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The influence of dipeptide composition on protein thermostability

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Abstract In this work, the influence of dipeptide composition on protein thermostability was studied. After comparing the normalized dipeptide composition between mesophilic proteins and (hyper)thermophilic proteins, we concluded that when organism optimal growth temperature increased, for archaeal proteins, the compositions of VK, KI, YK, IK, KV, KY, and EV increased significantly and the compositions of DA, AD, TD, DD, DT, HD, DH, DR, and DG decreased significantly; and for bacterial proteins, the compositions of KE, EE, EK, YE, VK, KV, KK, LK, EI, EV, RK, EF, KY, VE, KI, KG, EY, FK, KF, FE, KR, VY, MK, WK, and WE increased significantly and the compositions of WQ, AA, QA, MQ, AW, QW, QQ, RQ, QH, HQ, AD, AQ, WL, QL, HA, and DA decreased significantly. So these characteristic dipeptides are correlative to protein thermostability. At the same time, the influence of single amino acid composition on protein thermostability was also studied for comparison. We found that the influence of single amino acid composition could be deduced from the influence of dipeptide composition. So we thought that the influence of dipeptide composition on protein thermostability is larger than the influence of amino acid composition. The characteristic dipeptides not only describe the dipeptides that influence protein thermostability significantly but also show the relationship among significant single amino acids that influence protein thermostability.

Keywords: Dipeptide composition; Archaeal protein; Bacterial protein; Protein thermostability

1. Introduction

Protein amino acid composition has long been thought to be correlated to its thermostability. Several investigations have been carried out to illustrate the influence of amino acid on protein thermostability. Russell [1] compared the amino acid composition of citrate synthase from pig, *T. acidophilum* and *P. furiosus*. He concluded that as optimal temperature increased, so did the Ile, Tyr, Lys, and Glu content, but the content of thermolabile residues (i.e., Asn, Gln, and Cys) reduced. Haney [2] summarized the net change in amino acid composition between the mesophilic and thermophilic proteins, the thermophilic proteins are characteristically reduced in Ser, Asn, Gln, Thr, and Met and increased in Ile, Arg, Glu, Lys and Pro. Szilagyi [3] compared the amino acid composition of moderately thermophilic and extremely thermophilic proteins and their mesophilic homologues. He found that the percentage of charged residues (Lys, Arg, Glu, and Asp) is higher in thermophilic proteins than in mesophilic ones. The comparison of residue contents in hyperthermophilic and mesophilic proteins based on the genome sequences of eight mesophilic and seven hyperthermophilic organisms [4] showed that more charged residues exist in hyperthermophilic proteins (+3.24%) than in mesophilic proteins, and hyperthermophilic proteins also contain slightly more hydrophobic and aromatic residues than mesophilic proteins. Satoshi [5] performed systematic comparisons between proteins from thermophilic bacteria and mesophilic bacteria, in terms of the amino acid composition of the protein surface and the interior, as well as the entire amino acid chains, by using sequence information from the genome projects. He concluded that in contrast to the surface composition, the interior composition was not distinctive between the thermophilic and mesophilic proteins. Extracellular proteins from mesophilic bacteria had a reduced number of charged residues and richer in polar residues than thermophilic proteins.

In these studies, we found that the average amino acid composition of all sequences was not considered in comparing the difference of amino acid composition between thermophilic proteins and mesophilic proteins. In Swiss-Prot database, average amino acid composition in percent for the complete database is listed (http://cn.expasy.org/sprot/relnotes/relstat.html). Some amino acids such as Cys and Trp have a small composition in protein sequences, while some amino acids have a high composition. So, when analyzing the influence of amino acid composition, the result would be better if considering the average amino acid composition of all related proteins.

At the same time, from this diverse collection of studies, it is difficult to find out the influence of dipeptide composition on protein thermostability. In fact, the dipeptide composition is different in different types of proteins; the dipeptide composition may be correlated to protein thermostability. Here, we constructed a dataset containing 97 416 mesophilic bacterial protein sequences, 4452 mesophilic archaeal protein sequences,

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Abbreviations: T_{OGT}, organism optimal growth temperature; P_{ME_AR}, mesophilic archaeal proteins; P_{ME_BC}, mesophilic bacterial proteins; P_{TH_AR}, thermophilic archaeal proteins; P_{HTH_AR}, hyperthermophilic archaeal proteins; P_{HTH_BC}, hyperthermophilic bacterial proteins; Single amino acid is presented by three letters; dipeptide is expressed by dimer with a single letter of the amino acid

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3974 thermophilic archaeal protein sequences, 2960 hyperthermophilic bacterial protein sequences, and 12 227 hyperthermophilic archaeal protein sequences to study the relationship between dipeptide composition and protein thermostability. We also studied the influence of single amino acid composition on protein thermostability. Then, the relationship between the influence of dipeptide composition and the influence of single amino acid composition can be found out easily.

2. Materials and methods

2.1. Dataset

There are 10 hyperthermophilic organisms, three thermophilic organisms and 52 mesophilic organisms in NCBI COG database [6–8]. We selected the bacterial and archaeal organisms from them and retrieved useful protein sequences of each organism from NCBI database. Then, the final dataset was composed of 97 416 mesophilic bacterial protein sequences, 4452 mesophilic archaeal protein sequences, 3974 thermophilic archaeal protein sequences, 2960 hyperthermophilic bacterial protein sequences, and 12 227 hyperthermophilic archaeal protein sequences.

2.2. Method

By using Sequence Retrieval System (http://www.expasy.org/srs5/), we retrieved all the bacterial and archaeal protein sequences from Swiss-Prot database in Fasta format and calculated dipeptide composition and single amino acid composition of all prokaryotic sequences, these percents are regarded as average dipeptide composition and average amino acid composition, respectively. Then, the compositions of kinds of dipeptides and single amino acids from P_{ME_AR}, P_{ME_BC}, P_{TH_AR}, P_{HTH_AR} and P_{HTH_BC} were calculated, respectively.

The difference between dipeptide composition (or single amino acid composition) of each type of proteins and average dipeptide (or single amino acid) composition can be denoted by using the equation

$$D_{ji} = \frac{C_{ji} - \bar{C}_i}{\bar{C}_i},$$

where $j = 1, 2, 3, 4, 5$, it denotes P_{ME_AR}, P_{ME_BC}, P_{TH_AR}, P_{HTH_AR} and P_{HTH_BC}. i is single amino acid or dipeptide. C_{ji} is the percent of i in j. $\bar{C}_i$ is the average composition of i in Swiss-Prot database (only prokaryotic sequences).

It is obvious that the dipeptide or single amino acid is the positive correlation to protein thermostability when $D_{4i} > D_{3i} > D_{1i}$ or $D_{5i} > D_{2i}$, while i is the negative correlation to protein thermostability when $D_{4i} < D_{3i} < D_{1i}$ or $D_{5i} < D_{2i}$.

3. Results and discussion

3.1. Average dipeptide composition and average single amino acid composition

Different amino acids play a different role in determining protein structure and function, the number of each amino acid is also different. When considering the influence of amino acid composition on protein properties, the influence of average amino acid composition should be deducted. Some amino acids have a little composition, but a small change in these amino acid compositions may result in a big change in structure and function. So, when studying the influence of dipeptide composition on protein thermostability, we calculated the prokaryotes dipeptide composition in Swiss-Prot database as average dipeptide composition. We also calculated the prokaryotes single amino acid composition in Swiss-Prot database as average amino acid composition.

3.2. Variation of single amino acid composition

Normalized single amino acid compositions of each type of proteins and variation from mesophilic proteins to hyperthermophilic proteins were listed in Table 1. For archaeal proteins, the compositions of Lys and Arg increase when T_{OGT} increases, while the compositions of Asp, Thr, Gln, and His decrease when T_{OGT} increases. For bacterial proteins, the compositions of Lys, Glu, Tyr, Phe, Val, and Ile increase significantly and the compositions of Gln, Ala, His, Trp, Thr, and Asp decrease significantly when T_{OGT} increases.

Some researchers [4] are of the view that protein thermostability usually increased with the number of Pro introduced. Arg had been proposed [9] to replace Lys in thermostable proteins based on its ability to maintain charge and provide an additional hydrogen bond. Argos [10] thought a higher Ala content in thermophilic proteins was supposed to reflect the fact that Ala was the best helix-forming residue. These

Table 1
Relative single amino acid composition of all types of proteins

Amino acid	P_{ME_AR}	P_{TH_AR}	P_{HTH_AR}	P_{HTH_AR}–P_{ME_AR}	P_{ME_BC}	P_{HTH_BC}	P_{HTH_BC}–P_{ME_BC}
A	0.18	−0.14	−0.06	−0.24	0.21	−0.25	−0.46
C	−0.35	−0.42	−0.42	−0.07	−0.41	−0.50	−0.09
D	0.29	0.16	−0.06	−0.35	0.03	−0.11	−0.14
E	0.20	0.16	0.33	0.13	−0.04	0.45	**0.49**
F	−0.07	−0.02	−0.07	0.00	−0.01	0.21	**0.22**
G	0.12	0.06	0.06	−0.06	0.05	0.00	−0.05
H	−0.13	−0.22	−0.30	−0.17	−0.02	−0.27	−0.25
I	0.01	0.42	0.30	0.29	0.07	0.21	**0.14**
K	−0.21	−0.01	0.17	**0.38**	−0.14	0.39	**0.53**
L	−0.05	−0.10	0.04	0.09	0.08	0.05	−0.03
M	−0.07	0.28	−0.07	0.00	0.03	−0.10	−0.13
N	−0.23	−0.06	−0.22	0.01	−0.09	−0.16	−0.07
P	−0.09	−0.16	−0.08	0.01	−0.09	−0.15	−0.06
Q	−0.33	−0.47	−0.55	−0.22	0.01	−0.47	−0.48
R	0.00	0.12	0.14	**0.14**	0.03	0.00	−0.03
S	−0.12	0.00	−0.24	−0.12	−0.13	−0.24	−0.11
T	0.06	−0.14	−0.23	−0.29	−0.03	−0.20	−0.17
V	0.20	0.10	0.26	0.06	0.06	0.25	**0.19**
W	−0.19	−0.36	−0.11	0.08	0.03	−0.17	−0.20
Y	−0.04	0.23	0.19	0.23	−0.09	0.17	**0.26**

Bold numbers: amino acid compositions increase as T_{OGT} increases. Underlined numbers: amino acid compositions decrease as T_{OGT} increases.

preferences were not observed for the (hyper)thermophilic proteins we studied. The largest difference in single amino acid composition from mesophilic proteins to hyperthermophilic proteins we studied is that Lys appears to be prevalent and Gln, Asp, Thr, and His appear to be less prevalent in (hyper)thermophilic proteins, especially Asp.

3.3. Difference of dipeptide composition

Table 2 lists the normalized dipeptide composition of P_{ME_AR}, P_{ME_BC}, P_{TH_AR}, P_{HTH_AR} and P_{HTH_BC} which $|D_i|$ is larger than 0.60. The value in bracket in Table 2 is D_{ji}. From Table 2, we find that the numbers of significant dipeptides in thermophilic and hyperthermophilic proteins are more than in mesophilic proteins. That means that (hyper)thermophilic proteins are significantly different from mesophilic proteins in dipeptide composition. So the dipeptide composition is correlated to protein thermostability.

3.4. Characteristic dipeptide

For archaeal proteins, there are 68 positive correlation dipeptides ($D_{4i} > D_{3i} > D_{1i}$) and 97 negative correlation dipeptides ($D_{4i} < D_{3i} < D_{1i}$); and for bacterial proteins, there are 155 positive correlation dipeptides ($D_{5i} > D_{2i}$) and 245 negative correlation dipeptides ($D_{5i} < D_{2i}$). The influence of other dipeptides on protein thermostability cannot be sure.

Characteristic dipeptide is the dipeptide that has great variation when T_{OGT} increases. Here, if $|D_{4i} - D_{1i}|$ or $|D_{5i} - D_{2i}|$ is larger than 0.60, we regard i as the characteristic dipeptide. Positive and negative correlation characteristic dipeptides are listed in Tables 3–6.

Table 3 lists the dipeptides whose composition increased significantly from P_{ME_AR} to P_{HTH_AR}. Among 400 dipeptides, increasing the compositions of VK, KI, YK, IK, KV, KY, EV, protein thermostability can be increased significantly. As we know, both Lys and Glu carry a charge at typical biological pH, so forming hydrogen bonds make them be important for protein stability. Val, Ile and Tyr are hydrophobic amino acids, Ile side chain frequently adopts four different rotamers conformations that make it be better able to fill various voids that can occur during protein core packing [11]. Several studies [3–5] showed that (hyper)thermophilic proteins prefer to contain charged, aromatic, and hydrophobic residues compared with mesophilic proteins. From these positive correlative characteristic dipeptides, we can also draw these conclusions. In addition, in these seven dipeptides, Lys almost exists in each dipeptide, Val appears three times, Ile and Tyr appear twice, respectively, and Glu appears one time. Then, we can deduce that Lys in (hyper)thermophilic archaeal proteins must be much more than in mesophilic archaeal proteins, that accords with the conclusion drawn from variation of single amino acid (Table 1). We also presume that Val, Ile, Tyr, and Glu contents of (hyper)thermophilic proteins are more than mesophilic proteins from the characteristic dipeptides, while from the variation of single amino acid, the influence of these four amino acids on archaeal proteins thermostability cannot be determined. Referring to Table 1 again, if we only consider the mesophilic proteins and the hyperthermophilic proteins, these four amino acids contents increase.

Table 4 lists the dipeptides whose content decreased significantly from P_{ME_AR} to P_{HTH_AR}. From mesophilic archaeal proteins to hyperthermophilic archaeal proteins, the compositions of DA, AD, TD, DD, DT, HD, DH, DR, and DG decrease gradually. Similarly, Asp exists in each negative cor-

Table 3
Positive correlative characteristic dipeptides from mesophilic to hyperthermophilic archaea

Characteristic dipeptide	D_{1i}	D_{3i}	D_{4i}	$D_{4i} - D_{1i}$
VK	−0.20	0.24	0.62	0.82
KI	−0.12	0.41	0.58	0.70
YK	−0.36	−0.03	0.34	0.70
IK	−0.17	0.39	0.52	0.69
KV	−0.15	0.07	0.51	0.65
KY	−0.19	0.33	0.44	0.63
EV	0.22	0.24	0.83	0.61

Table 4
Negative correlative characteristic dipeptides from mesophilic to hyperthermophilic archaea

Characteristic dipeptide	D_{1i}	D_{3i}	D_{4i}	$D_{4i} - D_{1i}$
DA	0.99	0.02	−0.13	−1.12
AD	0.90	0.00	−0.22	−1.12
TD	0.53	0.01	−0.35	−0.88
DD	0.64	0.18	−0.21	−0.85
DT	0.54	−0.01	−0.31	−0.85
HD	0.52	−0.02	−0.33	−0.85
DH	0.39	0.05	−0.36	−0.75
DR	0.62	0.33	0.00	−0.62
DG	0.50	0.17	−0.10	0.60

Table 2
Significant dipeptides in all types of proteins

Type	Dipeptide ($D_i > 0.60$)/number	Dipeptide ($D_i < 0.60$)/number
Hyperthermophilic archaea	EV(0.83),VE(0.82),EI(0.75),RE(0.72), IE(0.66),EE(0.66),IV(0.63), VK(0.62)/**8**	CC(−0.78),QQ(−0.77),CQ(−0.74),QC(−0.73), HQ(−0.69),QH(−0.68),NQ(−0.67),QS(−0.66), DQ(−0.66),QT(−0.62),QN(−0.62),QP(−0.62), CW(−0.60)/**13**
Hyperthermophilic bacteria	KE(1.23),EK(1.08),EE(1.02),EI(0.88), YE(0.86),VK(0.84),KV(0.83),LK(0.79), EV(0.78),VE(0.78),EF(0.71),FE(0.68), KI(0.64),KK(0.63),VF(0.63),KG(0.62), RE(0.62),IE(0.61)/**18**	CQ(−0.74),CN(−0.69),QH(−0.68),CW(−0.67), QW(−0.67),MQ(−0.67),QS(−0.65),SC(−0.64), HQ(−0.63),QP(−0.62),QA(−0.60),WC(−0.60), AA(−0.60)/**13**
Thermophilic archaea	IM(0.89),II(0.82),RI(0.80),MD(0.75), MI(0.74),ME(0.69),EI(0.65),IE(0.65), IR(0.62),IY(0.62),GI(0.61),YI(0.61)/**12**	CC(−0.82),QQ(−0.75),CW(−0.75),QC(−0.73), CQ(−0.69),QP(−0.65),QH(−0.63),QW(−0.63), HQ(−0.63)/**9**
Mesophilic archaea	DA(0.99),AD(0.90),DD(0.64),DR(0.62)/**4**	CC(−0.74),CW(−0.60)/**2**
Mesophilic bacteria	/**0**	CC(−0.75),KC(−0.66),CK(−0.61)/**3**

Table 5
Positive correlative characteristic dipeptides from mesophilic to hyperthermophilic bacteria

Characteristic dipeptide	D_{2i}	D_{5i}	$D_{5i} - D_{2i}$
KE	−0.18	1.23	1.41
EE	−0.25	1.02	1.27
EK	−0.14	1.08	1.22
YE	−0.10	0.86	0.96
VK	−0.12	0.84	0.96
KV	−0.10	0.83	0.93
KK	−0.29	0.63	0.92
LK	−0.05	0.79	0.84
EI	0.06	0.88	0.82
EV	−0.01	0.78	0.79
RK	−0.19	0.57	0.76
EF	−0.05	0.71	0.76
KY	−0.27	0.49	0.76
VE	0.02	0.78	0.76
KI	−0.08	0.64	0.72
KG	−0.08	0.62	0.70
EY	−0.14	0.56	0.70
FK	−0.13	0.57	0.70
KF	−0.21	0.47	0.68
FE	0.01	0.68	0.67
KR	−0.16	0.49	0.65
VY	−0.08	0.56	0.64
MK	−0.17	0.46	0.63
WK	−0.24	0.39	0.63
WE	−0.10	0.52	0.62

Table 6
Negative correlative characteristic dipeptides from mesophilic to hyperthermophilic bacteria

Characteristic dipeptide	D_{2i}	D_{5i}	$D_{5i} - D_{2i}$
WQ	0.38	−0.55	−0.93
AA	0.30	−0.60	−0.90
QA	0.22	−0.60	−0.82
MQ	0.11	−0.67	−0.78
AW	0.39	−0.39	−0.78
QW	0.09	−0.67	−0.76
QQ	−0.06	−0.77	−0.71
RQ	0.13	−0.57	−0.70
QH	0	−0.68	−0.68
HQ	0.03	−0.63	−0.66
AD	0.29	−0.37	−0.66
AQ	0.22	−0.44	−0.66
WL	0.33	−0.32	−0.65
QL	0.07	−0.55	−0.62
HA	0.22	−0.39	−0.61
DA	0.25	−0.35	−0.60

relative characteristic dipeptide; Ala, Thr, and His appear twice, respectively; Arg and Gly appear one time, respectively. From variation of single amino acid composition, we know that the compositions of Asp, Thr, and His decrease dramatically from mesophilic archaeal proteins to hyperthermophilic archaeal proteins. We find that these single amino acids also appear in characteristic dipeptides. But Gln is an exception. We analyzed all the correlative dipeptides (the data were not shown) and found that all the dipeptides containing Gln are negative correlative dipeptides, the largest value being −0.46, while we define the dipeptide whose $|D_{4i} - D_{1i}| > 0.60$ is characteristic dipeptide, so Gln does not appear in negative correlative characteristic dipeptides.

From Tables 5 and 6, we found that the compositions of KE, EE, EK, YE, VK, KV, KK, LK, EI, EV, RK, EF, KY, VE, KI, KG, EY, FK, KF, FE, KR, VY, MK, WK, and WE increase significantly and the compositions of WQ, AA, QA, MQ, AW, QW, QQ, RQ, QH, HQ, AD, AQ, WL, QL, HA, and DA decrease significantly when T_{OGT} increases. From the frequency that single amino acid appears in characteristic dipeptide, we deduce that Lys, Glu, Val, Tyr, and Phe are positive correlative to temperature, and Gln, Ala, Trp, His, and Asp are negative correlative to temperature. It accords with the conclusion drawn from the variation of single amino acid.

In conclusion, when organism optimal growth temperature increases, for archaeal proteins, the compositions of VK, KI, YK, IK, KV, KY, and EV increase dramatically and the compositions of DA, AD, TD, DD, DT, HD, DH, DR, and DG decrease dramatically; for bacterial proteins, the compositions of KE, EE, EK, YE, VK, KV, KK, LK, EI, EV, RK, EF, KY, VE, KI, KG, EY, FK, KF, FE, KR, VY, MK, WK, and WE increase dramatically and the compositions of WQ, AA, QA, MQ, AW, QW, QQ, RQ, QH, HQ, AD, AQ, WL, QL, HA, and DA decrease dramatically. So these dipeptides are correlative to protein thermostability. At the same time, the influence of amino acid composition on protein thermostability is also studied for comparison. We find that the influence of most amino acid composition can be deduced from the influence of dipeptide composition. So we think that the influence of dipeptide composition on protein thermostability is larger than the influence of single amino acid composition. The characteristic dipeptides not only describe the dipeptides that influence protein thermostability significantly but also show the relationship and interaction among significant single amino acids that influence the protein thermostability.

It is worth noticing that there are some similarities and some differences between archaeal and bacterial proteins about the influence of dipeptide composition and the influence of single amino acid composition on protein thermostability. For single amino acid composition, the influence of Lys is positive in both types of proteins; the influence of Val, Tyr, Glu, and Thr cannot be determined in archaeal proteins, while they are positive amino acids in bacterial proteins; the influence of Arg in archaeal proteins is positive but it is negative in bacterial proteins. For dipeptide composition, positive correlative characteristic dipeptides contain more Lys in both archaeal and bacterial proteins; Asp exists almost in each negative correlative characteristic dipeptide in archaeal proteins, while Gln exists almost in each negative correlative characteristic dipeptide in bacterial proteins.

Here, we have to emphasize that whether from the influence of single amino acid composition on protein thermostability or from the influence of dipeptide composition on protein thermostability Asp is negative correlative to archaeal proteins thermostability which is different from the conclusion of early studies [3,12,13].

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