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Diamine acylation with amino acid derivatives: an example of proximity effect in organic reactivity induced by supramolecular aggregation

Carles Felip-León, María D. Segarra-Maset, Beatriu Escuder *, Juan F. Miravet *

Departament de Química Inorgànica I Orgànica, Universitat Jaume I, Avda. Sos Baynat s/n, 12071 Castelló de la Plana, Spain

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ABSTRACT

Unexpected high yields of diamide **3** are obtained in the reaction of 1,3-propanediamine with an activated ester of L-valine (**1**) under adverse proportions of the reactants, namely in the presence of an excess of 1,3-propanediamine. It is observed using different conditions that the yield of difunctionalized compound is considerably higher than that expected from a statistical distribution of products. Proximity effects associated to supramolecular interactions explain the described reactivity.

Introduction

Proximity effects are extensively described in the literature as a way to rationalize the enzymatic processes and biological mechanisms.[1–3] In a simplified way, it can be said that molecules that are disposed in spatially close positions tend to react faster than those without this feature. Examples of organic reactions that show proximity effects include intramolecular reactions[4,5] and more rarely intermolecular reactions in supramolecular complexes which are held together by interactions such as hydrogen bonding[6,7] or hydrophobic forces.[8] The natural extension of proximity effects is related, among other topics, with auto-replicative,[9] self-assembling systems,[10] and with systems chemistry in general.[11] Here we report an example of unusual substrate selectivity associated with a supramolecularly induced proximity effect. Activated ester **1**[12] reacts preferentially with the amine group of compound **2** in the presence of competing reagent 1,3-propanediamine.

Results and discussion

As a result of our work in supramolecular gels, we were interested in the synthesis of compound **3**[12] which is a low molecular weight gelator[13,14] and related molecule **2**.[15] These compounds can be prepared, respectively, by difunctionalization and monofunctionalization of 1,3-propanediamine (Scheme 1). The reaction corresponds to the acylation of 1,3-diaminopropane with an activated ester of N-protected valine (**1**) using THF as solvent. In order to optimize the preparation of compound **2** different assays were carried out using an excess of diamine. Unexpectedly, the yield of monofunctionalized product was not improved using a large excess of diamine. It was found that the yield of isolated difunctionalized compound **3** was significantly higher than that expected for a statistical product distribution (see Table 1, notice that yields are calculated based on the conversion of the limiting reagent, namely activated ester).

For example, when a large excess of diamine was used in a gram scale reaction with a 1:4 ratio of activated ester/diamine (8-fold excess considering the stoichiometric ratio of difunctionalized compound), a 54% yield of compound **3** was obtained after isolation. This yield is higher than that predicted from a statistical product distribution, 13%. As shown in Table 1, this effect was similar when 1:2 and 1:3 ratios of activated ester/diamine were employed, being the yield of difunctionalized product insensitive to the use of an increasing excess of diamine.

In order to gain further evidence of this effect, small scale assays were performed with variation of the reactant ratio in THF and MeOH at room temperature (Table 2). The ratio between mono and difunctionalized products was determined from the reaction crude by means of ^{1}H NMR. In this way, the possible effects of the isolation process in the final yield were avoided. The results fully agree with those described in Table 1 for gram scale reactions with isolation of difunctionalized compound **3**. As seen in Table 2, the yield of difunctional compound for a 1 to 1 ratio of reagents,

* Corresponding authors.
E-mail addresses: escuder@uji.es (B. Escuder), miravet@uji.es (J.F. Miravet).

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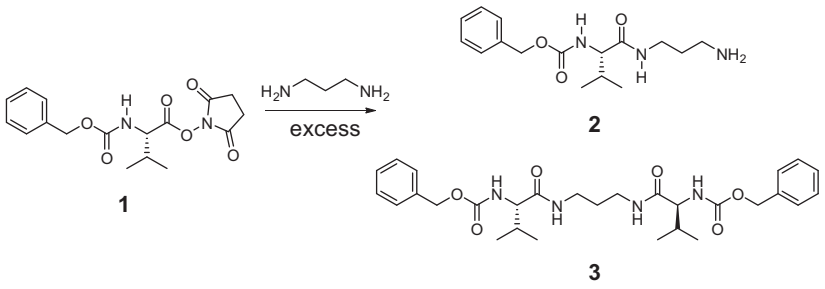


Scheme 1. Reaction under study.

Table 1
Yields of isolated difunctionalized product **3** calculated taking as limiting reagent compound **1**[16]

Ratio activated ester/diamine	Experimental yield (%)	Statistically predicted yield (%)
1:2	45	25
1:3	52	17
1:4	54	13

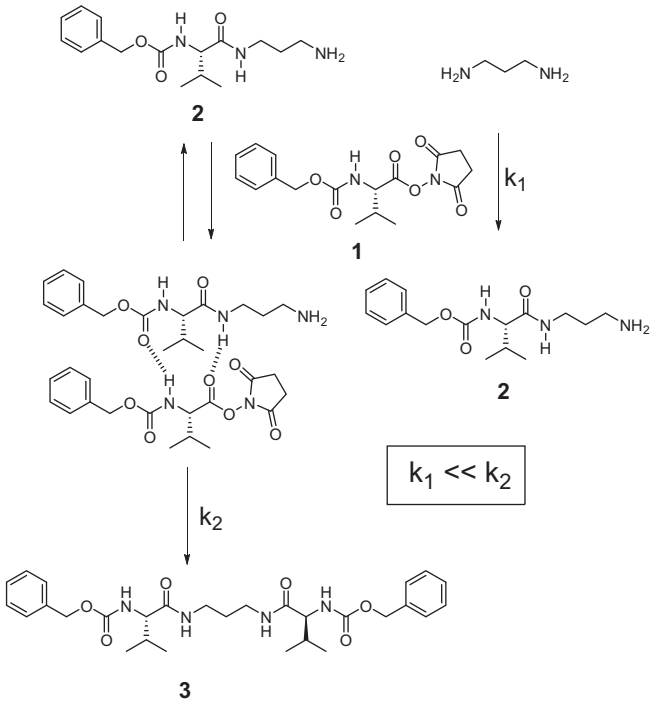
Table 2
Yields of difunctionalized product calculated taking as limiting reagent compound **1** and determined by ^{1}H NMR from reaction crudes[17]

Ratio activated ester/diamine	Solvent	Experimental yield (%)	Statistically predicted yield (%)
1:1	THF	85	50
1:2	THF	54	25
1:3	THF	55	17
1:3	Methanol	8	17
1:4	THF	51	13

calculated taking as limiting reagent compound **1**, is 85%, well above that calculated for a statistical product distribution. Noticeably, the yield of compound **3** is almost invariant, being around 50% in all cases, upon increasing the ratio of diamine from 1:2 to 1:4. Clearly, these results point to an 'activation' of the amine functionality after the first functionalization takes place. In other words, the amine groups from compound **2** seem to be more reactive that those from the starting compound 1,3-propanediamine. We have found that this effect is associated to the supramolecular interaction of compounds **2** and **1**. A schematic representation of the supramolecular complex is shown in Scheme 2. In this way the reactivity of the system is increased as a result of a proximity effect, being the reaction faster in the supramolecular complex and therefore favoring the formation of difunctionalized compound **3**.

Further evidences of the formation of the mentioned complex come from NMR studies carried out in THF-d_8 (Fig. 1) and $CDCl_3$ (see Supporting information). The interaction of **4**[14] (an analogue of compound **2** without the reactive amine unit) with the activated ester **1** was followed by ^{1}H NMR.[18] As can be seen in Figure 1, NH carbamate signal from **1**, as well as carbamate and amide NH signals of compound **4,** experience shifts revealing their involvement in intermolecular H-bonding. Control experiments reveal that the observed shifts are not due to self-association.

Another strong evidence of the involvement of supramolecular species in the observed reactivity comes from the reaction carried out using methanol as solvent (Table 2). This highly polar protic solvent minimizes intermolecular H-bonding interactions precluding aggregation of this type of molecules.[14] This fact is reflected in the poor yield, 8%, of compound **3** obtained for a 1:3 activated



Scheme 2. Proposed mechanism for the observed substrate selectivity.

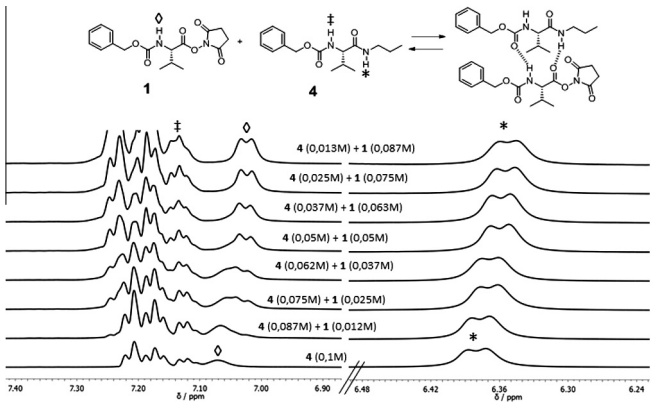


Figure 1. Partial ^{1}H NMR spectra obtained in the study of the interaction of compound **4** with compound **1** in THF-d_8 at 30 °C.

ester/diamine ratio (6-fold diamine excess). The major product in this case was the monofunctionalized one. In THF the reaction provides a much higher 55% yield of difunctionalized compound **3**. It is also noticeable that the yield of **3** in methanol is lower than that statistically calculated, revealing that in this solvent the amine function at **2** is less reactive than at 1,3-propanediamine.

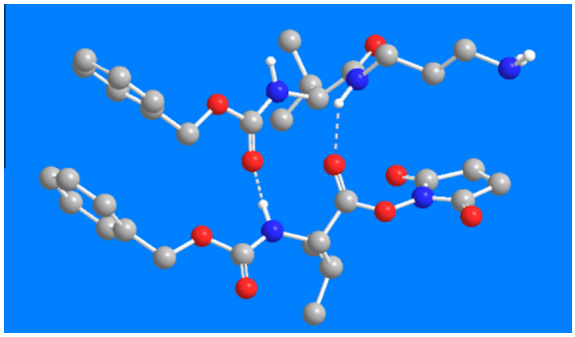


Figure 2. Energy minimized structure (AMBER* force field) of the supramolecular complex between **1** and **2**.

Molecular models obtained with molecular mechanics calculations agree with the association proposed for the supramolecular complex in Scheme 1. As shown in Figure 2, an energy minimized model is obtained which presents two intermolecular H-bonds between carbonyl units and carbamate and amide NHs. The aromatic units are stacked in the model, hinting a possible π–π stacking favorable interaction.

Summarizing, the first acylation of 1,3-propanediamine provokes an activation of the remaining amine group which becomes more reactive. In this way the reaction is driven toward the formation of difunctionalized products under unfavorable relative concentration values of the reagents. The capability of monofunctionalized compound **2** to form a supramolecular complex with activated ester **1** explains the observed substrate selectivity by means of proximity effects. The supramolecular interaction is demonstrated to take place via at least two H-bond interactions involving carbamate and amide NHs as H-donors and oxygen atoms of carbonyl groups as H-bond acceptors. The reported example represents a case of supramolecular control of reactivity which is related to the chemistry of life, whose efficiency and selectivity are based very often on proximity effects associated to supramolecular interactions.

Acknowledgments

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Supplementary data

Supplementary data (^{1}H and ^{13}C NMR spectra. Determination of statistical yields.) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.01.094. These data include MOL files and InChiKeys of the most important compounds described in this article.

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15. For characterization purposes, compound **2** can be prepared univocally using protecting groups. 2.68 g of *tert*-butyl-(3-(2-(((benzyloxy)carbonyl)amino)-3-methylbutanamido)propyl)carbamate (6.26 mmol) was dissolved in 103 mL of CH_2Cl_2 and 13.2 mL of TFA was added under N_2 atmosphere. The mixture was left under stirring for 3 h at room temperature. Finally the solvent was eliminated under vacuum and a white solid appeared corresponding to the trifluoroacetate salt of **2**. (0.624 g, 2.03 mmol 33%). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.90 (s, 1H), 7.42–7.15 (m, 5H), 5.02 (s, 2H), 3.77 (t, 1H), 3.26–2.87 (m, 4H), 2.50 (t, 1H), 2.02–1.87 (m, 1H), 1.54–1.37 (m, 2H), 0.83 (dd, J = 6.7, 3.9 Hz, 6H).^{13}C NMR (125 MHz, DMSO-d_6): δ = 171.42 (C=O), 156.53 (C=O), 137.57 (CH), 128.76 (×2) (CH), 128.18 (×2) (CH), 128.05 (CH), 65.80 (CH_2), 60.87 (CH_2), 36.63 (CH), 33.27 (CH_2), 30.67 (CH), 19.55 (CH_3), 18.68 (CH_3). HRMS (ESI-TOF, positive mode): m/z calcd for $C_{16}H_{25}N_3O_3^+$ 308.1969; found 308.1974 $[M+H]^+$ (Δ = 0.5 ppm).
16. In a representative example, 1.16 g of 3.4 mmol activated ester was dissolved in 50 mL of THF. Then 2 mL of a 1.66 M solution of 1,3-diaminopropane in THF, 3.4 mmol were added at once at 25 °C under vigorous stirring. After 4 h the solvent was evaporated. To isolate compound **3** the solid residue was washed thrice with aqueous KOH 1 M, then with distilled water and then dried overnight at 60 °C.
17. In a representative example, 57.7 mg of 0.17 mmol activated ester was dissolved in 0.9 mL of THF. Then 0.1 mL of a 1.66 M solution of 1,3-diaminopropane in THF, 0.17 mmol were added at once at 25 °C under vigorous stirring. After 5 minutes 1 mL of a solution of 20% acetic acid in THF was added in order to protonate the excess of diamine. Then the solvent was evaporated and the solid residue dried and homogenized with an agate mortar. The solid was dissolved in DMSO-d_6 to analyze the proportion of compounds present in the crude by ^{1}H NMR.
18. Solutions of compounds **4** and **1** in THF-d_8 or $CDCl_3$ (0.1 M) were mixed in varying amounts and NMR spectra recorded at 30 °C.