are consistent with the anti conformation being more activating than syn, if only slightly so.

A different explanation for the variation of *k* in each ester series involves the activating effect of the amide group. Electron-withdrawing groups in esters are known to facilitate acyl transfer.

Table 2
Rate constants for ester solvolysis, IR frequencies of the amide carbonyl, and NMR chemical shifts of the amide carbonyl

Compound	k (10^{-5} s^{-1})	$\nu_{C=O}$[a] (cm^{-1})	$\delta_{C=O}$[b,c] (ppm)
1a	3.3	1663	160.8, 161.7
1b	0.099	1644	169.5, 169.7
1c	0.044	1644	172.5, 172.7
1d	0.034	1645	176.0, 176.5
1e	0.00053	1622	176.9
2a	8.1	1668	163.0, 163.2
2b	2.6	1646	171.2, 171.5
2c	1.7	1648	174.3, 174.6
2d	1.3	1646	177.5, 177.6
2e	0.22	1631	178.1
3a	0.10	1654	161.8
3b	0.32	1651	171.8
3c	0.22	1652	174.6
3d	0.22	1640	178.6
3e	0.0045	1628	178.7
4	2.1	1682	175.7
5	3.6	1688	175.2
6[d]	0.031	—	—
7[e]	0.094	—	—
8[f]	0.27	—	—

[a] Obtained for neat compounds.
[b] Obtained for $CDCl_3$ solutions.
[c] Values are given for both amide conformations, if observed.
[d] Ethyl cyclopentanecarboxylate.
[e] Ethyl butanoate.
[f] Ethyl acetate.

The relative power of such groups depends on their specific electronic character. If the amide group increases ester reactivity by acting as an electron-withdrawing group or an electron sink, two different amides need not be alike in this respect. Different *N*-acyl R groups, by sponsoring differences in mean and dynamic amide geometry, orbital structure, and charge distribution, may afford differences in electron-withdrawing power and charge accommodation.

Modeling of the syn conformation in series **1** was done to predict the impact of R on amide geometry. Some details are shown in Table 3. As the size of R increases, the R–C–N angle (opposite the carbonyl oxygen) and the adjacent C–N–C angle are each predicted to widen. The O=C and C–N bonds of the O=C–N substructure are each predicted to lengthen slightly.

That the R group does affect amide electronic character is indicated empirically by the amide carbonyl stretching frequencies, listed in Table 2. The value of $\nu_{C=O}$ drops significantly from the smallest to the largest R group within each series. However, the value of $\nu_{C=O}$ is almost constant when R = Me, Et, and *i*-Pr within each series, so R is probably not affecting C=O stretching by its specific mass or by a through-bond effect. The jumps in $\nu_{C=O}$ correspond to the expected increases in crowding between the R group and nitrogen's other substituents. In series **1**, for example, while the size of the R group increases from **1a** (R = H) to **1b** (R = CH_3), the value of $\nu_{C=O}$ decreases by about 20 cm^{-1}. From **1b** to **1c** and **1d**, the size of R increases again, but the R groups in **1c** and **1d** can be rotated to avoid additional crowding relative to **1b**. This may explain why $\nu_{C=O}$ varies little over this sub-series. From **1d** (R = *i*-Pr) to **1e** (R = *t*-Bu), however, an increase in crowding cannot be avoided through facile bond rotations, and $\nu_{C=O}$ drops again by about 20 cm^{-1}. Low values of $\nu_{C=O}$ are not unusual for crowded amides and ketones.[11–13]

The ^{13}C NMR chemical shifts of the amide carbonyl also indicate an interesting impact by the R group (Table 2). For each series of compounds, the signal is near 160 ppm when R = H. When R = Me, it is in the range of 169–172 ppm. When R = Et, it is 3–4 ppm further downfield, and when R = *i*-Pr, it is 3–4 ppm still further downfield. When R = *t*-Bu, however, the C=O signal appears at a frequency similar to that seen when R = *i*-Pr. A linear trend of C=O signals toward lower field with increasing alkyl substitution at the alpha carbon is known for several functional groups.[14,15] The chemical shifts of **1e**, **2e**, and **3e** represent deviations from this trend.

Such deviations have been reported previously for crowded ketones.[13,16] They make sense in terms of the expected impact of crowding on the C=O carbon hybridization. Consider that if the R–C–N angle of the amide group widens for any reason, carbon's atomic orbital in the sigma bond to oxygen would gain in *p* character. This is shown in simple form in Figure 3, comparing three hybrid states for the C=O carbon based on benchmark R–C–N angles of 109°, 120°, and 180°. Only carbon's sigma-bonding orbitals are shown. From left to right in this series, carbon uses an *sp*, sp^2, or *p* orbital, respectively, to make its sigma bond to oxygen. As the R–C–N angle widens, each increase in *p* character increases the relative volume of the orbital's minor lobe (pointed away from oxygen), thereby favoring an incremental shift of the bond's electron density slightly closer to carbon. The carbon might therefore gain 'extra' shielding by ^{13}C NMR, appearing further upfield than expected (as seen for **1e**, **2e**, and **3e**). Each loss in the volume of the major lobe would also remove density from the C/O internuclear space, thereby tending to weaken the C=O sigma bond and possibly lowering $\nu_{C=O}$ as we observe.

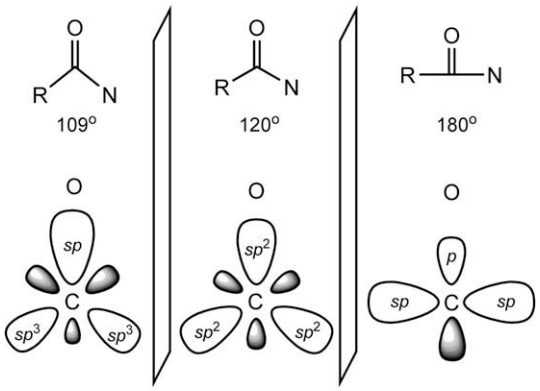

Figure 3. Comparison of hybrid states for the amide carbonyl carbon as a function of R–C–N angle. Only sigma-bonding orbitals of the carbonyl carbon are shown.

Are the data consistent with the hypothesis that differences in amide electronic character affect ester reactivity? Certainly the largest decreases in rate constant correspond to the largest decreases in $\nu_{C=O}$ in each series. The hypothesis seems reasonable for now if we suppose that *k* and $\nu_{C=O}$ might each be affected by multiple factors.

Table 3
Calculated bond angles and bond lengths at the amide group in compounds **1a–e**, syn conformation (Hartree–Fock level, 6-31G* basis set)

Ester	R–C–N	C–N–C	O=C (Å)	C–N (Å)
1a	113.49°	125.33°	1.197	1.343
1b	117.13°	126.88°	1.203	1.355
1c	117.01°	127.06°	1.203	1.356
1d	118.59°	127.69°	1.205	1.355
1e	122.31°	130.75°	1.206	1.362

3. Conclusion

The nature of the amide group in *N*-acyl amino acid esters influences the acyl transfer reactivity of the ester group. The rate constant varies positively with the infrared stretching frequency of the amide carbonyl and negatively with the size of the *N*-acyl group. A high importance of direct crowding between the *N*-acyl and ester groups is not generally indicated by the present data. Conformation within the amide group is judged to be at least somewhat important. Crowding within the amide group is probably most responsible for variation in the amide's electronic character, evident by IR and NMR, which may in turn affect ester reactivity. Further tests of these ideas with dipeptide and tripeptide esters are in progress.

Acknowledgments

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References and notes

1. Fan, Y.-H.; Grégoire, C.-A.; Haseltine, J. *Bioorg. Med. Chem.* **2004**, *12*, 3097.
2. Amide-esters **1a–e**, **2a–e**, and **3a–e** were prepared by N-acylation of proline ethyl ester·HCl,[3] sarcosine ethyl ester·HCl (Aldrich), and *N*-(*t*-butyl)glycine ethyl ester,[4] respectively. Formylations were performed in ethyl formate using excess triethylamine and/or heat and pressure. Lactam-ester **4** was prepared by alkylating the sodium salt of 2-pyrrolidinone (NaH/DMF) with ethyl bromoacetate. Lactam-ester **5** was prepared from its corresponding methyl ester by treatment with K_2CO_3/ethanol.[5]
3. Proline ethyl ester·HCl was prepared by applying the method of Garbers, C. F.; Schmid, H.; Karrer, P. *Helv. Chim. Acta* **1955**, *38*, 1490.
4. Gribble, G. W.; Hirth, B. H. *J. Heterocycl. Chem.* **1996**, *33*, 719.

5. Williams, P. D.; Perlow, D. S.; Payne, L. S.; Holloway, M. K.; Siegl, P. K. S.; Schorn, T. W.; Lynch, R. J.; Doyle, J. J.; Strouse, J. F.; Vlasuk, G. P.; Hoogsteen, K.; Springer, J. P.; Bush, B. L.; Halgren, T. A.; Richards, A. D.; Kay, J.; Veber, D. F. *J. Med. Chem.* **1991**, *34*, 887.
6. Each compound in Table 2 that is not well known (**1a**, **1c**, **2c**–**e**, **3a**–**e**, and **5**) gave satisfactory ^{1}H 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 $ln\ (\%RCO_2Et) = -kt + C$. Each value in Table 2 is the average of at least two determinations.
8. Mitton, C. G.; Schowen, R. L.; Gresser, M.; Shapley, J. *J. Am. Chem. Soc.* **1969**, *91*, 2036.
9. Mitton, C. G.; Gresser, M.; Schowen, R. L. *J. Am. Chem. Soc.* **1969**, *91*, 2045.
10. If deuteration next to the ester carbonyl and acyl transfer were both occurring by a single mechanism, for example, via ketene formation, then the rate constant for deuteration could equal or exceed one-half *k*. The factor of one-half arises from the fact that in such a mechanism, one N–CH_2CO_2Et proton would be lost per event versus two $CO_2CH_2CH_3$ protons.
11. Kondo, K.; Iida, T.; Fujita, H.; Suzuki, T.; Yamaguchi, K.; Murakami, Y. *Tetrahedron* **2000**, *56*, 8883.
12. Rao, Y.; Li, X.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2009**, *131*, 12924.
13. Qin, X.-r.; Ishizuka, Y.; Lomas, J. S.; Tezuka, T.; Nakanishi, H. *Magn. Reson. Chem.* **2002**, *40*, 595.
14. Levy, G. C.; Lichter, R. L.; Nelson, G. L. *Carbon-13 Nuclear Magnetic Resonance Spectroscopy*, 2nd ed.; Wiley: New York, 1980. pp 137–152.
15. Breitmaier, E.; Voelter, W. *Carbon-13 NMR Spectroscopy*, 3rd ed.; VCH: Weinheim, Germany, 1990. pp 216–232.
16. Jackman, L. M.; Kelly, D. P. *J. Chem. Soc. (B)* **1970**, 102.