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ORIGINAL ARTICLE

Arginine in the salt-induced peptide formation reaction: enantioselectivity facilitated by glycine, L- and D-histidine

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Abstract The salt-induced peptide formation reaction has been proposed as a conceivable preliminary to the prebiotic evolution of peptides. In the present paper, the behaviour of arginine is reported for this reaction together with a discussion of the catalytic effects of glycine, and L- and D-histidine. Importantly, the behaviour of the two histidine enantiomers is different. Both histidine enantiomers perform better than glycine in enhancing the yields of arginine dipeptide with L-histidine being more effective than D-histidine. Yields in the presence of histidine are up to 70 times greater than for arginine solutions alone. This compares with 4.2 times higher in the presence of glycine. This difference is most pronounced in the most concentrated (containing 80 mM arginine) reaction solution where arginine has the lowest reactivity. A distinct preference for dimerisation of L-arginine also appears in the 80 mM cases for catalyses of other amino acids. This phenomenon is different from the behaviour of aliphatic amino acids, which display obvious inherent enantioselectivity for the L-stereomers in the SIPF reaction on their own rather than when catalysed by glycine or histidine.

Keywords Homochirality · Arginine peptide formation · Copper complex · Chemical evolution

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Introduction

The salt-induced peptide formation (SIPF) reaction

Because of the ease of reaction under relatively simple and crude conditions, the SIPF reaction, discovered in the late 1980s (Schwendinger and Rode 1989a, b), has been shown to provide an important pathway for the formation of peptides as the first amino acids emerged on the primitive earth about 4 billion years ago (Rode 1999). Peptide formation in aqueous solutions containing copper (II) chloride and sodium chloride takes place under slightly elevated temperature (80–90°C) within a couple of days and the conditions for the SIPF reaction can be adapted to all amino acids investigated so far and especially the α-amino acids of biological significance (Schwendinger et al. 1995). There are many geological settings in which the SIPF process could have taken place on the primordial earth including in the oceans, after rainfall, evaporation in lagoons, and in coastal tidal zones and at a time of high heat flux and igneous activity, NaCl and copper would have been readily available in the Precambrian (Asael et al. 2007; Hardie 2003).

The reaction mechanism of the SIPF reaction involves the unsaturated first hydration shell of Na^+ in concentrations over 3 M (Limtrakul and Rode 1985; Limtrakul et al. 1985) which enables NaCl to function as a dehydration agent in the SIPF process. The role of Cu^{2+} is to form a coordination centre in a distorted octahedral complex with two amino acids, two water molecules at an elongate distance due to the Jahn–Teller effect and a chloride ligand. In this structure, one amino acid as the bidentate ligand chelates the Cu centre with its amino nitrogen atom and carboxylate oxygen atom, while the other monodentally bound amino acid becomes the N-terminal of the peptide bond

formed by the SIPF reaction (Liedl and Rode 1992; Schwendinger and Rode 1989a, b).

Previous work has shown a fairly significant enantiomeric excess in the dipeptide yields of several amino acids and especially those with pure alkyl side chains (Fitz et al. 2008; Li et al. 2009; Plankensteiner et al. 2004, 2005). Thus the SIPF reaction is chirally selective and could play a role in explaining the occurrence of biological homochirality (Fitz et al. 2007). The chiral selectivity of the reaction may be attributed to the geometrical structure of the intermediate complex $[CuCl(aa)(aaH_2)(H_2O)_2]^+$, where aa refers to a deprotonated and chelate-coordinated amino acid ligand and aaH_2 represents a double-protonated and carboxylate-coordinating amino acid ligand (Liedl and Rode 1992). The equatorial distortion is caused by the different properties of the ligands and the Jahn–Teller effect keeps axial H_2O ligands at a longer distance, making them less relevant to the reaction. Such a pyramid-like configuration can raise the inherent chirality of the complex because of its lack of symmetry (Lahamer et al. 2000) in addition to the atomic chirality of the copper centre (Hegstrom and Kondepudi 1990) depending on Z^6, Z being the atomic number. Consequently, for copper complexes with amino acid enantiomers, the small parity violation energy difference (PVED) that derives from parity violation in the weak interactions (Lee and Yang 1956; Weinberg 1980; Wu et al. 1957) and is predicted, or measured, to be weak or negligible (Quack 2002), might be magnified to a considerable extent. Thus these copper complexes formed by L- and D-amino acid, respectively, may have different physical and chemical properties just like diastereomers.

Arginine in molecular evolution

Arginine is terminated by a guanidinium group at the distal end of the alkyl side chain and is the most hydrophilic (Eisenberg 1984; Kyte and Doolittle 1982) of the 20 naturally occurring amino acids. It usually functions as the binding site in proteins via its guanidinium group, where a delocalised positive charge is formed by resonance hybrids (Yamauchi et al. 2002). The multiple hydrogen bonds formed between the positively charged guanidinium group and the backbone carbonyl oxygen help to maintain the tertiary structure of proteins (Borders et al. 1994).

Such multiple hydrogen bonds are also found between arginine and nucleobases such as adenine and guanine in zinc finger protein–DNA (Miller and Pabo 2001), implying a plausible link between the RNA and protein worlds. Moreover, a significant and particular affinity between arginine ligand and arginine codons contained in RNA aptamers was observed in an in vitro evolution experiment (Landweber 1999), revealing an exceptional role that arginine might have played in the origin of genetic code.

Arginine in the SIPF reaction

Because of the importance that arginine might have had in early chemical evolution and the specific features of the arginine molecule, it is of interest to investigate the behaviour of arginine in the SIPF reaction. In fact, a suggestion of the involvement of the SIPF reaction in early evolution, viz., the notable peptide sequence distribution favoured by Cu^{2+} and NaCl in the SIPF reaction, still exists in some of the earliest surviving biosomes like archaea and other prokaryotes (Rode et al. 1997) and even in prions which may be a relic of this hypothesised peptide-catalysed evolution (Rode et al. 1999). NaCl has also been shown to be able to enhance the oligomerisation of arginine peptide up to 10-mers when activated by *N,N′*-carbonyldiimidazole in homogenous solution especially with 3 M NaCl (Xin et al. 2006), which is compatible with computational results (Limtrakul and Rode 1985; Limtrakul et al. 1985) related to the conditions of the SIPF reaction. Therefore, it is deemed quite an attractive prospect to investigate the arginine peptide formation by the SIPF mechanism.

The present work is based on statistical averages of five repeats for each experimental system. Different concentrations of arginine were dissolved in the SIPF solutions and subject to the evaporation cycles up to 14 days, respectively. Glycine, L- and D-histidine, whose catalytic effects have been shown previously in several systems (Fitz et al. 2008; Li et al. 2009; Reiner et al. 2006; Suwannachot and Rode 1999), were also added separately to the reaction solutions at levels of 1/8 of the arginine concentration. The main issues for discussion include the percent yields of arginine dipeptide, the catalytic effectiveness of glycine and histidine enantiomers, and the possible enantiomeric excess of L-Arg-L-Arg with the implication for the provenance of homochirality.

Experimental

Materials and reagents

L- and D-Arginine and L-Arg-L-Arg standard compounds were supplied by Bachem AG, Switzerland. No D-Arg-D-Arg standard was required as L-Arg-L-Arg and D-Arg-D-Arg have the same thermodynamic properties in the achiral HPLC column used, and the L–D or D–L forms of arginine dipeptide were not counted because the racemisation rate in the SIPF reaction is not high especially in dilute concentrations (Fitz et al. 2008). Sodium *n*-hexanesulfonate monohydrate as the ion-pairing reagent and acetonitrile

(super-gradient grade for HPLC) was obtained from Sigma–Aldrich GmbH, Germany. NaCl and $CuCl_2 \cdot 2H_2O$ were manufactured by Merck, D-Darmstadt. KH_2PO_4 and concentrated phosphoric acid were provided by Fluka Chemie AG, Switzerland. Water used for solution preparation was purified to ultrapure (18 MΩ cm) using a Barnstead system.

Evaporation cycle experiments

The formation of peptide bonds in the SIPF reaction was carried out in drying-and-wetting cycle experiments that simulate the environment in tidal lagoons on a primordial earth. The SIPF solution consisting of 500 mM NaCl and 40 mM $CuCl_2$ was used with different starting concentrations of 80, 40 and 20 mM of arginine dissolved independently. In the case of experiments using another amino acid as a catalyst, glycine or L- or D-histidine were added, respectively, to the solutions above, at 1/8 (10, 5 and 2.5 mM) of the arginine concentrations.

After mixing, 1 ml aliquots of the reacting solutions were transferred into 2 ml HPLC vials and then held in a thermostatic oven at 85°C to start the first evaporation cycle within 24 h. After each cycle, 1 ml of ultrapure water was refilled to the residue for next cycle under the same conditions. After 0, 1, 4, 7 and 14 cycles, the evaporated samples were removed and frozen dry at −20°C for HPLC analysis.

HPLC analysis

Samples prepared as above were redissolved, filtered and then analysed by reversed-phase ion-pairing HPLC on an Agilent 1100 series system with diode array detector. The qualitative and quantitative results were obtained by comparing the retention times, the UV/vis spectra and the response factors with the standard reference diarginine peptide.

2 µl of a sample solution were injected into an Agilent Hypersil ODS column (5 µm, 2.1 × 200 mm), equipped with a 20 mm precolumn of the same material and a precolumn filter. Solvent A was prepared from 50 mM KH_2PO_4 and 7 mM n-$C_6H_{13}SO_3Na$ in ultrapure water, adjusted to pH 2.3 with concentrated H_3PO_4 and filtered by 0.2 µm hydrophilic polypropylene membrane filters (GH Plypro. Pall Gelman Laboratory, USA); solvent B was pure acetonitrile at super-gradient grade. The gradient conditions were: 0 min 7% B, 14 min 7% B, 20 min 20% B, 23 min 20% B, 24 min 7% B, stop time 30 min, flow rate 0.35 ml/min, column temperature 35°C. The UV/vis detector was set at 200 nm, 4 nm bandwidth and with a reference wavelength at 550 nm, 100 nm bandwidth.

Results and discussion

General

The efficiency of the SIPF reaction is probably determined by the interactions of several factors which are mostly related to the properties of the reacting amino acids: solubility, hydrophilicity, molecular size, electro/nucleophilicity electric charge of the side chain, etc. In the present work, diarginine was identified as the target product because of the confined experimentation, although the possibility to form some longer peptides or other by-products cannot be ruled out.

There is no evidence to show that the side chain of arginine can participate in the SIPF process as a binding site for the copper ions, since it is almost always positively charged because of the high pK_a value (p$K_a > 12$) of the guanidinium side chain (Henchoz et al. 2007). This means the side chain of arginine always remains protonated in most aqueous environments and so the conventional explanation of the SIPF mechanism is still applicable in the case of arginine.

According to the data in Table 1, the relative yield of diarginine shows a very high dependence on the ratio of arginine to copper when no other amino acid is involved as a catalyst. At higher concentrations (80 and 40 mM) of arginine, dimerisation occurs slowly and weakly. In contrast, the $T = 14$ (T/day, being the reaction time) L-Arg-L-Arg yield starting with 20 mM arginine is almost 20-fold as high as the counterpart in 80 mM system. Overall, the reactivity of arginine in the SIPF reaction is relatively low even compared with lysine (Fitz et al. 2008), which has a side-chain of similar scale and which is also positively charged at the distal end, although arginine has good solubility and the strongest hydrophilicity. An assumed explanation for this low reactivity is that arginine's protonated guanidinium group can form multiple hydrogen bonds with up to five water molecules (Borders et al. 1994; Gao et al. 2009). The resulting strong steric hindrance caused by such a large hydrated structure is amplified by repulsion of Cu^{2+} by the delocalised positive charge of the arginine side chain leading to low overall reactivity.

Catalyses of glycine and histidine

The yield of diarginine is catalysed by the presence of other amino acids. The catalytic factor "P" in Tables 2 and 3 is defined as the ratio of the diarginine yield with glycine or histidine to the corresponding yield without any other amino acid. $P_{\text{G-LR}}$, for instance, means the catalytic factor of glycine on the formation of L-Arg-L-Arg starting with L-arginine, and similar formulae apply to the "P" factors with other subscripts.

Table 1 L–L- and D–D-diarginine yields (%) with standard deviations averaged by five runs of independent experiments and corresponding enantioselectivity factors '*R*' without another amino acid as catalyst in the SIPF reaction

Starting concentration	Evaporation cycles	Arg-Arg yield (%)		R_X
		L–L	D–D	
80 mM	1	0.0013 ± 0.0008	0	–
	4	0.0076 ± 0.0019	0	–
	7	0.0121 ± 0.0030	0	–
	14	0.0383 ± 0.0075	0.0132 ± 0.0033	2.89
40 mM	1	0.0013 ± 0.0005	0	–
	4	0.0142 ± 0.0055	0.0075 ± 0.0046	1.90
	7	0.0372 ± 0.0095	0.0305 ± 0.0094	1.22
	14	0.0844 ± 0.0094	0.0754 ± 0.0042	1.12
20 mM	1	0.0061 ± 0.0032	0.0009 ± 0.0030	6.88
	4	0.1074 ± 0.0359	0.1019 ± 0.0321	1.05
	7	0.2832 ± 0.0747	0.2745 ± 0.0615	1.03
	14	0.6229 ± 0.0989	0.6197 ± 0.0822	1.01

Table 2 L-L- and D-D-diarginine yields (%) with standard deviations averaged by five runs of independent experiments and corresponding catalytic factors P and enantioselectivity factors R, catalysed by glycine in the SIPF reaction

Starting concentration	Evaporation cycles	Arg-Arg yield (%)		Catalytic factor		R_G
		L–L	D–D	$P_{G\text{-}LR}$	$P_{G\text{-}DR}$	
80 mM	1	0.0027 ± 0.0005	0	2.00	–	–
	4	0.0238 ± 0.0080	0.0062 ± 0.0040	3.14	–	3.81
	7	0.0511 ± 0.0109	0.0206 ± 0.0062	4.21	–	2.48
	14	0.1193 ± 0.0397	0.0549 ± 0.0072	3.12	4.15	2.17
40 mM	1	0.0024 ± 0.0018	0.0009 ± 0.0051	1.83	–	2.68
	4	0.0286 ± 0.0137	0.0202 ± 0.0109	2.00	2.68	1.42
	7	0.0562 ± 0.0159	0.0500 ± 0.0229	1.51	1.64	1.12
	14	0.0958 ± 0.0098	0.0840 ± 0.0107	1.13	1.11	1.14
20 mM	1	0.0083 ± 0.0041	0.0016 ± 0.0033	1.37	1.80	5.23
	4	0.0935 ± 0.0378	0.0910 ± 0.0242	0.87	0.89	1.02
	7	0.2571 ± 0.0780	0.2289 ± 0.0610	0.91	0.83	1.12
	14	0.5561 ± 0.0712	0.5350 ± 0.0659	0.89	0.86	1.04

The effect of glycine on arginine dimerisation varies consistently with the starting concentration. In the 80 mM system "*P*" varies from 2 to 4.21 (Table 2) while the "*P*" values are lower and in the range 1.11–2 for the 40 mM group. The extreme case occurs in the most dilute concentration 20 mM where diarginine yields are highest in the pure arginine SIPF system. Here, glycine actually functions negatively on the formation of diarginine after four evaporation cycles or more, although the actual percentage yields are still highest because of arginine's good reactivity in 20 mM solutions.

As shown in Table 3, histidine shows a higher catalytic efficiency than glycine, especially in the most condensed concentration of 80 mM where the diarginine yields are increased by 7 to 71 times. Unlike glycine in the 20 mM system, histidine still gives a positive effect on catalysing the formation of diarginine by factors 1.1–10.3 although *P*-factors were observed of around 0.5 after 14 cycles in the 40 mM case. With such a dramatically different result from glycine, the influence of the imidazole side chain of histidine must be taken into account.

The pronounced catalytic capability of histidine on high arginine concentrations in SIPF solutions may be attributable to the influence of the environmental pH value on the imidazole side chain with the $pK_a = 6.02$ (Henchoz et al. 2007). This means that the imidazole ring is positively charged only below pH 6 and will be neutral at pH values over 6. As shown in Table 4, it is known that the pH values of SIPF solutions containing arginine and 1/8 histidine are much lower than 6 in 40 and 20 mM systems, while the pH for the 80 mM case is 8.11. Thus the histidine imidazole side chain is uncharged in 80 mM arginine SIPF solutions and this neutral imidazole group can interact more strongly with Cu^{2+} via its lone electron pair of nitrogen atom than

Table 3 L–L- and D–D-diarginine yields (%) with standard deviations averaged by five runs of independent experiments and corresponding catalytic factors P and enantioselectivity factors

Starting concentration	Evaporation cycles	Arg-Arg yield (%)				Catalytic factor				R_{LH}	R_{DH}
		L–L by L-His	D–D by L-His	L–L by D-His	D–D by D-His	$P_{LH\text{-}LR}$	$P_{LH\text{-}DR}$	$P_{DH\text{-}LR}$	$P_{DH\text{-}DR}$		
80 mM	1	0.0947 ± 0.0116	0.0178 ± 0.0064	0.0827 ± 0.0085	0.0159 ± 0.0045	70.87	–	61.92	–	5.31	5.22
	4	0.1932 ± 0.0398	0.1074 ± 0.0154	0.1813 ± 0.0233	0.0953 ± 0.0107	25.54	–	23.97	–	1.80	1.90
	7	0.2468 ± 0.0248	0.1741 ± 0.0167	0.2424 ± 0.0181	0.1623 ± 0.0106	20.33	–	19.97	–	1.42	1.49
	14	0.2981 ± 0.0157	0.2566 ± 0.0036	0.2937 ± 0.0073	0.2472 ± 0.0073	7.79	19.41	7.67	18.69	1.16	1.19
40 mM	1	0.0131 ± 0.0033	0.0068 ± 0.0037	0.0108 ± 0.0028	0.0071 ± 0.0040	9.88	–	8.12	–	1.94	1.52
	4	0.0431 ± 0.0132	0.0351 ± 0.0099	0.0420 ± 0.0107	0.0346 ± 0.0097	3.02	4.66	2.94	4.59	1.23	1.21
	7	0.0478 ± 0.0120	0.0394 ± 0.0076	0.0513 ± 0.0066	0.0404 ± 0.0069	1.28	1.29	1.38	1.33	1.22	1.27
	14	0.0487 ± 0.0056	0.0317 ± 0.0061	0.0464 ± 0.0039	0.0301 ± 0.0058	0.57	0.42	0.55	0.40	1.54	1.53
20 mM	1	0.0130 ± 0.0043	0.0091 ± 0.0058	0.0111 ± 0.0043	0.0071 ± 0.0056	2.15	10.30	1.83	8.03	1.43	1.57
	4	0.3441 ± 0.1033	0.3533 ± 0.0994	0.3025 ± 0.1236	0.3073 ± 0.1035	3.20	3.47	2.81	3.02	0.97	0.98
	7	0.6851 ± 0.0853	0.6431 ± 0.0801	0.6389 ± 0.0810	0.6489 ± 0.0650	2.41	2.34	2.26	2.36	1.07	0.98
	14	0.7818 ± 0.0819	0.7576 ± 0.0461	0.7277 ± 0.0501	0.6832 ± 0.0693	1.26	1.22	1.17	1.10	1.03	1.07

R: catalysed by L- and D-histinine in the SIPF reaction

Table 4 The pH values of the SIPF solutions without and with different concentrations of arginine and 1/8 concentrated glycine or histidine

Solvent composition	Arginine concentration		
	80 mM	40 mM	20 mM
Arg	8.897	5.528	5.080
Arg + 1/8 Gly	8.892	4.618	4.237
Arg + 1/8 His	8.113	4.603	4.350
SIPF solution	4.150		

in the positively charged case. In addition, Cu^{2+} starts to hydrolyse at pH > 6 but remains abundant in solutions even at pH > 8 due to its high concentration (Vuceta and Morgan 1977), and such a reduction of Cu^{2+} caused by the pH impact might also be implicated in the low Arg-Arg yields in the 80 mM case in Table 1.

Chiral preference

The enantioselectivity of arginine dimerisation in the SIPF reaction is denoted by the factor "R", the ratio of the L-Arg-L-Arg yield to the D-Arg-D-Arg yield under the same reaction conditions. Specifically, R_X is the factor R calculated with the dipeptide yields from the reaction without another amino acid as catalyst, and thus R_{LH} means the factor R for the reaction catalysed by L-histidine.

To obtain good blank values, Arg-Arg yields were measured in initial blank solutions at $T = 0$ (day) before any SIPF reaction. For the D-isomers, this showed a significant "diarginine impurity" up to 0.015% contained in the D-arginine commercial product. This was therefore measured and deducted to yield corrected values for diarginine yields by the SIPF reaction. This leads to the void data (actually below zero) for D-Arg-D-Arg yields shown in Tables 1 and 2. Such dimer impurity in the L-arginine purchased from the same company is not detectable and only the D-Arg-D-Arg data were corrected in this way by measuring the 0-day impurity. As a result, almost all the R values in Tables 1, 2, 3 are "apparently" higher than 1, indicating a preference from L-arginine for dipeptide formation.

The apparent preference shown by the L-form is not completely reliable because of the 0-day off-set as explained above. It is therefore necessary for comparison to re-calculate the R' values shown in Table 5 with the original D-Arg-D-Arg yield data but without deducting the impurity. The L–L data reported here are unaffected since no L-Arg-L-Arg impurity exists. It is clear that all the R' values in Table 5 are more or less lower than the corresponding R values in Tables 1, 2, 3, and most R' values in the 40 and 20 mM rows decrease to below 1 resulting from

Table 5 The enantioselectivity factors R' calculated by experimental data without a deduction of D–D-diarginine impurity

Starting concentration	Evaporation cycles	R'_X	R'_G	R'_{LH}	R'_{DH}
80 mM	1	0.16	0.21	2.79	2.65
	4	0.73	1.10	1.57	1.64
	7	0.84	1.42	1.30	1.36
	14	1.34	1.70	1.09	1.12
40 mM	1	0.10	0.17	0.56	0.47
	4	0.60	0.84	0.84	0.84
	7	0.80	0.88	0.86	0.92
	14	0.92	0.98	1.01	1.01
20 mM	1	0.35	0.50	0.50	0.49
	4	0.91	0.88	0.93	0.94
	7	0.97	1.05	1.04	0.96
	14	0.98	1.01	1.01	1.04

the impurity in the D-arginine reagent. Nevertheless, in the 80 mM case, especially from the data columns of R'_{LH} and R'_{DH}, values step up to 1.09–2.79, so do the R'_G values varying between 1.10 and 1.70 from four cycles onwards. This suggests an evident "L-form preference" for peptide formation from concentrated arginine catalysed by glycine or histidine, and the latter seems more effective in catalysing the L-form preference.

There is a minor difference in the catalytic efficiency of the histidine enantiomers and almost all the catalytic factor $P_{LH\text{-}LR}$ and $P_{LH\text{-}DR}$ values in Table 3 are higher than the $P_{DH\text{-}LR}$ and $P_{DH\text{-}DR}$ counterparts. L-Histidine appears more effective as a catalyst on arginine peptide formation in the SIPF reaction, and this might form part of general development of biological homochirality in which L-amino acids were favoured in reactions involved in prebiotic evolution.

Conclusion

Arginine, the most basic and ionic of the naturally occurring amino acids, is the first case hitherto discovered in which L-histidine shows a slightly stronger catalytic efficiency than the D-analogue for peptide formation in the SIPF reaction. This is especially true for the most concentrated system investigated where arginine has the strongest impact on increasing the pH of the reaction solution. Such a high pH value in the 80 mM system renders histidine more reactive with the copper centre because of its neutral imidazole side chain and this may be related to the remarkable performance of histidine both in catalytic efficiency and enantioselectivity. An obvious excess of L-Arg-L-Arg yield was found in the 80 mM cases with amino acid catalysts despite interference from the noticeable amount of initial D-Arg-D-Arg impurity in the D-arginine reactant, thus showing a strong chiral preference under these reaction conditions. Overall, the results generalise the applicability of the SIPF reaction to initial processes of chemical evolution towards the origin of life, since the involvement of histidine and glycine can boost enantioselectivity for diarginine formation and the L-form preference is no longer monopolised by aliphatic amino acids.

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