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Enantioselective aldol reaction catalysed by polyleucines

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Abstract—Polyleucines of various lengths act as enantioselective catalysts in the aldol condensation between cyclohexanone and a series of aromatic aldehydes, a reaction which may be of prebiotic significance.

1. Introduction

The aldol reaction, which forms C–C bonds, is a key reaction in organic synthesis, with remarkable biological and prebiological significance.[1] Following the seminal experiments by List, Lerner and Barbas in polar organic solvents, many asymmetric aldol reactions have been reported in the literature.[2] Simple α-amino acids are known to catalyse not only intramolecular, but also intermolecular aldol reactions with high enantioselectivity and high yield in organic solvent reaction media[3] and in aqueous solutions,[2a] which may be of prebiotic significance.[3a] These experiments demonstrated the role of (*S*)-proline in promoting asymmetric aldol reactions, as well as the catalytic asymmetric effect of non-racemic alanine and valine in a water-based prebiotic carbohydrate synthesis from glycoaldehyde and formaldehyde.[4] These results were extended with the report of the efficient peptide-catalysed stereoselective synthesis of tetroses by aldol condensation of glycolaldehyde.[5] Moreover, Cordova et al. have recently reported that small peptides catalyse the asymmetric condensations with up to 99% ee, that is, with stereoselectivities comparable with those of natural enzymes.[6] The possibility that these results are also of prebiotic significance has been raised.[7] The thermodynamic control of asymmetric amplification based on the equilibrium solid–liquid phase behaviour of amino acids in solution has been described.[3]

These reports are consistent with our results on the behaviour of polyamino acids, such as L-polyleucine (PLL), which are known to act as synthetic enzymes in the asymmetric epoxidation of chalcone and other electron-deficient alkenes (the Julià–Colonna reaction).[8] The kinetics and mechanism of this reaction, which have been investigated using a soluble PEG–polyleucine conjugate, exhibited saturation kinetics for both chalcone and hydrogen peroxide, indicating that polyleucine has an enzyme-like behaviour.[9] Enantioselective catalysis was achieved with peptides with as few as five residues while scalemic catalysts showed high chiral amplification.[10] On the basis of these results, we speculated that simple compounds such as leucine and small oligopeptides derived from it, such as polyleucine, could have played a role in the enantioselective formation of carbon–carbon bonds, not available by other abiotic mechanisms. Leucine, together with alanine and other amino acids of the pyruvate family, has been obtained on mildly reducing mixtures [11]; on the other hand it is likely that polyleucine and leucine-containing oligomers were present in the prebiotic environment.[12] Following this approach, we decided to investigate the role of leucine and polyleucine of various lengths as potential synthetic enzymes in the aldol condensation reactions.

2. Results and discussion

We report here the organocatalysed cross aldol reaction between cyclohexanone and aromatic aldehydes promoted by sub-molar quantities of alanine, leucine and several leucine

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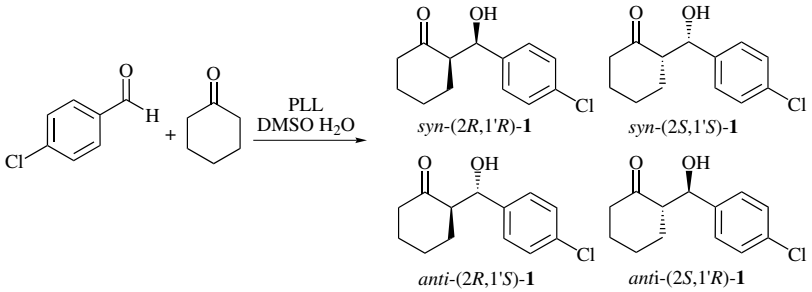


Scheme 1. Aldol condensation of 4-chlorobenzaldehyde with cyclohexanone.

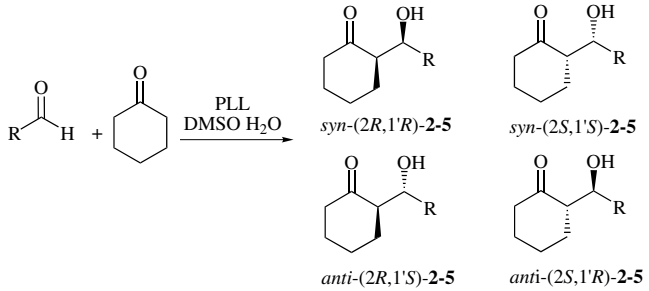
oligomers of different lengths in DMSO/H_2O as solvent.[13] The 4-chlorobenzaldehyde was chosen as a model substrate (Scheme 1), but the reaction with four other aromatic aldehydes (see below) has also been investigated. L-Leucine and L-alanine have been employed for the sake of comparison. When cyclohexanone is the source of the enolate, as in the present work, an *E*-enolate is formed, and it gives as expected predominance of the *anti* products.[14]

As shown in Table 1, *anti*aldols were formed preferentially in all cases, albeit with low yields. Enantioselectivity was high for the leucine-catalysed reaction, but lower values were observed for the different polyleucines. The results we observed are comparable with previous reports.[3a,5,7a] They extend the repertoire of the Julià–Colonna reaction as a possible model of a prebiotic reaction, but also raise a number of issues that require further study. PLL-Bayer,[15] which contains seven to eight leucine residues on average, gave the best results in terms of chemical yield, enantio- and diastereoselectivies. The *anti*/*syn* diastereomeric ratio, determined independently by ^{1}H NMR and chiral HPLC, was 5/1, while the prevailing diastereoisomer with the (2*R*,1′*S*) absolute configuration[16] was obtained in 54% ee (Table 1, line 3). The further addition of 10 mol % equiv of PLL-Bayer (Table 1, line 4) led to a reasonable increase both in enantioselectivity (65% ee) and in diastereoselectivity (7/1 dr). Unexpectedly, when commercial PLL-Alfa Aesar was used (Table 1, line 5), the prevailing *anti* diastereoisomer had the (2*S*,1′*R*) absolute configuration, that is, the configuration opposite to that found with PLL-Bayer, whereas both the dr and the ee were practically the same. The decrease in chemical yield can be explained by the higher degree of polymerisation of the catalyst, which contains 64 leucine units on an average. The higher degree of polymerisation might affect the topological properties of the PLL-Alfa Aesar catalyst, thus affording compound *anti*-**1** with opposite configuration with respect to the other catalysts. The PEG–polyleucine conjugate (PLL–PEG) was inactive, in contrast with the excellent enantioselectivities and chemical yield in the epoxidation reaction. L-Leucine and L-alanine competed favourably with both PLLs in terms of chemical yield, dr and ee (Table 1, lines 1 and 2) and the prevailing *anti* diastereoisomer again had the (2*R*,1′*S*)-absolute configuration. DMSO/H_2O in a 20:1 ratio was the solvent of choice with L-leucine as catalyst; no reaction was observed in THF/H_2O and dioxane/H_2O in a 20/1 ratio. The presence of tetrabutyl ammonium sulphate as a phase transfer catalyst (PTC) (Table 1, line 7) increased the yield but decreased the dr and ee values. As a first step towards the better understanding of the catalytic role of small peptides in the reactions involving keto-bearing compounds, we extended our study to other related aromatic aldehydes and to α-methyl cinnamaldeyde (Scheme 2).

Table 1. Aldol condensation of 4-chlorobenzaldehyde with cyclohexanone catalysed by amino acids and L-polyleucine (PLL)

Catalyst	Reaction time (h)	Yield (%)	dr[e] (*anti*/*syn*)	ee[e] *anti* (%)	ee[e] *syn* (%)
L-Alanine[a]	96	44	18:1	92	33
L-Leucine[a]	144	35	30:1	95	21
PLL-Bayer[b]	120	28	5:1	54	19
PLL-Bayer[c]	240	33	7:1	65	6
PLL-Alfa Aesar[b]	168	9	3:1	48	15
PLL–PEG[b]	11 days	0			
L-Leucine + PTC[d]	168	79	4:1	83	15

[a] Reaction conditions: cyclohexanone (1.5 mmol), 4-chlorobenzaldehyde (0.5 mmol), amino acid catalyst (0.1 mmol) in DMSO/H_2O (2.0 mL/0.1 mL).
[b] PLL catalyst (0.05 mmol) was used.
[c] PLL catalyst (0.1 mmol) was added in two aliquots.
[d] Amino acid catalyst (0.1 mmol) and tetrabutyl ammonium sulfate (0.06 mmol) were used.
[e] Determined by chiral phase HPLC analysis using an AD Chiralcel column, which base-line separated the four stereoisomers.



Scheme 2. For R see Table 2.

Moderate to high enantio- and diastereoselecivities were obtained with L-leucine as a catalyst with benzaldehyde (Table 2, entry 1), 1-naphthaldehyde (Table 2, entry 4) and α-methyl cinnamaldehyde (Table 2, entry 8). The enantio- and diastereoselectivities with PLL-Baeyer and benzaldehyde (Table 2, entry 2), 1-naphthaldehyde (Table 2, entry 5), 4-nitrobenzaldehyde (Table 2, entry 6) and

Table 2. Aldol condensation of various aldehydes with cyclohexanone in the presence of PLLs

Entry	R	Product	Catalyst	Reaction time (h)	Yield (%)	dr[c] (*anti*/*syn*)	ee[c] (%) *anti*	ee[c] (%) *syn*
1	–Ph	**2**	L-Leucine[a]	144	85	14:1	94 (2*S*,1′*R*)	22 (2*S*,1′*S*)
2	–Ph	**2**	PLL-Bayer[b]	120	7	8:1	40 (2*S*,1′*R*)	33 (2*R*,1′*R*)
3	–Ph	**2**	PLL-Alfa Aesar[b]	168	4	3:1	56 (2*R*,1′*S*)	37 (2*R*,1′*R*)
4	-1-Naphthyl	**3**	L-Leucine[a]	144	28	16:1	⩾99 (2*R*,1′*S*)	5
5	-1-Naphthyl	**3**	PLL-Bayer[b]	168	7	23:1	59 (2*S*,1′*R*)	19
6	–Ph-4-NO_2	**4**	PLL-Bayer[b]	168	34	6:1	21 (2*S*,1′*R*)	34
7	–Ph-4-NO_2	**4**	PLL-Alfa Aesar[b]	168	17	5:1	71 (2*S*,1′*R*)	47
8	-3-Phenyl-2-propen-2-yl	**5**	L-Leucine[a]	144	15	7:1	74 (2*S*,1′*R*)	29
9	-3-Phenyl-2-propen-2-yl	**5**	PLL-Bayer[b]	168	13	19:1	69 (2*S*,1′*R*)	45

[a] Reaction conditions: cyclohexanone (1.5 mmol), aldehyde (0.5 mmol), amino acid catalyst (0.1 mmol) in DMSO/H_2O (2.0 mL/0.1 mL).
[b] PLL catalyst (0.05 mmol) was used.
[c] Determined by chiral phase HPLC analysis using an AD/OJ Chiralcel column.

α-methyl cinnamaldehyde (Table 2, entry 9) were of the same order of magnitude as those observed with model substrate **1**. In all cases, the prevailing *anti*-diastereisomer had the (2*S*,1′*R*)-absolute configuration. With α-methyl cinnamaldehyde, the results with PLL-Bayer were comparable (yield and enantioselectivity) or even higher (diastereoselectivity) than those obtained with leucine (Table 2, entries 8 and 9). PLL-Alfa Aesar gave better results in terms of enantioselectivity with respects to PLL-Bayer with benzaldehyde (Table 2, entries 2 and 3) and 4-nitrobenzaldehyde (entries 6 and 7, Table 2). Surprisingly, with PLL-Alfa-Aesar the replacement of a hydrogen atom with a nitro group gave the opposite stereochemical course, that is, (2*R*,1′*S*) for **2** (Table 2, entry 3) and (2*S*,1′*R*) with aldol **4** (Table 2, entry 7). In order to ascertain the possible role of the lengthy polypeptides in chiral amplification, scalemic polyleucine was also explored. As shown in Table 3, in contrast with the amplification effect observed in the asymmetric epoxidation of chalcone with hydrogen peroxide in alkaline medium,[10] the effect of PLL on the aldol condensation of cyclohexanone with 4-chlorobenzaldehyde was negligible. This may be due to the higher degree of polymerisation of the catalyst, which is formed by 64 leucine units on average. Work is currently in progress which will address this issue. Interestingly non-linear effects in the acyclic amino acid catalysed aldol reaction of cyclohexanone with 4-nitrobenzaldehyde in heterogeneous wet DMSO have recently been reported.[17] The prebiotic availability of the reactants used in our model experiments may be highly speculative. By the same token, it can be argued that the DMSO/water medium employed here and by others[3a] is not compatible with prebiotic conditions. However, the results reported herein suggest the existence of facile routes to homochirality that may help to understand the enantioselective formation of carbon–carbon bonds.

Table 3. Aldol condensation of 4-chlorobenzaldehyde with cyclohexanone in the presence of PLLs

Catalyst[a] (%)	Reaction time (h)	Yield (%)	dr[b] (*anti*/*syn*)	ee[b] *anti* (%)	ee[b] *syn* (%)
D-PLL ee 9.1	168	0			
D-PLL ee 20	168	2	1.8:1	11	12
L-PLL ee 20	168	7	1.8:1	7	7
L-PLL ee 42.9	168	10	1.3:1	4.5	14

[a] Reaction conditions: cyclohexanone (1.5 mmol), 4-chlorobenzaldehyde (0.5 mmol), PLL catalyst (0.05 mmol) in DMSO/H_2O (2.0 mL/0.1 mL).
[b] Determined by chiral phase HPLC analysis using AD Chiralcel column.

3. Conclusions

The results presented herein show the catalytic role of various polyleucines (and of simple amino acids such as L-alanine and L-leucine) in the enantioselective intermolecular aldol condensation between cyclohexanone and a series of aromatic aldehydes. They extend previous observations on the catalytic role of amino acids, and strengthen the hypothesis that these and other simple compounds (including oligopeptides) could play a key role in prebiotic catalysis.

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13. *Typical procedure for aldol condensation catalysed by PLLs.* The appropriate aldehyde (0.5 mmol) was dissolved in a mixture of DMSO/H_2O (2 mL/0.1 mL), then cyclohexanone (1.5 mmol) after which the PLLs (see Tables 1–3) were added. The reaction mixture was stirred at 250 rpm at room temperature for the indicated time (see Tables 1–3). The reaction progress was monitored by TLC using petroleum ether/ethyl acetate (8/2) as mobile phase. After the appropriate reaction time, the mixture was filtered through a silica cake to remove DMSO/H_2O mixture, the filter was washed with petroleum ether/ethyl acetate (9/1, 100 mL) and (8/2, 100 mL). The recovered organic layer was concentrated under reduced pressure. The crude was purified by flash chromatography using petroleum ether/ethyl acetate (8/2) as eluant. The isolated products were characterised according to ^1H NMR, mass analysis and the collected data were in accordance to those known in the literature. For compounds **1**, **2**, **4** see Ref. 16; for compounds **3** and **5**; see Denmark, S. E.; Stavenger, R. A.; Wong, K. T.; Su, X. *J. Am. Chem. Soc.* **1999**, *121*, 4982–4991.
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