The Solubility and Conformation of Protected Tri- to Heptapeptides in a Variety of Organic Solvents and the Classification of Organic Solvents Based on Their Solvating Potential for Protected Peptides[1)]

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The solubility in a variety of organic solvents was examined for 75 kinds of protected tri- to heptapeptide fragments of *E. coli* ribosomal protein L7/L12. The organic solvents examined were classified into six groups mainly by considering their solvating potential and supplementarily by using their acceptor number (AN) and donor number (DN). The result of the classification of the organic solvents was practically explained by the DN and AN of the organic solvents, indicating that the electron-donating or -accepting ability of organic solvents is much more important for the solvation of protected peptides than their ability to form van der Waals interactions. Nevertheless, the solvation mechanism of protected peptides in organic solvents could be explained by two types of intermolecular interactions, namely, intermolecular hydrogen bonding and van der Waals interactions. The $<SP_\beta>$ values of protected peptieds, difined in a previous paper, properly reflected their β-sheet-structure stability in a variety of organic solvents regardless of their amino acid sequence. The solubility of protected peptides in organic solvents was also strongly related to their $<SP_\beta>$ values. In fact, peptides having a low $<SP_\beta>$ value were easily soluble in various organic solvents and had an unordered structure in solution.

The insolubility of protected peptides in organic solvents brings about difficulties in further chain elongation, purification, and homogeneity assessment. Thus, the elucidation of the solvation mechanism of protected peptides in organic solvents is significant for the successful achievement of peptide and protein synthesis.[2—7)]

Principally, the insolubility of protected peptides in organic solvents originates from their aggregation through two types of intermolecular interactions, namely, intermolecular hydrogen bonding and van der Waals interactions. Especially, the former causes the formation of an intermolecular hydrogen bonded β-sheet structure and plays an important role in insolubility. As pointed out in previous papers,[2,8—11)] the stability of the β-sheet aggregation in organic solvents is influenced by two factors: the natures of the organic solvents and the protected petides. In regards to the former, we found that the electron-acceptor and -donoer numbers (AN and DN)[15)] of organic solvents were useful for estimating their β-sheet-structure-disrupting potential. The solvating potentials for peptide main chains forming hydrogen bonds between peptide main chains and solvents are formed through electron donor-acceptor interactions between them.[11—14)] In fact, as the AN or DN of the solvents increased, their solvating potential became higher. With respect to the nature of the protected peptide, we found that the β-sheet-structure stability of a protected peptide was strongly dependent on both the peptide chain length and the amino acid composition,[8—10)] and could be estimated using the $<SP_\beta>$ value of the peptide, which was defined as the arithmetic average of the β-sheet-structure-stabilizing potentials, SP_β, of the amino acid residues in the protected peptides.[8,16,17)]

Based on the groundwork mentioned above, we here attempt the classification of organic solvents by considering mainly their solvating potential for protected peptides and demonstrate that, in a variety of organic solvents, the electron-donating or -accepting ability of organic solvents is much more important for the solvation of protected peptides than their ability to form van der Waals interactions.

Experimental

Materials. The seventy-five kinds of protected tri- to heptapeptide fragments of *E. coli* ribosomal protein L7/L12 are those previously used for the estimation of the β-sheet-structure stability of protected peptides.[17)]

IR Absorption Spectra Measurements. IR absorption spectra measurements were carried out as described in a previous paper.[17)]

Results

The organic solvents examined are summarized in Tables 1, 2, 3, 4, and 5. On the whole, they are placed in order by considering mainly their solvating potential and by using their AN and DN supplementarily. The solubility in the organic solvents was examined for the protected tri- to heptapeptides assembled in Tables 1, 2, 3, 4, and 5. The peptides are fragments of *E. coli* ribosomal protein L7/L12 and their amino acid sequences are shown in Tables 1, 2, 3, 4, and 5 by one-letter symbols. The *N*- and *C*-terminals of the peptides were protected by Boc and Pac groups, respectively, and their side chain functional groups were also protected by suitable groups commonly used in peptide synthesis. Namely, Asp, Glu, Ser, Thr, and Tyr were blocked by a Bzl group, and Arg and Lys by Mts and Z groups, respectively. Met was converted to Met (O). All the protecting groups in the peptides are omitted

Table 1. The Solubility of Tripeptides [a] in a Variety of Organic Solvents [b]

	$<SP_\beta>$	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
KDQ	3.0	C	C	C	C	C	B	A	B	A	A	B	A	A	A	A	A	A	A	A	A	A	A	A
AKD	3.0	C	C	C	C	B	A	A	A	A	B	A	A	A	A	A	A	A	A	A	A	A	A	A
VMD	3.3	C	C	C	C	B*	B*	A	A	A	B	B*	A	A	A	A	A	A	A	A	A	A	A	A
AEE	3.7	C	C	C	B	B	A	A	A	A	B	B	A	A	A	A	A	A	A	A	A	A	A	A
KEG	3.7	C	C	C	C	C	B	A	A	A	B	B	B	A	A	A	A	A	A	A	A	A	A	A
KKA	3.7	C	C	C	C	B*	B	B*	B*	B	C	B	A	A	A	A	A	A	A	A	A	A	A	A
DVI	4.0	C	C	C	B	A	A	A	A	A	A	B	A	A	A	A	A	A	A	A	A	A	A	A
ISA	4.0	C	C	C	C	B	A	A	A	A	C	A	A	A	A	A	A	A	A	A	A	A	A	A
KFG	4.0	C	C	C	C	C	B	B	B	A	C	B	B	A	A	A	A	A	A	A	A	A	A	A
GLG	4.3	C	C	C	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A
EAG	4.3	C	C	C	C	B*	A	A	B	A	C	A	A	A	A	A	A	A	A	A	A	A	A	A
AAG	5.0	C	C	C	C	C	B	B	B	B	B	B	A	A	A	A	A	A	A	A	A	A	A	A
AAA	5.0	C	C	C	C	B*	B	A	A	B	A	A	A	A	A	A	A	A	A	A	A	A	A	A
AVA	5.3	C	C	C	C	B*	B	A	B*	B	B	B	A	A	A	B*	A	A	A	A	A	A	A	A
AVI	5.3	C	C	C	C	B*	A	A	A	A	B	B	A	A	A	A	A	A	A	A	A	A	A	A
VRG	5.7	C	C	C	C	C	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A

a) Solubility: A, completely soluble at room temperature; B, completely soluble at 80°C or refluxing temperature and no deposit after cooling to room temperature; B*, completely soluble at 80°C or refluxing temperature and deposit after cooling to room temperature; C, partially or nearly insoluble at 80°C or refluxing temperature. b) Solvents: **1**, hexane; **2**, Et_3N; **3**, Et_2O; **4**, CCl_4; **5**, benzene; **6**, AcOEt; **7**, acetone; **8**, acetonitrile; **9**, dioxane; **10**, formamide; **11**, EtOH; **12**, MeOH; **13**, TMP; **14**, THF; **15**, CH_2Cl_2; **16**, $CHCl_3$; **17**, pyridine; **18**, DMF; **19**, NMP; **20**, DMSO; **21**, AcOH; **22**, TFE; **23**, HFIP; abbreviations, see Ref. 1.

Table 2. The Solubility of Tetrapeptides [a] in a Variety of Organic Solvents [b]

	$<SP_\beta>$	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
DDAE	2.5	B*	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A
ESAP	2.8	C	C	C	B*	B	B	A	B	B	B	B*	A	A	A	A	A	A	A	A	A	A	A	A
TKDQ	2.8	C	C	C	C	C	C	C	C	B	C	B*	B*	A	B	B	B	A	A	A	A	A	A	A
EAKD	3.0	C	C	C	C	B	B	A	A	A	B	B	A	A	A	A	A	A	A	A	A	A	A	A
SVMD	3.0	C	C	C	C	C	C	C	B*	A	B	C	B*	A	A	A	A	A	A	A	A	A	A	A
LKEG	3.5	C	C	C	C	C	C	B	A	A	C	B	B	A	A	A	A	A	A	A	A	A	A	A
LKKA	3.5	C	C	C	C	C	C	C	C	A	C	B	A	A	A	B	A	A	A	A	A	A	A	A
TGLG	3.8	C	C	C	C	B*	B	A	B	A	A	A	A	B	A	A	A	A	A	A	A	A	A	A
LISA	3.8	C	C	C	C	C	B	B	B	A	C	B*	B	B	B	A	C	A	A	A	A	A	A	A
EKFG	3.8	C	C	C	C	C	C	B	B	A	C	C	B	B	A	A	A	A	A	A	A	A	A	A
EEAG	4.0	C	C	C	C	B*	B	A	C	A	C	B	A	A	A	A	A	A	A	A	A	A	A	A
AAEE	4.0	C	C	C	C	B	B	C	B*	A	A	B	A	B	B	A	A	A	A	A	A	A	A	A
FDVI	4.0	C	C	C	C	B*	B	A	B*	A	C	B*	B*	C	A	B*	A	A	A	A	A	A	A	A
VEVK	4.5	C	C	C	C	C	C	B	B*	B	C	C	B	B	A	A	A	A	A	A	A	A	A	A
KAAG	4.5	C	C	C	C	C	B	B	B	A	B	B	B	A	A	B	A	A	A	A	A	A	A	A
EAVA	4.8	C	C	C	C	C	C	C	C	B	C	C	C	B	B	C	B	A	A	A	A	A	A	A
AAAA	5.0	C	C	C	C	C	C	C	B*	C	B	C	B	B	C	C	B	A	A	A	A	A	A	A
VAAG	5.3	C	C	C	C	C	C	C	B*	C	B*	B	A	B*	A	B*	A	B	A	A	A	A	A	A
AVRG	5.5	C	C	C	C	C	A	A	B	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A
VAVI	5.5	C	C	C	C	B*	B*	B*	B*	B	C	B*	B	B	A	A	A	A	A	A	A	A	A	A

a) Solubility and b) Solvents, see Table 1.

in Tables 1, 2, 3, 4, and 5. In Tables 1, 2, 3, 4, and 5, the $<SP_\beta>$ values of the peptides are given and the peptides are placed in order of lower to higher $<SP_\beta>$ values. The solubility (c=1. 0 g·dl^{-1}) was divided into the following three classes: (A) completely soluble at room temperature, (B) completely soluble at 80°C or refluxing temperature, and (C) partially or nearly insoluble at 80°C or refluxing temperature.

In relation to the solubility of protected peptides in organic solvents, the conformation of typical peptides in solution was examined by measuring their IR absorption spectra (Fig. 1). The bands around 3280 and 1630 cm^{-1} are assigned to a β-sheet structure and those around 3420 and 1670 cm^{-1} are assigned to an unordered structure. Those around 3320 and 1660 cm^{-1} are mainly due to intramolecular hydrogen-bonded N–H and C=O groups, respectively. Except for tripeptides, in many cases, symbol A in Tables 2, 3, 4, and 5 mostly corresponds to an unordered structure of a peptide in solution. Insoluble peptides, symbol C, have a β-sheet

Table 3. The Solubility of Pentapeptides [a] in a Variety of Organic Solvents [b]

	<SP$_\beta$>	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
KDDAE	2.6	C	C	C	C	C	B	B	B	A	C	B*	A	A	A	A	A	A	A	A	A	A	A	A
KEAKD	3.0	C	C	C	C	C	C	B	B*	A	C	C	C	A	A	A	A	A	A	A	A	A	A	A
MSVMD	3.0	C	C	C	C	C	C	C	B*	B	C	C	C	B*	B	B*	C	A	A	A	B	B	B	A
ITKDQ	3.2	C	C	C	C	C	C	B*	B*	B	C	C	B*	A	B	B	B	A	A	A	A	A	A	A
VESAP	3.4	C	C	B	A	A	A	A	A	A	C	B*	B*	A	A	A	A	A	A	A	A	A	A	A
ELISA	3.6	C	C	C	C	C	C	C	B	B	B	B*	B*	C	B	A	B	B	A	A	A	A	B	A
EEKFG	3.6	C	C	C	C	C	C	C	C	C	C	C	B*	B	A	A	B	B	A	A	A	A	A	A
EFDVI	3.8	C	C	C	C	B	B	B	B*	B	C	B*	B	A	B	A	B	A	A	A	A	A	A	A
ALKKA	3.8	C	C	C	C	C	B	B*	B*	A	C	B	A	A	A	A	A	A	A	A	A	A	A	A
LEEAG	3.8	C	C	C	C	C	B	A	B*	A	C	B	B	A	A	A	A	A	A	A	A	A	A	A
ALKEG	3.8	C	C	C	C	C	C	B*	A	A	C	B*	B	A	A	A	A	A	A	A	A	A	A	A
EAAEE	3.8	C	C	C	C	C	C	C	C	A	B	C	C	C	C	C	A	B	C	A	A	B	C	C
ATGLG	4.0	C	C	C	C	C	B*	B*	B	B*	A	B*	A	A	B	B	B	A	A	A	A	B	A	A
EVEVK	4.2	C	C	C	C	C	C	C	C	C	A	C	C	C	B	B	A	A	A	A	A	A	A	A
LKAAG	4.2	C	C	C	C	C	C	C	C	B	B	B	A	B	B	B	A	A	A	A	A	A	A	A
SAAAA	4.4	C	C	C	C	C	C	C	C	C	C	C	C	B*	C	C	C	C	A	A	A	B	B	A
IEAVA	4.8	C	C	C	C	C	C	C	C	C	C	C	C	C	B	C	B*	A	A	A	A	A	A	A
KAVRG	5.0	C	C	C	C	C	C	C	C	A	A	B*	B	A	A	A	A	A	A	A	A	A	A	A
KVAVI	5.0	C	C	C	C	C	C	B*	C	C	C	B	B	B	B	B*	B	A	A	A	B	A	A	A
AVAAG	5.2	C	C	C	C	C	C	C	C	C	C	B	B	B*	C	C	C	B	A	A	A	A	A	A

a) Solubilty and b) Solvents, see Table 1.

Table 4. The Solubility of Hexapeptides [a] in a Variety of Organic Solvents [b]

	<SP$_\beta$>	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
SKDDAE	2.5	C	C	C	C	C	C	C	C	C	C	C	B	C	A	A	A	A	A	A	A	A	A	A
LKEAKD	3.0	C	C	C	C	B*	B*	B*	B*	B*	C	B*	B*	A	A	A	A	A	A	A	A	A	A	A
SITKDQ	3.0	C	C	C	C	C	C	C	C	B	C	B	B	B	B	B	B	A	A	A	A	A	A	A
LVESAP	3.3	C	C	C	B*	B	A	A	B*	A	B*	B*	B*	A	A	A	A	A	A	A	A	A	A	A
AMSVMD	3.3	C	C	C	C	C	B	B	B	B	B	B	B	B	B	B	B	A	A	A	A	A	A	A
MEEKFG	3.5	C	C	C	C	C	C	C	C	B	C	C	C	B	A	A	B	A	A	A	B	A	A	A
TEFDVI	3.5	C	C	C	C	B	B	A	B	C	C	B	B	B	B	A	C	A	A	A	A	A	A	A
AALKEG	4.0	C	C	C	C	C	C	B	B	B	C	B	B	B	B	A	A	A	A	A	A	A	A	A
VELISA	4.0	C	C	C	C	B	C	B	B	B	C	C	B	B	A	A	A	A	A	A	A	A	A	A
VEAAEE	4.2	C	C	C	C	C	C	C	B	C	B	C	B	A	A	A	A	A	C	C	A	A	A	A
AEVEVK	4.3	C	C	C	C	C	C	C	C	B	C	C	C	B	B	A	A	A	A	A	A	A	A	A
VSAAAA	4.7	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	A	A	A
IIEAVA	4.8	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	B*	C	A	A	B	B	A
VAVAAG	5.3	C	C	C	C	C	C	C	C	C	C	C	C	B	C	C	C	A	B	A	A	A	A	A
NKVAVI	5.3	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	A	B	A	A	A	A	A

a) Solubility and b) Solvents, see Table 1.

Table 5. The Solubility of Heptapeptides [a] in a Variety of Organic Solvents [b]

	<SP$_\beta$>	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
VSKDDAE	3.0	C	C	C	C	C	C	C	C	C	C	C	C	B	A	A	A	A	A	A	A	A	A	A
KTEFDVI	3.4	C	C	C	C	C	C	C	C	B	C	C	C	B	B	A	B	A	A	A	A	A	A	A
PVEAAEE	3.7	C	C	C	C	C	C	C	C	C	C	C	C	B	A	A	A	A	A	A	A	A	A	A
ANKVAVI	5.1	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	B	A	A	B	B	A

a) Solubility and b) Solvents, see Table 1.

structure in the suspended state. Peptides having symbol B hold an unordered structure and/or a β-sheet structure in solution.

Discussion

The solubility results in Tables 1, 2, 3, 4, and 5 indicate that the organic solvents examined can be approximately classified into six groups (Table 6) mainly by considering their solvating potential and supplementarily by using their AN and DN.[15] In Table 6, unexplored solvents given in parentheses are also classified mainly by using their AN and DN. The first group con-

Table 6. The Classification of Variety of Organic Solvents

First group	DN	AN	Second group	DN	AN	Third group	DN	AN
Hexane	—	0.0	AcOEt	17.1	—	Formamide	24	39.8
Et_3N	61.0	—	Acetone	17.0	12.5	EtOH	20	37.1
Et_2O	19.2	3.9	Acetonitrile	14.1	18.9	MeOH	19	41.3
CCl_4	(0.0)	8.6	Dioxane	14.8	10.8	(H_2O)	18	54.8
Benzene	0.1	8.2	(PDC)	15.1	18.3			
Fourth group	DN	AN	Fifth group	DN	AN	Sixth group	DN	AN
TMP	23.0	—	Pyridine	33.1	14.2	AcOH	—	53
THF	20.0	8.0	DMF	26.6	16.0	TFE	—	59
CH_2Cl_2	(0.0)	20.4	NMP	27.3	13.3	(Phenol)	—	70
$CHCl_3$	(0.0)	23.1	DMSO	29.8	19.3	HFIP	—	88
			(TBPO)	(40)				

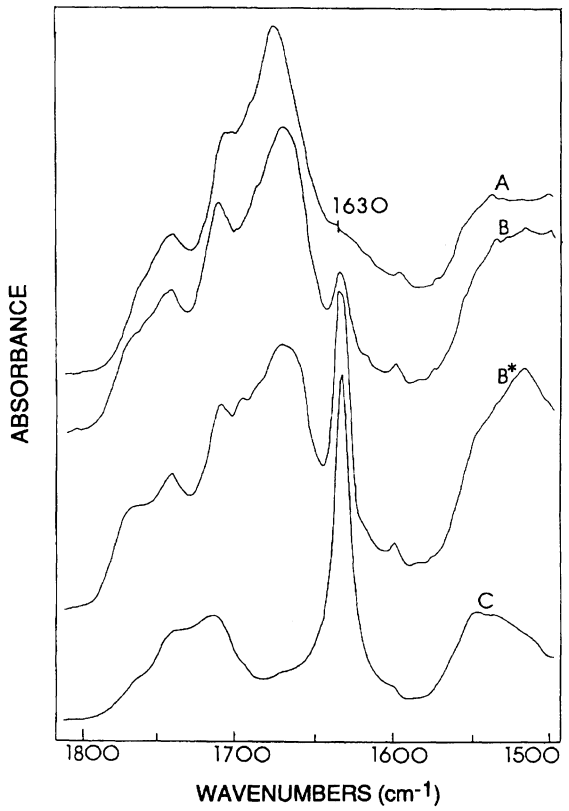

Fig. 1. Typical IR absorption spectra in the amide I region of the protected peptides in organic solvents. A) LKKA in DMSO, soluble at room temperature B) LKKA in CH_2Cl_2, soluble at 80°C or refluxing temperature with no deposit after cooling to room temperature B*) FDVI in CH_2Cl_2, soluble at 80°C or refluxing temperature with deposit after cooling to room temperature C) LKKA in CH_3CN, insoluble at 80°C or refluxing temperature.

tains six solvents and their solvating potential is quite low even for the tripeptides. Except for Et_3N, Et_2O, and H_2O, their AN and DN are below 10, which accounts for their poor solvating potentials. Although Et_3N has the highest DN of 61, its solvating potential is very poor due to steric hindrance. This is in contrast with the solvating potential of pyridine (the fifth group) having a DN of 33. Similarly, the AN and DN of Et_2O resemble those of THF and dioxane, but its solvating potential is also poor due to the steric hindrance of the two ethyl groups. The ring structures of pyridine, THF, and dioxane clearly release steric hindrance and strengthen their electron-donating potential for peptide N–H groups. The poor solubility of protected peptides in H_2O is apparently due to its inability to form van der Waals interactions with peptide side chains. The second group has both an AN and DN around 15, and the third group has an AN around 40 and a DN around 20. The solvating potentials of the solvents in both groups resemble each other and are rather poor for peptides longer than a pentapeptide. The fourth group consists of two types of solvents. One type is represented by CH_2Cl_2 and $CHCl_3$. They have an AN around 20 and a DN around 0. The other is typified by THF and TMP, which have a DN around 20 and an AN below 10. The solvating potentials of the fourth group resemble closely each other and are moderate for peptides as long as a hexapeptide. The fifth group have a DN around 30 and an AN around 15 and their solvating potential is high for peptides shorter than a heptapeptide, but poor to moderate for those longer than an octapeptide. The AN and DN of the sixth group are above 50 and below 20, respectively. The DN of the sixth group solvents is estimated from that of the second group solvents. The solvating potential of the sixth group is the highest and is moderate or high even for peptides longer than an octapeptide. The result of the classification of organic solvents clearly denotes that their solvating potentials for protected peptides is strongly dependent on their AN and DN, namely, their electron-accepting and -donating abilities.[11—14]

A peptide bond is estimated to have an AN around 40 and a DN around 27 judging from the values of formamide, DMF and NMP. In the solvents of the second to fourth groups, which have moderate values of AN and DN, peptide N–H and C=O groups interact moderately with electron-donating and -accepting groups of the solvents, respectively. On the other hand, in the fifth group solvents, peptide N–H groups predominantly interact with the C=O, S=O, P=O groups of

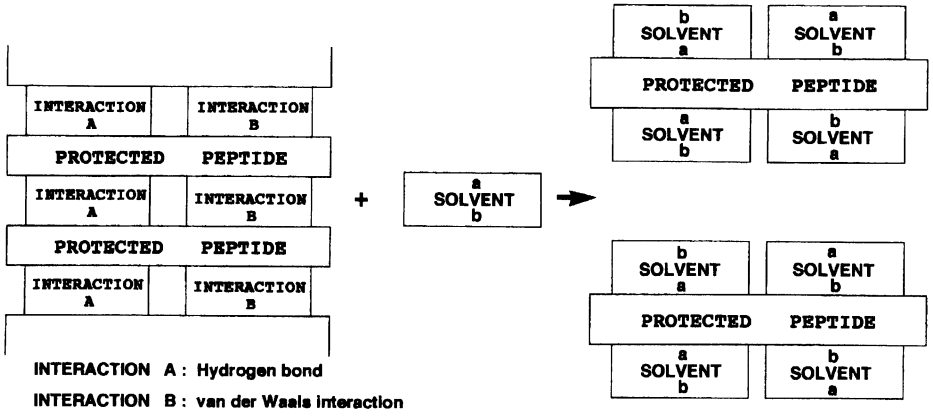

Fig. 2. Schematic view of the solvation mechanism of protected peptides in a single solvent. Solvent a: ability to form intermolecular hydrogen bonds between the solvent and the peptide bond; Solvent b: ability to form van der Waals interactions between the solvent and the peptide side chain.

the solvents through electron donor–acceptor interactions. In the sixth group solvents, peptide C=O groups predominantly interact with OH groups of the solvents through electron donor-acceptor interactions. In a previous paper,[9] we demonstrated that the solubility of protected peptides in organic solvents can be qualitatively described by Eq. 1:

$$-RT\ln K - \Delta G_2^\circ = n\Delta G_1^\circ, \quad (1)$$

where K is the solubility equilibrium constant, ΔG_1° is the difference in Gibbs free energy of one peptide bond between the peptide in solution and in the solid state, ΔG_2° is the difference in Gibbs free energy of the total side-chain groups between the peptide in solution and in the solid state, and n is the number of the N-terminal urethane and peptide bonds in the peptide. The dependence of peptide solubility on peptide chain length suggests that ΔG_1° is a determinant of peptide solubility and that ΔG_2° is not so important.[4,5] In the solid state, protected peptides aggregate through two types of intermolecular interactions, namely, intermolecular hydrogen bonding and van der Waals interactions, and other interactions such as Coulomb forces and ion–dipole interactions are negligible. Thus, ΔH_1° (the enthalpy term of ΔG_1°) is mainly related to hydrogen bonding, and ΔH_2° (the enthalpy term of ΔG_2°), to van der Waals interactions. As the bonding energy through electron donor–acceptor interactions is known to have a linear relationship with the product between AN and DN, it is estimated that, relating to electron donor–acceptor interaction, namely, hydrogen bonding between peptide bonds and the solvent, ΔH_1° has a linear relationship with the product between the AN of a peptide bond and the DN of a solvent or the product between the DN of a peptide bond and the AN of a solvent. The result of the classification of organic solvents in this study is practically well-explained by the DN and AN of organic solvents, suggesting that the hydrogen-bonding ability of solvents is much more important for the solvation of peptide bonds than their van der Waals interaction ability.

Nevertheless, the insolubility of protected peptides in H_2O strongly indicates that the van der Waals interactions of organic solvents with peptide side chains are important as well. Practically, the remarkable increase in solubility observed in mixed organic solvents may be due to the increase in the ability to form van der Waals interactions between peptide side chains and the mixed solvents. As electron donor–acceptor interactions, namely, hydrogen-bonding interactions, can be considered to be orthogonal to van der Waals interactions, the solvation mechanism of protected peptides in a single solvent can be explained by two types of intermolecular interactions, namely, intermolecular hydrogen bonding with the peptide bonds and van der Waals interactions with the side chains as depicted in Fig. 2. The classification of organic solvents in Table 6 was done without consideration of the van der Waals interaction ability of organic solvents since it was difficult to evaluate this ability in this study. The solvation mechanism depicted in Fig. 2 indicates that the classification of organic solvents should be supplemented with the ability to form van der Waals interactions of organic solvents with peptide side chains as follows: Solvents having a low ability to form van der Waals interactions and solvents having moderate or high abilities to form van der Waals interactions.

As demonstrated in a previous paper,[17] the $<SP_\beta>$ value of protected peptides is also a determinant for the solvation of protected peptides in organic solvents. With respect to tetra- to heptapeptides, as their $<SP_\beta>$ values increase, their solubilities in the solvents of the second to fourth groups actually become lower (Tables 2, 3, 4, and 5). This fact also supports the conclusion in the previous paper that the $<SP_\beta>$ values of protected peptides reflect their β-sheet-structure stabil-

ity, so well that they are useful for the estimation of the stability, that is, the difficulty in solvation of protected peptides in organic solvents.

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References

1) The abbreviations for amino acids are recommended by the IUPAC-IUB Commission on Biochemical Nomenclature, *J. Biol. Chem.*, **247**, 977 (1972). Amino acid symbols except for Gly denote the L-configuration. Additional abbreviations used are the following: Et_3N, triethylamine; Et_2O, ethylether; AcOEt, ethyl acetate; EtOH, ethanol; MeOH, methanol; PDC, propylene carbonate; TMP, trimethyl phosphate; THF, tetrahydrofuran; DMF, *N,N*-dimethylformamide; NMP, *N*-methyl-2-pyrrolidinone; DMSO, dimethyl sulfoxide; TBPO, tributylphosphine oxide; AcOH, acetic acid; TFE, 2,2,2-trifluoroethanol; HFIP, 1,1,1,3,3,3-hexafluoro-2-propanol; Boc, *t*-butoxycarbonyl; Pac, phenacyl; Bzl, benzyl; Z, benzyloxycarbonyl; IR, infrared.

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