# Enhancement of Homochirality in Oligopeptides by Quartz

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Dedicated to Professor *Dieter Seebach* on the occasion of his 65th birthday

The onset of homochirality in oligopeptide chains is spontaneous. We show that the oligomerization of dilute racemic NCA (*N*-carboxyanhydride = cyclic anhydride) – leucine in the presence of quartz in aqueous solution yields oligopeptides that are characterized by a high degree of homochiral ($L_n$ and $D_n$) sequences on the quartz surface. A similar effect is also observed, although to a lesser extent, for hydrophilic chains, namely in the oligomerization of racemic NCA – glutamic acid in presence of hydroxylapatite. We argue that these findings may be relevant for the chemical evolution of homochirality.

**Introduction.** – One traditional way to explain the origin of homochirality in the biopolymers of life is to assume that the chiral discrimination has taken place at the level of the racemic $\alpha$-amino acid and nucleic acid precursor monomer mixture by producing a rather small enantiomeric imbalance [1–4]. This process appears statistically rather improbable because, in the following sequence of oligomerizations, the relative abundance of the homochiral oligomers will become negligible with increasing chain length [5–7]. We present here a system for the enhancement of such homochiral oligomers on mineral surfaces. This approach emphasizes that chiral discrimination may take place at the macromolecular level. The shift of emphasis highlights the greater adsorption properties of longer oligopeptide and oligonucleotide chains.

Two lines of observations prompted us to investigate the possible role of minerals in the enhancement of homochirality. The first one is based on the 'adsorbed template' model, in which minerals serve as adsorbents for organic molecules (*e.g.*, amino acids, oligopeptides, and sugars) and/or as catalysts for a variety of organic reactions (*e.g.*, protein synthesis) [8–12]. The other observation stems from our own recent work, which shows that the oligomerization of activated $\alpha$-amino acid racemates (NCA – amino acids [13][14]) in aqueous solution yields oligopeptides with a significant degree of homochirality ($L_n$ and $D_n$) [15][16]. In this context, it is important to note that NCA – amino acids, or their thio equivalents, are considered as possible prebiotic compounds [17][18]. In terms of chemical evolution, it appeared, therefore, interesting to check whether the surface properties of minerals in general can enhance the naturally occurring homochirality.

Naturally existing quartz displays enantiomorphic dextrorotatory (+) or levorotatory (−) chiral crystals [19][20]. In this study, we will focus on the oligomerization of racemic NCA – Leu in aqueous solution in presence of racemic quartz ((±)-quartz: equivalent amounts of (+)- and (−)-quartz). These are realistic conditions since (+)-

and (−)-quartz crystals are equally distributed on the earth [21]. Reactions are carried out with racemic mixtures of perdeuterated *N*-carboxyanhydride (NCA)−L-Leu (= NCA−($D_{10}$)L-Leu) and non deuterated NCA−D-Leu (5.7 mM initial monomer concentrations) in the presence and absence (reference bulk in aqueous solution) of (±)-quartz. The products in the bulk aqueous solution, adsorbed products, and products in the supernatant of the quartz system are analyzed by reverse-phase high-performance liquid chromatography mass spectrometry (RP-HPLC/MS). The use of a perdeuterated L-Leu allows us to distinguish between different stereoisomeric subgroups ($[D\text{-Leu}]_p[(D_{10})L\text{-Leu}]_q$) by the (selected-ion-monitoring (SIM) MS) [22]. This means that the ($[D\text{-Leu}]_p[(D_{10})L\text{-Leu}]_q$)-subgroups having the same degree of oligomerization $n = p + q$ will be separated by at least 10 and maximally $10\,n$ Da [15][16]. As a comparison, reactions are also carried out with racemic mixtures of deuterated NCA−L-Glu (= NCA−($D_5$)L-Glu) and NCA−D-Glu (80 mM initial monomer concentrations) in the presence and absence (reference in bulk aqueous solution) of hydroxylapatite (anion-exchange mineral), which will afford oligopeptides that are highly hydrophilic. In this case, product analysis is performed with normal-phase high-performance liquid chromatography mass spectrometry (NP-HPLC/MS). The different stereoisomeric subgroups ($[D\text{-Glu}]_p[(D_5)L\text{-Glu}]_q$) can also be distinguished by SIM-MS.

**Experimental.** – *Quartz Preparation.* (+)- and (−)-Quartz crystals of *Japanese Industrial Standard* (*JPS*) quality were a gift of *Toyo Communication Equipment Co*. The meshed crystals were cleaned and activated with 2M HCl then washed with doubly destilled $H_2O$ until a pH of $\leq 7$ was reached. Then, the quartz crystals were washed with acetone and dried for 12 h at 120°.

*Amino Acid Condensation* (Leucine). A soln. (21.4 µl) of 40 mM racemic NCA−D-Leu/NCA−($D_{10}$)L-Leu in 0.4M 1*H*-imidazole buffer (pH 7) was mixed with 150 µl 0.4M imidazole buffer (pH 7) containing 20 mg quartz powder (10 mg each (+)- and (−)-quartz) in a 1.5 ml eppendorf tube and incubated with shaking for 12 h. After sedimentation or centrifugation at 8000 rpm for 1 min the supernatant was set aside. Then, 150 µl buffer was added to the remaining quartz powder and again 21.4 µl of a soln. of 40 mM racemic NCA−D-Leu/NCA−($D_{10}$)L-Leu in 0.4M 1*H*-imidazole buffer (pH 7) was added. After 12 h, this procedure was repeated, then, the quartz was washed 20 × with *Millipore* $H_2O$, and, after each washing cycle followed by sedimentation or centrifugation at 8000 rpm for 1 min, the supernatents were set aside. Then, the adsorbed products were desorbed and solubilized by adding 3 × 500 µl 100 mM $Na_4P_2O_7$ (pH 10.4, desorption) and 3 × 500 µl MeCN/$H_2O$ 2:1 (solubilization) to the quartz powder. The pyrophosphate and MeCN/$H_2O$ solns. were combined and analyzed by RP-HPLC/MS. Ref. reactions were carried out without quartz. At the end of the 12-h reaction, an equal vol. of MeCN was added to bring all oligomers into soln. These homogeneous solns. were analyzed by RP-HPLC/MS.

*Amino Acid Condensation* (Glu). 300 µl of a 80 mM racemic NCA−D-Glu/NCA−($D_5$)L-Glu soln. in 0.4M 1*H*-imidazole buffer (pH 7.0) was either kept in an eppendorf tube for 12 h on a shaker or added to an eppendorf tube containing 25 mg hydroxylapatite (> 99.0%, *Fluka*, CH-Buchs) and also kept for 12 h on a shaker. After 12 h, the supernatant from centrifugation at 8000 rpm for 2 min was set aside, and, again, 300 µl of an 80 mM racemic NCA−D-Glu/NCA−($D_5$)L-Glu soln. was added to the hydroxylapatite. Then, the eppendorf tubes were centrifuged at 8000 rpm, and the hydroxylapatite washed 5 × with 300 µl Millipore $H_2O$. Products were desorbed by adding 3 × 300 µl 100 mM $Na_4P_2O_7$ (pH 10.4) to the hydroxylapatite. The pyrophosphate fractions were combined, and MeCN/$H_2O$ 1:1 was added. In the experiments without hydroxylapatite, again 300 µl of the racemic soln. was added to the mixture and incubated for another 12 h. At the end of the reaction, MeCN/$H_2O$ 1:1 was added to bring all oligomers into soln. For the determination of the binding of the $Glu_n$ on hydroxylapatite, typically, a 80 mM soln. of NCA−L-Glu (pH 7.0) was kept for 24 h in an eppendorf tube and then incubated for 24 h with 25 mg of hydroxylapatite. The binding curves were calculated according to the SIM-area ratios of the $Glu_n$ for a constant *n* in the eluate (bound fraction) and in the supernatant (unbound fraction).

*LC/MS.* Product analysis was achieved by HPLC (*P4000*, *Thermo Finnigan*, San Jose, CA) with diode-array (*UV 6000 LP*, *Thermo Finnigan*) and ion-trap MS detection (*LCQ-Deca*, *Thermo Finnigan*). To separate the

$Leu_n$ condensation products, a $C_{18}$-reversed-phase column (*EC 250/4 Nucleosil 100-5*, *Macherey-Nagel*, CH-Oensingen) was used, with a 1 ml/min flow rate, r.t.; solvent (A (0.1% aq. TFA) and B (99.9% MeCN, 0.1% aq. TFA) program: 2 min isocratic at 20% B followed by a gradient to 90% B at a rate of 1.84% B/min. Relative hydrophobicities were determined under the same conditions [24]. Separation of the $Glu_n$ condensation products was achieved on a normal-phase column (*TSK gel Amide-80*, 25 × 0.46 cm i.d., *Tosoh Biosep*, D-Stuttgart); 0.7 ml/min flow rate, r.t., solvent (C (97% MeCN, 3% $H_2O$, 0.1% aq. TFA) and D (55% MeCN/45 % $H_2O$, 0.1% aq. TFA) program: 2 min isocratic flow at 100% C followed by a gradient to 100% D at a rate of 2.63% D/min. The different stereoisomeric subgroups of $Leu_n$ and $Glu_n$ oligomers were monitored by ion-trap MS with selected ion monitoring (SIM). For quantification, the SIM peaks of the different stereoisomeric subgroups of $Leu_n$ and $Glu_n$ oligomers were integrated over time. The total of all SIM areas of a particular oligomer corresponds to 100% (calculation used for the *Table*). For the determination of the total homochirality on quartz, the SIM-peak areas of the adsorbed oligomers ($5 \leq n \leq 7$) were integrated over time; the sum of these areas corresponded to 100%. The electrospray ionization (ESI) sensitivity for each oligomer length was determined by comparing the UV signal at 215 nm with the SIM signal. It was generally found that longer oligopeptides show somewhat higher ESI sensitivities than shorter ones. Furthermore, it was determined that oligopeptides 6–11 units long showed, in a first approximation, similar ESI sensitivities. It was also discovered that stereoisomers of the same length exhibited, in a first approximation, similar ionization sensitivities, and it is, therefore, reasonable to assume that the MS-SIM signals are directly proportional to the conc. of each diastereoisomer in soln. (see also [7]). Typical settings were 350° capillary temp., 80 units sheath-gas flow rate, 20 units auxiliary-gas flow rate, 4.50 kV I-spray voltage, 3–39 V capillary voltage and −60 to +25 V tube-lens offset.

**Results and Discussion.** – Let us first consider the oligomerization of activated racemic Leu. In typical experiments, we obtain oligomers $Leu_n$ with $2 \leq n \leq 6$ in bulk aqueous solution and $Leu_n$ with $2 \leq n \leq 7$ in presence of quartz. In the case of the quartz system, it can be seen that all of the shorter oligopeptides (up to $n = 4$) are removed by washing with water (*Fig. 1,a*). After 20 washing cycles no more product is removed (*Fig. 1,b*). The desorption of the longer oligopeptides ($5 \leq n \leq 7$) becomes possible only when the washing is carried out with a 100 mM $Na_4P_2O_7$ solution, pH 10.4 (*Fig. 1,c*). It is assumed that mostly pyrophosphate anions replace the oligopeptides on the quartz surface [23]. Also, the reduction of the activity of the water bound to the pyrophosphate salt may further decrease the affinity of $Leu_n$ for the surface [23]. It is further important to note that the solvent mixture MeCN/$H_2O$ 2:1, which would normally solubilize $Leu_n$ oligomers that are simply precipitated and are not bound to the quartz surface, does not desorb any oligopeptides.

These results show that the affinity of $Leu_n$ oligomers for the quartz surface increases with increasing $n$, indicating that increasing hydrophobicity is the main driving force for binding to the surface. In agreement with these observations, we find that increasing the amount of quartz and keeping the Leu monomer concentration constant, there is a shift in size distribution on the quartz surface towards longer chains (data not shown). Our findings are consistent with data reported in the literature for the adsorption of short hydrophobic homo-oligopeptides on silica, which showed a linear dependence of the binding constants with increasing chain length [10]. Concerning the yields of adsorbed peptides the following can be said for typical racemic NCA–Leu condensations in the presence of quartz. Approximately 50% of the initial amount of leucine used is transformed into peptides with $n \geq 2$. Because the shorter peptides (up to $n = 4$) are not adsorbed (they remain mostly in the supernatant or are removed from the quartz surface after multiple washings), finally, only *ca.* 10% of the product is adsorbed onto the quartz surface (this calculation is based on the SIM-peak areas of the $Leu_n$ chains present after desorption in the supernatant and present in

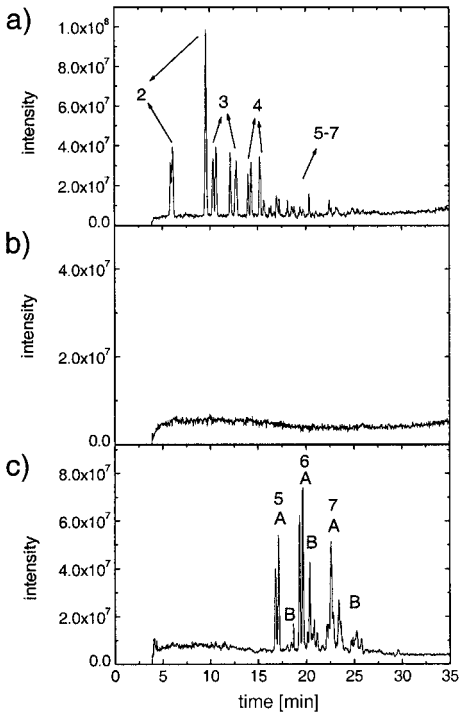


Fig. 1. *Typical total ion current (TIC) chromatograms for washing and desorption of the* $Leu_n$ *products from the mineral surface for racemic NCA–Leu condensations in the presence of (±)-quartz powder* a) *after one wash with Millipore* $H_2O$, b) *after 20 washes with Millipore* $H_2O$, *and* c) *after 20 washes with added 100 mM* $Na_4P_2O_7$ (pH 10.4). The numbers indicate the degree [%] of oligomerization, A = homochiral products and B = heterochiral products of adsorbed $Leu_n$ ($5 \leq n \leq 7$).

all washing fractions). In other words, 10% of the products consist of oligopeptides with $5 \leq n \leq 7$ (*Fig. 1,c*). Since we expose the quartz surface three times to a 5.7 mM racemic NCA–Leu solution (see *Exper. Part*), we obtain *ca.* 0.9 mM of longer ($5 \leq n \leq 7$) peptide chains adsorbed.

Let us consider now the determination of the homochirality of the longer adsorbed stereoisomers of $Leu_n$. For this determination, we make two comparisons:

*i*) First, we compare the percentage of homochiral $Leu_n$ found experimentally with that calculated assuming a purely random oligomerization (binominal distribution) [7][15][16]. *ii*) Second, we compare the percentage of homochiral $Leu_n$ found experimentally with that found in bulk aqueous solution (reference reaction). The percentage of homochirality ($P_{Ho}$) can be determined for the homochiral $Leu_n$ adsorbed on the quartz surface, left in the supernatant, and present in the control experiment in bulk aqueous solution.

It can be seen that the $P_{Ho}$ for $n = 5$, 6, and 7 experimentally determined on quartz is one order of magnitude larger than that expected according to a purely random oligomerization (*i.e.*, 13-fold higher for $n = 5$, 15-fold higher for $n = 6$, and 17-fold higher for $n = 7$, *Figs. 2* and *3*). This indicates that the generation of homochirality is actually a rather spontaneous process in the oligomerization of racemic NCA–Leu in presence of quartz. The comparison of the stereoisomer distribution of the oligo-Leu adsorbed on quartz with the stereoisomer distribution in bulk aqueous solution shows a strong enhancement of homochirality on the surface with respect to the aqueous solution (*Table*). Furthermore, it can be seen that the enhancement is clearly strongest

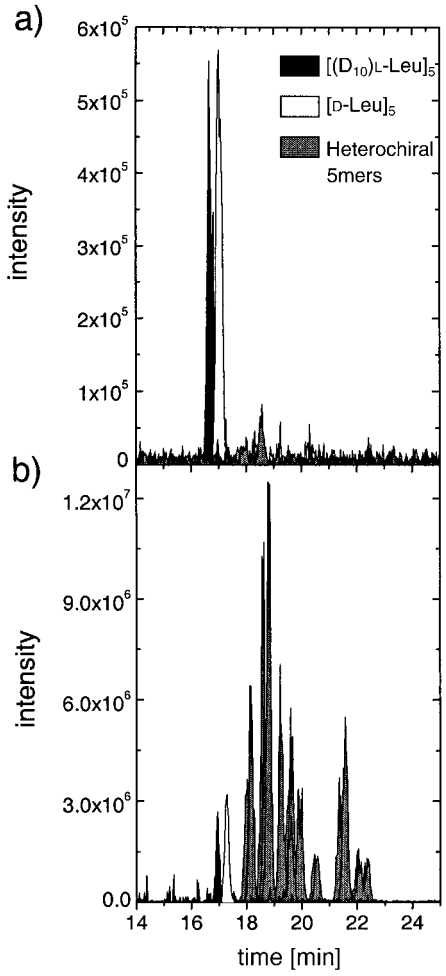


Fig. 2. *Stereoisomer distribution of Leu$_5$* a) *adsorbed on (±)-quartz,* b) *in the supernatant.* The corresponding $m/z$ values (positive ESI, $z = 1$) of the stereoisomeric subgroups are 634.8 Da for [(D$_{10}$)L-Leu]$_5$, 584.43 Da for [D-Leu]$_5$, 624.74 Da for [D-Leu][(D$_{10}$)L-Leu]$_4$, 614.67 Da for [D-Leu]$_2$[(D$_{10}$)L-Leu]$_3$, 604.59 for [D-Leu]$_3$[(D$_{10}$)L-Leu]$_2$, and 594.51 Da for [D-Leu]$_4$-[(D$_{10}$)L-Leu].

for $n = 5$. (*Fig. 2*, *Table*). It can also be seen for $n = 5$ and $n = 6$ that the percentage of homochiral oligopeptides in the supernatant is much lower than in bulk aqueous solution (for $n = 6$ the percentage is actually 0) (*Table*). These findings indicate that (±)-quartz can strongly selectively adsorb the longer ($5 \leq n \leq 7$) homochiral Leu$_n$ oligomers out of a huge mixture of different stereoisomers. The calculation of the relative abundance of the homochiral blocks of the adsorbed oligomers (according to all SIM peaks of the stereoisomeric subgroups for $5 \leq n \leq 7$) gives a value of $47 \pm 6\%$. This is a remarkably high value, considering that we started with a monomeric racemic mixture of NCA–Leu.

The increasing percentage of heterochiral stereoisomers for $n = 6$ and $n = 7$ may appear, at first sight, surprising. In this regard, note that, in general, the relative hydrophobicities of the adsorbed heterochiral chains expressed as % MeCN are strongly shifted towards the relative hydrophobicities of the pure homochiral products

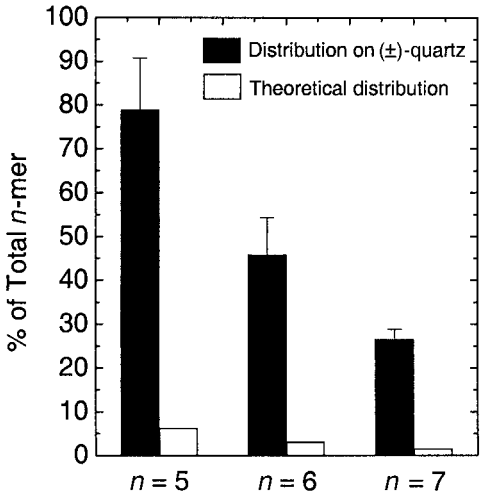


Fig. 3. *Comparison of the experimentally determined relative abundances of the adsorbed homochiral stereoisomers on the (±)-quartz surface.* Values [%] calculated on the basis of a purely random oligomerization. Mean values of three measurements, with standard deviations as error bars.

Table. *Effect of Quartz on Leu$_n$ Stereoisomer Distribution.* Distribution determined for stereoisomers adsorbed on quartz surface, remaining in the supernatant, and present in bulk aqueous solution after racemic NCA–Leu condensation. Reported values are means of three measurements.

| Degree of oligomerization | Distribution on (±)-quartz [%] | Distribution in the supernatant [%] | Distribution in bulk aqueous solution [%] | Relative hydrophobicity [%][a]) |
|---|---|---|---|---|
| $n=5$: | | | | |
| L$_n$ and D$_n$ | 79 ± 12 | 5 ± 1 | 19 ± 4 | 47–49 |
| Heterochiral | 21 ± 12 | 95 ± 1 | 81 ± 4 | 50–59 (51)[b]) |
| $n=6$: | | | | |
| L$_n$ and D$_n$ | 46 ± 8 | 0 | 13 ± 1 | 51–52 |
| Heterochiral | 54 ± 8 | 100 | 87 ± 1 | 53–66 (61)[b]) |
| $n=7$: | | | | |
| L$_n$ and D$_n$ | 27 ± 2 | n.d.[c]) | n.d.[c]) | 57–59 |
| Heterochiral | 73 ± 2 | n.d.[c]) | n.d.[c]) | 59–62 (62)[b]) |

[a]) Expressed as % MeCN required to effect elution on $C_{18}$-RP-HPLC. [b]) Values in parentheses correspond to the upper limit of the relative hydrophobicity of the adsorbed heterochiral stereoisomers. For $n=7$, the relative hydrophobicity could be determined for only the adsorbed stereoisomer. [c]) Not detectable.

(*Fig. 2*, *Table*). This, first of all, shows that there are fewer different stereoisomers present on the quartz surface than in bulk aqueous solution, and it is also a strong indication that the adsorbed Leu$_n$ stereoisomers are of a more stereoregular type (*i.e.*, more block oligopeptides) than found for the reference reaction in aqueous solution. The detectable adsorbed heterochiral stereoisomers for $n=5$, for example, belong only to the stereoisomeric subgroups of [D-Leu][(D$_{10}$)L-Leu]$_4$ and [D-Leu]$_4$[(D$_{10}$)L-Leu] (*Fig. 2*,*a*). The higher hydrophobicities of the long heterochiral chains ($5 \leq n \leq 7$) should be considered together with the observation that the homochiral sequences are retained more strongly on the quartz surface (*Table*). This indicates that the stronger adsorption of homochiral sequences most likely reflects structural features (*i.e.*,

secondary structure in homochiral oligomers). It will be of interest to study in the future in more detail the molecular aspects of this process.

The results of the present study refer to the amino acid oligomerization in presence of racemic quartz. One important question is whether the use of chiral quartz (*i.e.*, (+)-quartz or (−)-quartz) will induce a preferential adsorption of one of the two enantiomeric longer ($5 \leq n \leq 7$) homochiral sequences (*i.e.*, preferential adsorption of L-$Leu_5$ over D-$Leu_5$ on (−)-quartz). Here, for $Leu_n$ oligomers under our experimental conditions, we found no evidence for such behavior (data not shown).

Let us consider now the spontaneous onset of homochirality in the oligomerization of racemic NCA−Glu in aqueous solution and in presence of hydroxylapatite. The polycondensation of NCA−Glu on minerals was reported by *Orgel* and co-workers several years ago [12]. The authors could show that longer $Glu_n$ peptides are retained more strongly than shorter ones on mineral surfaces (namely on illite and on hydroxylapatite), and they were able to reach polymerization degrees of $Glu_n$ up to 55. It appeared, then, interesting to see whether these minerals have also the ability to enhance homochirality in oligopeptides. Under our conditions, the yields of $Glu_n$ with $n \geq 2$ are typically about 75% (integration of the peptide-bond UV signals at 220 nm). The highest detectable degree of oligomerization in typical NCA−L-Glu (or NCA−D-Glu) polycondensations is 12–14%. The binding affinity for hydroxylapatite follows exponential behavior, which indicates that very long $Glu_n$ chains will be bound almost irreversibly (*Fig. 4*, *b*). Concerning the oligomerization of racemic NCA−Glu, it can be seen that the oligomerization is stereoselective (*Fig. 4*, *a*). Indeed, the relative abundance of the homochiral $Glu_8$ oligomers (the highest detectable degree of oligomerization in racemic NCA−Glu polycondensations) is *ca.* 3.3 times higher than the relative abundance expected from a purely random oligomerization. This is an important observation, as it indicates that the preferential formation of homochiral oligopeptides in aqueous solution, observed so far for hydrophobic NCA−amino acid racemates and for mixtures of different hydrophobic NCA−amino acid racemates [15][16], occurs also with activated hydrophilic NCA−amino acid racemates. The preferential formation of homochiral oligopeptides may, therefore, be a general phenomenon.

However, the enhancement of homochirality for $Glu_n$ oligomers on hydroxylapatite is much weaker than that for $Leu_n$ on quartz (*Fig. 4*, *c*). The homochirality determined for the adsorption of $Glu_7$ oligomers (the highest detectable degree of oligomerization on hydroxylapatite) is *ca.* twice as much as that found in bulk aqueous solution (*Fig. 4*, *c*).

**Conclusions.** – We have shown that quartz can significantly enhance the homochirality on its surface by selectively adsorbing the preferentially produced homochiral chains starting from a dilute mixture of activated racemic NCA−Leu. Although this study refers mostly to Leu oligomers adsorbed on quartz and partly to Glu oligomers adsorbed on hydroxylapatite, it is most likely that these findings can be extended to a larger number of amino acid racemates that are condensed in the presence of different kind of minerals. Work with alanine as well as with mixtures of different amino acids is in progress in our group.

Our findings on homochirality do not directly concern the breaking of symmetry in nature. However, they can be relevant in this regard, as they show how the relative

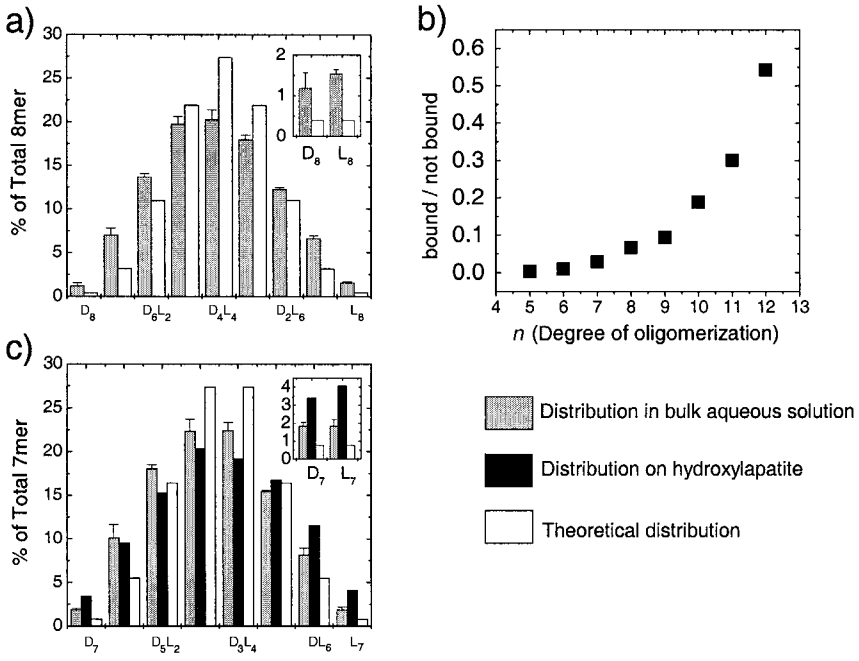


Fig. 4. *Stereoselectivity in the racemic NCA–Glu oligomerization and effect of hydroxylapatite on the stereoisomer distribution. a*) Relative abundances for $D_pL_q$-stereoisomer groups of the $Glu_8$ oligomers in bulk aqueous solution. Mean values of three measurements, with standard deviations as error bars. *Inset:* enlarged view of relative abundances of homochiral $Glu_8$ oligomers. *b*) Binding curve for $Glu_n$ on hydroxylapatite. *c*) Relative abundances for $D_pL_q$-stereoisomer groups of the $Glu_7$ in bulk aqueous solution and adsorbed on hydroxylapatite. *Inset:* enlarged view of relative abundances of homochiral $Glu_7$ oligomers. Note that because of limited space, not all the $D_pL_q$-stereoisomer group symbols are included.

abundance of homochiral oligomers may have been enhanced in prebiotic times. In our opinion, two complementary observations are very important in this context: *i*) Racemic amino acid oligomerizations show preferential formation of homochiral oligopeptides. *ii*) Relatively long homochiral chains can be accumulated on mineral surfaces and separated from shorter ones simply by washing with water.

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