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Enthalpies of interaction of some amino acids and peptides with crown ethers in water at 25°C

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Abstract

Enthalpies of dilution of ternary aqueous solutions containing glycine, diglycine, triglycine, L-α-alanine, L-α-alanyl-L-α-alanine and 12-crown-4, 15-crown-5, 18-crown-6, 1,10-diaza-18-crown-6 at 298.15 K have been determined. The results have been analysed in terms of the McMillan–Mayer formalism to obtain the enthalpic virial coefficients for heterotactic interactions. It is concluded that the solvation state and the macrocycle size of the crown ethers do not determine the entire change of the cross enthalpic coefficients h_{xy} for the peptide–crown interaction. On the contrary, the influence of specific contributions to the host–guest interaction leads to linearity of the dependence of h_{xy} values for 18-crown-6/peptide interaction versus the heat capacity of solution $\Delta_{sol}C_p$ of glycyl peptides. The effect of the solvent on the selectivity of the peptide–crown interaction is also discussed.

INTRODUCTION

In the last few years there has been significant interest in the investigation of interactions of zwitterionic α-amino acids and peptides with different molecules of biological importance, based on the McMillan–Mayer approach [1]. The peptide–urea interactions have been studied and information about the mechanism of action of the urea in the denaturation processes has been reported [2, 3]. Recently, several papers by Barone and co-workers have appeared [4, 5] dealing with the weak interactions between α-amino acids, small peptides and alcohols or saccharides. The enthalpies of interaction of α-amino acids with alkali metal chlorides [6–8] and resorcinol [9] have been determined and the contribution of electrostatic interactions has been discussed by Lilley and co-workers [7–9]. In addition to the weak interactions, the complex formation of amino acids with macrocyclic ligands, such as crown ethers and cryptand, in alcohols have been studied [10–12].

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The host–guest complexation between biologically important molecules provides new prospects in supramolecular chemistry. In the previous papers of this series [13, 14], the authors demonstrated the special role of non-covalent interactions, i.e. hydrogen bonds and electrostatic forces, resulting in the formation of new supramolecular complexes consisting of zwitterionic peptides and crown ethers. As previously determined [14] by X-ray diffractometry, the dipeptide molecules are bound to 18-crown-6 through a set of –NH···O hydrogen bonds (Fig. 1). Although a bonding to three of the six

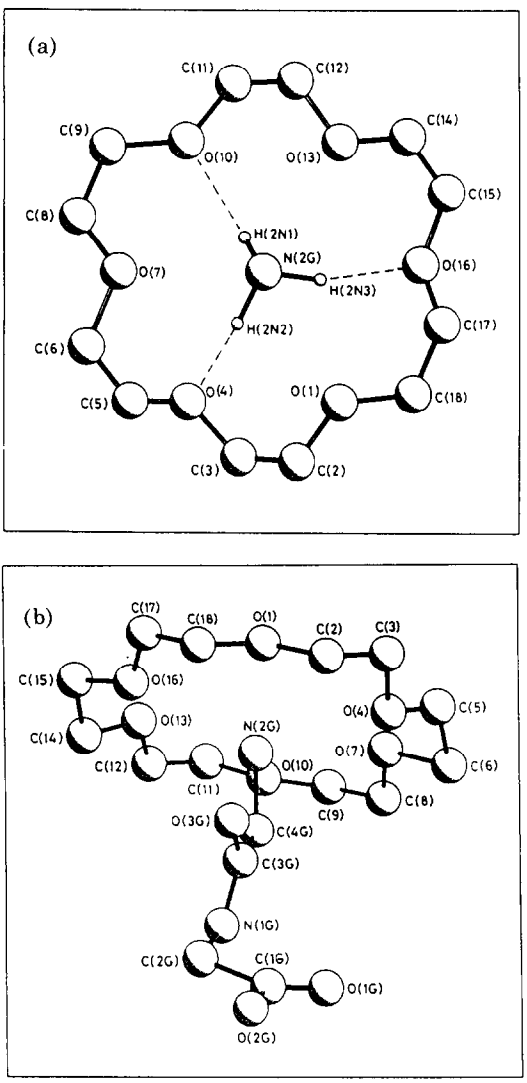

Fig. 1. The structure of the complexes of 18-crown-6 with glycylglycine. In (a), the bonding pattern of 18-crown-6 to the NH_3^+ moiety of glycylglycine is shown.

macrocycle oxygen atoms would be preferable with respect to the orientation of their lone electron pairs towards the peptide $-NH_3^+$ group, it should be noted, however, that the N···O distances from the remaining three oxygens are within the range of hydrogen bonding. A significant difference in the "depth of penetration" of the $-NH_3^+$ groups into the macrocycle cavity for 18-crown-6/diglycine and 18-crown-6/L-α-alanyl-L-α-alanine was also found.

Considering the importance of the study of such interactions in the solvent media, the enthalpies of dilution of ternary aqueous solutions containing glycine, diglycine, triglycine, L-α-alanine, L-α-alanyl-L-α-alanine, and 12-crown-4, 15-crown-5, 18-crown-6, 1,10-diaza-18-crown-6 at 298.15 K have been determined in the present work. The results have been analysed using the McMillan–Mayer formalism [15–17] in order to obtain the enthalpic virial coefficients for heterotactic interactions characterizing the enthalpy of interaction between the solute species.

EXPERIMENTAL

The crown ethers used were synthesized in the Institute of Chemical Reactives and Pure Chemical Substances (Moscow). Their purity was above 99 mol%, as proved by chromatographic and mass spectrometric analysis. As verified by melting point determinations using a Du Pont 1090 DSC calorimeter, the purity of 18-crown-6 was 99.1 mol% and that of 1,10-diaza-18-crown-6 was 99.9 mol%. All compounds were used without further purification.

Chromatographically homogeneous peptides were produced by Reanal (Hungary). Each peptide was purified by recrystallization from a water + ethanol mixture and dried under vacuum for 72 h at 320 K. The purity of the peptides was above 99 mol% (melting point determination). The solutions were prepared by weight using twice-distilled and deionized water. The potassium and sodium ion contents in the solutions studied, as determined by flame spectroscopy, did not exceed 2×10^{-4} mass%.

The measurements of the enthalpies of dilution of the ternary solutions were performed with a batch LKB 10700-2 microcalorimeter at 298.15 ± 0.01 K. The accuracy of the heats of dilution measurements was 0.1%. The dilutions of the ternary solutions were carried out at three ratios of the molalities of the peptides m_x and of the crown ethers m_y (0.5, 1.0, 2.0). The ^1H NMR spectra of the dipeptides in aqueous solutions of the crown ethers at 298.15 K were obtained using a Bruker 500 spectrometer. The spectrometer operated at 500 MHz in the "locked" mode using the signal from acetone (C_2D_6CO) which was placed in a spherical inner container to eliminate the correction for the bulk susceptibility. The estimated error for measurements was 0.001 ppm.

TREATMENT OF THE EXPERIMENTAL DATA

The treatment of the experimental data concerning the dilution experiments for the aqueous solutions is based on the excess enthalpy expression [3, 15, 18]

$$H^e = H - H_w^\ominus - \sum_{x=1}^{n} m_x \bar{H}_x \tag{1}$$

where H^e and H represent the amount of solution containing 1 kg of water and $m_1 \ldots m_n$ moles of each solute species, H is the enthalpy of the solution, $H_w^\ominus$ is the standard enthalpy of 1 kg of water, and $\bar{H}_x$ denotes the standard partial molal enthalpy of each solute species. Using the McMillan–Mayer formalism [1], the excess enthalpy of the ternary solution per 1 kg of water can be expressed as a power series in the molalities [15–17]

$$H^e(m_x m_y) = h_{xx} m_x^2 + 2h_{xy} m_x m_y + h_{yy} m_y^2 + h_{xxx} m_x^3 + 3h_{xxy} m_x^2 m_y + 3h_{xyy} m_x m_y^2 + h_{yyy} m_y^3 + \ldots \tag{2}$$

where h_{ij} and h_{ijk} are the enthalpic virial coefficients characterizing the pair-wise and triplet interactions of the solvated species and m_x and m_y are the molalities of the solutes x and y, respectively. The corresponding expression for the binary solution of a solute x is

$$H^e(m_x) = h_{xx} m_x^2 + h_{xxx} m_x^3 + \ldots \tag{3}$$

The experimental enthalpy of dilution of the ternary solution can be represented as a sum of the three terms. For the calculation of the coefficients of eqn. (2) on the basis of the dilution data, the auxiliary function has been introduced [18, 19]

$$\Delta H^{**} = \Delta H_{dil}[(m_x^i m_y^i) \rightarrow (m_x^f m_y^f)] - \Delta H_{dil}(m_x^i \rightarrow m_x^f) - \Delta H_{dil}(m_y^i \rightarrow m_y^f) \tag{4}$$

where the first term on the right-side of the equation denotes the enthalpy of dilution of the ternary solution, the second and the third terms are the enthalpies of dilution of the corresponding binary solutions and m^i and m^f are the initial and final molalities of the solute, respectively. According to eqn. (3), the enthalpy of dilution of the binary solution is defined as

$$\Delta H_{dil}(m_x^i \rightarrow m_x^f) = h_{xx} m_x^f (m_x^f - m_x^i) + h_{xxx} m_x^f [(m_x^f)^2 - (m_x^i)^2] + \ldots \tag{5}$$

The relation of the enthalpy of dilution of the ternary solution to the excess enthalpy can be expressed as

$$\Delta H_{dil}[(m_x^i m_y^i) \rightarrow (m_x^f m_y^f)] = H^e(m_x^f m_y^f) - (m_y^f / m_y^i) H^e(m_x^i m_y^i) \tag{6}$$

The equation for the cross interaction coefficients can be evaluated from the combination of eqns. (4)–(6)

$$\Delta H^{**} = 2h_{xy}m_y^f(m_x^f - m_x^i) + 3h_{xxy}m_y^f[(m_x^f)^2 - (m_x^i)^2] + 3h_{xyy}m_y^f(m_x^f - m_x^i)(m_y^f + m_y^i) + \ldots \quad (7)$$

$$\Delta H^{**}/m_y^f(m_x^f - m_x^i) = 2h_{xy} + 3h_{xxy}(m_x^f + m_x^i) + 3h_{xyy}(m_y^f + m_y^i) + \ldots \quad (8)$$

Values of ΔH^{**} were obtained from the experimental heats of dilution of the ternary solutions presented in Table 1. The heats of dilution of the aqueous binary solutions of α-amino acids and peptides are given in analytical form in the literature [20–23] and the data on the solutions of crown ethers were obtained previously [24].

TABLE 1

Enthalpies of dilution of ternary aqueous solutions of peptides (x) and crown ethers (y) at 298.15 K

m_x^i/ mol kg^{-1}	m_x^f/ mol kg^{-1}	m_y^i/ mol kg^{-1}	m_y^f/ mol kg^{-1}	ΔH_{dil}/ J kg^{-1}	ΔH^{**}/ J kg^{-1}
Glycine + 18-crown-6					
0.3108	0.2031	0.3083	0.2015	74.59	178.4
0.2031	0.1334	0.2015	0.1323	63.24	108.3
0.1334	0.0884	0.1323	0.0877	41.83	61.4
0.2522	0.1657	0.2539	0.1668	65.16	136.1
0.1657	0.1093	0.1668	0.1100	52.87	84.0
0.1093	0.0725	0.1100	0.0730	33.84	47.5
0.3068	0.2021	0.1551	0.1022	79.54	100.3
0.2021	0.1339	0.1022	0.0677	51.24	60.2
0.1339	0.0888	0.0677	0.0449	30.96	34.9
0.2162	0.1434	0.1243	0.0825	59.49	74.0
0.1434	0.0952	0.0825	0.0548	36.72	43.1
0.0952	0.0635	0.0548	0.0365	20.87	23.7
0.1474	0.0967	0.2985	0.1957	7.08	110.4
0.0967	0.0637	0.1957	0.1290	19.58	64.8
0.0637	0.0422	0.1290	0.0855	15.39	35.2
0.1232	0.0813	0.2520	0.1663	17.29	91.2
0.0813	0.0537	0.1663	0.1097	18.04	50.9
0.0537	0.0356	0.1097	0.0727	12.94	27.4
Diglycine + 18-crown-6					
0.3171	0.2059	0.3170	0.2058	48.56	151.8
0.2059	0.1348	0.2058	0.1348	46.55	90.7
0.1348	0.0891	0.1348	0.0891	33.61	52.6
0.2531	0.1653	0.2515	0.1643	49.84	115.1
0.1653	0.1086	0.1643	0.1079	40.43	68.6
0.1086	0.0722	0.1079	0.0717	26.81	39.0
0.0722	0.0480	0.0717	0.0477	15.91	21.3
0.3044	0.1980	0.1529	0.1036	63.96	76.6
0.1980	0.1305	0.1036	0.0683	42.97	49.6
0.1305	0.0870	0.0683	0.0455	26.10	28.9
0.2548	0.1691	0.1260	0.0836	54.07	62.8
0.1691	0.1118	0.0836	0.0552	35.40	39.2

TABLE 1 (continued)

m_x^i/ mol kg^{-1}	m_x^f/ mol kg^{-1}	m_y^i/ mol kg^{-1}	m_y^f/ mol kg^{-1}	ΔH_{dil}/ J kg^{-1}	ΔH^{**}/ J kg^{-1}
Diglycine + 18-crown-6					
0.1118	0.0740	0.0552	0.0366	21.14	22.8
0.1519	0.0991	0.3056	0.1994	−12.18	94.7
0.0991	0.0652	0.1994	0.1312	9.71	55.9
0.0652	0.0432	0.1312	0.0868	11.06	31.3
0.1292	0.0846	0.2551	0.1672	3.11	78.0
0.0846	0.0562	0.1672	0.1109	11.93	44.3
0.0562	0.0371	0.1109	0.0734	10.44	24.9
Triglycine + 18-crown-6					
0.2940	0.1910	0.2949	0.1915	48.18	121.9
0.1910	0.1249	0.1915	0.1252	43.70	74.8
0.1249	0.0826	0.1252	0.0828	23.91	37.2
0.2375	0.1550	0.2513	0.1640	31.75	87.3
0.1550	0.1019	0.1640	0.1079	36.23	60.0
0.1019	0.0673	0.1078	0.0712	20.84	31.1
0.3083	0.1996	0.1540	0.0997	61.65	58.0
0.1315	0.0870	0.0657	0.0435	21.11	20.0
0.2501	0.1638	0.1234	0.0808	47.24	43.8
0.1638	0.1084	0.0808	0.0535	27.63	25.8
0.1084	0.0719	0.0535	0.0355	16.60	15.7
0.1477	0.0966	0.2968	0.1942	−15.38	80.9
0.0966	0.0635	0.1942	0.1277	4.67	46.6
0.0635	0.0420	0.1277	0.0845	6.81	25.1
0.1260	0.0821	0.2517	0.1641	−2.71	67.4
0.0821	0.0540	0.1641	0.1080	7.70	37.8
0.0540	0.0356	0.1080	0.0712	6.70	19.9
L-α-Alanine + 18-crown-6					
0.2897	0.1888	0.2965	0.1932	3.75	112.5
0.1888	0.1240	0.1932	0.1269	12.13	59.0
0.1240	0.0818	0.1269	0.0838	12.50	32.9
0.2541	0.1654	0.2518	0.1639	14.41	93.8
0.1654	0.1092	0.1639	0.1082	16.14	50.0
0.1092	0.0730	0.1082	0.0723	11.14	25.9
0.2982	0.1945	0.1497	0.0976	30.41	62.3
0.1945	0.1295	0.0976	0.0650	20.75	34.2
0.1295	0.0858	0.0650	0.0431	12.59	18.6
0.2432	0.1593	0.1236	0.0809	26.39	48.1
0.1593	0.1057	0.0809	0.0537	15.82	25.1
0.1057	0.0709	0.0537	0.0360	9.46	13.5
0.1489	0.0969	0.3001	0.1952	−32.19	76.2
0.0969	0.0636	0.1952	0.1282	−7.19	39.3
0.0636	0.0424	0.1282	0.0855	−0.56	19.5
0.1218	0.0795	0.2491	0.1626	−18.58	56.6
0.0795	0.0524	0.1626	0.1073	−3.28	29.1

TABLE 1 (continued)

m_x^i/ mol kg^{-1}	m_x^f/ mol kg^{-1}	m_y^i/ mol kg^{-1}	m_y^f/ mol kg^{-1}	ΔH_{dil}/ J kg^{-1}	ΔH^{**}/ J kg^{-1}
L-α-Alanyl-L-α-Alanine + 18-crown-6					
0.3044	0.1972	0.3058	0.1982	−79.36	49.5
0.1972	0.1296	0.1982	0.1302	−22.74	32.1
0.2555	0.1666	0.2529	0.1649	−47.19	42.0
0.1666	0.1095	0.1649	0.1084	−12.18	26.3
0.1095	0.0722	0.1084	0.0714	−1.07	15.8
0.1325	0.0872	0.1314	0.0865	−4.39	20.2
0.3095	0.2028	0.1565	0.1025	−21.65	25.9
0.2028	0.1338	0.1025	0.0676	−2.29	18.5
0.3569	0.2342	0.1795	0.1178	−33.98	28.1
0.2342	0.1541	0.1178	0.0775	−5.96	21.4
0.2868	0.1881	0.1433	0.0940	−15.61	24.8
0.1501	0.0977	0.3009	0.1959	−75.44	36.8
0.0977	0.0640	0.1959	0.1283	−26.75	21.6
0.0640	0.0423	0.1283	0.0848	−8.67	12.2
0.1274	0.0836	0.2548	0.1671	−51.43	29.3
0.0836	0.0550	0.1671	0.1099	−17.64	17.7
Diglycine + 12-crown-4					
0.3264	0.2136	0.3313	0.2169	−69.97	−16.70
0.2136	0.1406	0.2169	0.1428	−29.83	−6.74
0.1406	0.0931	0.1428	0.0945	−13.23	−3.16
0.2463	0.1608	0.2508	0.1637	−39.35	−8.34
0.1608	0.1062	0.1637	0.1081	−17.11	−3.86
0.3103	0.2062	0.1540	0.1023	−8.01	−7.77
0.2062	0.1361	0.1023	0.0675	−3.54	−3.61
0.1361	0.0906	0.0675	0.0449	−1.71	−1.80
0.2658	0.1753	0.1343	0.0886	−6.48	−6.02
0.1753	0.1160	0.0886	0.0586	−2.88	−2.80
0.1590	0.1042	0.3210	0.2104	−68.91	−7.16
0.1042	0.0689	0.2104	0.1391	−30.19	−3.31
0.0689	0.0457	0.1391	0.0923	−13.34	−1.44
0.0835	0.0552	0.1707	0.1128	−20.03	−2.14
Diglycine + 15-crown-5					
0.3056	0.2002	0.3020	0.1978	−40.23	22.70
0.2002	0.1314	0.1978	0.1299	−16.79	10.70
0.1314	0.0868	0.1299	0.0858	−6.78	5.21
0.2603	0.1704	0.2591	0.1696	−29.85	17.10
0.1704	0.1124	0.1696	0.1119	−12.19	8.16
0.1124	0.0747	0.1119	0.0744	−5.04	3.89
0.3120	0.2058	0.1566	0.1033	4.21	10.20
0.2058	0.1358	0.1033	0.0682	2.62	5.12
0.1358	0.0903	0.0682	0.0453	1.43	2.48
0.2559	0.1665	0.1290	0.0839	3.39	7.52
0.1665	0.1105	0.0839	0.0557	2.01	3.66
0.1541	0.1011	0.3043	0.1996	−60.38	14.60

TABLE 1 (continued)

m_x^i/ mol kg^{-1}	m_x^f/ mol kg^{-1}	m_y^i/ mol kg^{-1}	m_y^f/ mol kg^{-1}	ΔH_{dil}/ J kg^{-1}	ΔH^{**}/ J kg^{-1}
Diglycine + 15-crown-5					
0.1011	0.0667	0.1996	0.1317	−26.52	6.40
0.0667	0.0444	0.1317	0.0876	−11.71	2.76
0.1286	0.0846	0.2553	0.1680	−42.25	11.00
0.0846	0.0558	0.1680	0.1107	−18.53	5.01
L-α-Alanyl-L-α-alanine + 12-crown-4					
0.3082	0.1998	0.3080	0.1996	−126.80	−49.40
0.1998	0.1314	0.1996	0.1313	−55.54	−21.80
0.1314	0.0869	0.1313	0.0869	−24.49	−9.71
0.2501	0.1634	0.2526	0.1650	−88.14	−34.70
0.1634	0.1080	0.1650	0.1095	−37.91	−14.90
0.1080	0.0716	0.1095	0.0726	−16.88	−6.63
0.3109	0.2036	0.1536	0.1005	−59.11	−25.70
0.2036	0.1346	0.1005	0.0665	−25.96	−11.30
0.1346	0.0891	0.0665	0.0440	−11.56	−5.05
0.2562	0.1678	0.1342	0.0879	−43.69	−19.30
0.1678	0.1107	0.0879	0.0580	−19.19	−8.56
0.1107	0.0736	0.0580	0.0386	8.39	−3.72
0.1547	0.1011	0.3009	0.1967	−88.04	−24.90
0.1011	0.0665	0.1967	0.1294	−38.34	−11.00
0.1170	0.0772	0.2568	0.1694	−60.96	−15.70
0.0510	0.0339	0.1119	0.0744	−12.04	−3.24
L-α-Alanyl-L-α-alanine + 15-crown-5					
0.3084	0.2014	0.3077	0.2009	−128.80	−29.20
0.2014	0.1324	0.2009	0.1321	−59.09	−13.10
0.1324	0.0872	0.1321	0.0871	−24.71	−5.79
0.2522	0.1657	0.2489	0.1635	−86.17	−20.80
0.1091	0.0727	0.1076	0.0718	−16.72	−4.15
0.3116	0.2052	0.1552	0.1022	−56.33	−17.30
0.2052	0.1353	0.1022	0.0674	−24.53	−7.16
0.2597	0.1721	0.1290	0.0855	−39.17	−12.00
0.1721	0.1137	0.0855	0.0565	−17.28	−5.00
0.1531	0.1003	0.3024	0.1981	−97.18	−14.40
0.1003	0.0658	0.1981	0.1301	−42.67	−6.34
0.1299	0.0854	0.2550	0.1677	−69.62	−10.30
0.0854	0.0564	0.1678	0.1107	−30.57	−4.43
Diglycine + 1,10-diaza-18-crown-6					
0.2559	0.1664	0.2533	0.1647	−83.01	−34.40
0.1664	0.1096	0.1647	0.1085	−35.95	−17.80
0.1096	0.0725	0.1085	0.0717	−18.19	−11.20
0.2005	0.1308	0.2005	0.1308	−38.89	−10.10
0.0862	0.0570	0.0862	0.0570	−13.10	−8.94
0.0570	0.0379	0.0570	0.0379	−6.07	−4.43
0.2002	0.1308	0.0993	0.0649	−21.23	−20.50
0.1308	0.0867	0.0649	0.0430	−11.76	−11.70

TABLE 1 (continued)

m_x^i/ mol kg^{-1}	m_x^f/ mol kg^{-1}	m_y^i/ mol kg^{-1}	m_y^f/ mol kg^{-1}	ΔH_{dil}/ J kg^{-1}	ΔH^{**}/ J kg^{-1}
Diglycine + 1,10-diaza-18-crown-6					
0.0867	0.0576	0.0430	0.0286	−6.22	−6.30
0.1664	0.1089	0.0811	0.0531	−15.45	−15.30
0.1089	0.0723	0.0531	0.0353	−6.57	−6.69
0.0723	0.0485	0.0353	0.0237	−3.22	−3.33
0.0631	0.0417	0.1289	0.0852	−17.55	−5.06
0.0417	0.0277	0.0852	0.0566	−7.68	−2.70
0.0853	0.0559	0.1646	0.1078	−27.77	−6.16
0.0559	0.0371	0.1078	0.0716	−12.14	−3.83
0.0371	0.0247	0.0716	0.0477	−5.41	−2.04
L-α-Alanyl-L-α-alanine + 1,10-diaza-18-crown-6					
0.1893	0.1238	0.1903	0.1245	−56.02	−17.50
0.2541	0.1610	0.2501	0.1585	−99.55	−28.20
0.1610	0.1056	0.1585	0.1039	−42.79	−16.70
0.1056	0.0697	0.1039	0.0686	−19.90	−9.46
0.0697	0.0463	0.0686	0.0456	−9.82	−5.55
0.1632	0.1071	0.0814	0.0534	−21.89	−11.80
0.1071	0.0712	0.0534	0.0355	−11.28	−7.09
0.2011	0.1309	0.1002	0.0652	−35.15	−19.70
0.1309	0.0866	0.0652	0.0432	−15.74	−9.40
0.0866	0.0575	0.0432	0.0287	−8.09	−5.36
0.1257	0.0814	0.2514	0.1629	−86.84	−25.10
0.0814	0.0536	0.1629	0.1073	−34.08	−10.50
0.0993	0.0645	0.2041	0.1325	−49.03	−9.96
0.0427	0.0283	0.0878	0.0582	−11.02	−4.99

RESULTS

The enthalpies of dilution of aqueous solutions containing α-amino acids, peptides and crown ethers are given in Table 1 together with the initial and final molalities of the two solutes. The molality range of 0.03–0.3 mol kg^{-1} was used for these measurements. Three different m_x/m_y ratios were chosen in order to obtain an adequate description and effective values of the coefficients h_{ij} and h_{ijk} [18]. The pair-wise and triplet enthalpic interaction coefficients for the solutions studied are reported in Table 2. The cross coefficients are either negative or positive depending on the stereochemistry and the size of the crown ethers. The enthalpy of interaction of the α-amino acids and peptides with 18-crown-6 produces a very high exothermic effect which is caused by the host–guest complexation in these solutions. The other pairs, except 15-crown-5/diglycine, are characterized by an endothermic interaction effect and by positive h_{xy} values.

TABLE 2

Enthalpic pair-wise and triplet interaction coefficients for aqueous solutions of peptides (x) and of crown ethers (y) at 298.15 K [a]

Solutes $x + y$	h_{xy} / J kg mol^{-2}	h_{xxy} / J kg^2 mol^{-3}	h_{xyy} / J kg^2 mol^{-3}
Glycine + 18-crown-6	−11666 (264)	6953 (412)	4322 (740)
Diglycine + 18-crown-6	−10345 (388)	7302 (1137)	3649 (1075)
Triglycine + 18-crown-6	−8039 (277)	6652 (950)	1292 (777)
L-α-Alanine + 18-crown-6	−6294 (175)	3521 (133)	1655 (420)
Dialanine + 18-crown-6	−3864 (285)	2862 (305)	1162 (637)
Diglycine + 12-crown-4	392 (22)	52 (38)	−148 (62)
Dialanine + 12-crown-4	1332 (15)	−55 (22)	−192 (33)
Diglycine + 15-crown-5	−748 (23)	496 (49)	−218 (43)
Dialanine + 15-crown-5	762 (36)	106 (52)	−165 (67)
Diglycine + 1,10-diaza-18-crown-6	3081 (120)	2425 (168)	−6440 (402)
Dialanine + 1,10-diaza-18-crown-6	3248 (342)	−3038 (1431)	−667 (1343)

[a] The number in parentheses represents the 95% confidence range.

DISCUSSION

As can be seen in Table 2, the interaction of crown ethers with dipeptides is characterized by positive and negative cross interaction coefficients h_{xy}. There are several ways of interpreting their sign. The process of interaction of two solvated species can be represented as consisting of two successive stages: the partial desolvation of the solutes and the further direct interaction caused by the short-range molecular forces [8, 25]. However, most of the peptide interactions studied, for example with urea, sugars and alcohols, can be defined as weak and solvent-mediated [5, 26–28]. Due to the weak interaction, the solute–solute virial coefficients will include any contribution from a structural rearrangement of the solvent [25]. However, direct solute–solute interactions cannot be completely excluded [8, 26].

As can clearly be seen in Fig. 2, the inversion of the sign of the cross interaction coefficients from positive to negative for the interaction of diglycine and dialanine with crown ethers proceeds in the direction: 1,10-diaza-18-crown-6 > 12-crown-4 > 15-crown-5 > 18-crown-6. Using the concept of overlap of the co-spheres of the solutes [16, 25], it can be concluded that this is caused by the change in the mechanism of the peptide–crown interaction. The hydration of the 18-crown-6 and the diaza-18-crown-6 produces an exothermic effect [29, 30] caused by the formation of hydrogen bonds with water. Therefore, the dehydration of both crown ethers is an intense endothermic process. The small differences in the positive h_{xy} coefficients (enthalpically unfavourable interactions) for 1,10-diaza-18-crown-6/diglycine and 1,10-diaza-18-crown-6/dialanine can be explained by assuming that the endothermic dehydration process mainly occurs from the

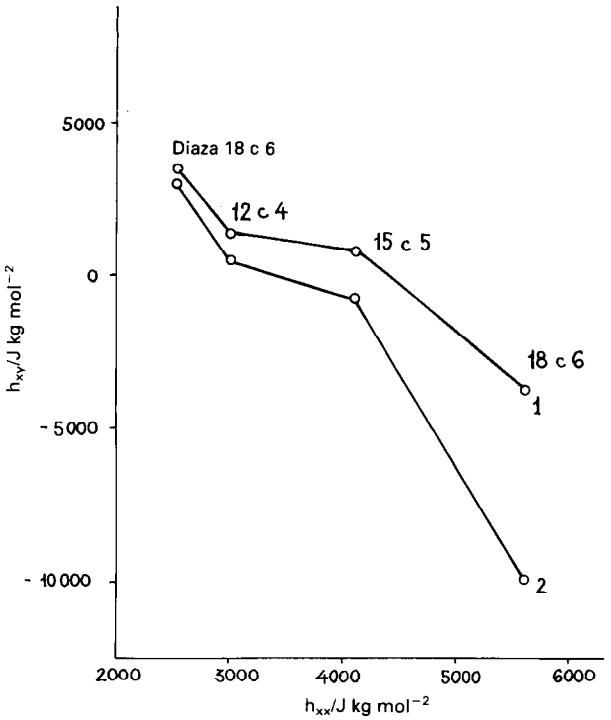

Fig. 2. Cross interaction coefficients for the systems containing L-α-alanyl-L-α-alanine (1) and glycylglycine (2) and crown ethers versus the self coefficients of the crown ethers.

more labile macrocycle solvation shell, under the action of the strongly solvated peptide zwitterion. On substitution of the amino groups by oxygen atoms and on the increase in size of the macrocycle, direct interaction of the charged ammonium NH_3^+ group of the dipeptides with the oxygen atoms of crown ethers becomes more favourable. This process is exothermic and it would lead to a decrease in the positive h_{xy} values. A similar situation was found for the interaction of glycine with an electrolyte [8, 31]. The result obtained shows that as the halide anion radius increases, the enthalpic virial coefficients become increasingly negative [8]. In contrast, the h_{xy} values for interaction with cations are, within experimental uncertainty, the same [31]. It can be suggested that the mode of interaction of glycine with anion and cation is quite different [8] and has similar features to the peptide–crown interaction.

The values of the cross interaction coefficient for 18-crown-6/diglycine and 18-crown-6/dialanine pairs differ significantly as compared with small differences in the h_{xy} values for the dipeptide interaction with 1,10-diaza-18-crown-6 (Table 2). The 18-crown-6/dipeptide interaction is realized by the NH_3^+ end-group of the peptide through three hydrogen bonds with the macrocycle [13]. The three $N^+\cdots O$ electrostatic interactions [11, 12] next stabilize the complex formation. Evidently, the significant contribution of

TABLE 3

^1H shifts (ppm) of the dipeptide groups (NH, CH_2, CH_3) in aqueous solutions containing crown ethers

Peak	Water	12-Crown-4	15-Crown-5	18-Crown-6
Diglycine				
NH (amide group)	7.385	7.380	7.340	7.370
CH_2 (adjacent to NH_3^+)	2.925	2.927	2.907	2.898
CH_2 (adjacent to CO_2^-, doublet)	2.884	2.884	2.872	2.890
	2.872	2.873	2.861	2.879
Dialanine				
NH (amide group, doublet)	7.331	7.314	7.287	7.425
	7.343	7.327	7.301	7.439
CH_3 (adjacent to NH_3^+, doublet)	0.620	0.625	0.614	0.608
	0.605	0.610	0.600	0.594
CH_3 (adjacent to CO_2^-, doublet)	0.424	0.428	0.426	0.433
	0.409	0.414	0.412	0.418

these specific interactions makes the 18-crown-6/dipeptide interaction enthalpically more selective.

The analysis of the ^1H NMR data can explain the details of the influence of crown ethers on the state of the peptide groups. The chemical shifts related to protons of the amide NH group, the methylene CH_2 groups of diglycine, and the methyl CH_3 groups of dialanine are presented in Table 3. The proton shifts of the NH and CH_2 groups of diglycine are weakly sensitive to the addition of 12-crown-4 and they are clearly shifted by the presence of 15-crown-5 and 18-crown-6 (especially for the protons of the CH_2 group near the charged ammonium group). The addition of 12-crown-4 and 15-crown-5 does not affect significantly the chemical shifts of the protons of both methyl groups in dialanine. A stronger effect is found for the CH_3 protons on addition of 18-crown-6 and also a significant effect is revealed for the NH proton shift induced by the presence of 15-crown-5 and 18-crown-6. In addition, protons of the two methyl groups have the opposite behaviour; the peaks of the methyl group adjacent to the CO_2^- group shift nearer to the water signal, but the proton peaks of the methyl groups adjacent to NH_3^+ go to the opposite field in the presence of 15-crown-5 and 18-crown-6. The NH proton behaves similarly in the presence of 18-crown-6. Thus, the proton shifts of the peptide groups are increasingly sensitive to the presence of 15-crown-5 and 18-crown-6, respectively. This confirms the "orientational effect" arranging the NH_3^+ peptide group nearer to the macrocycle ring, at least in solutions of these two crown ethers.

Thus, the solvation of host and guest molecules is an important factor in the complex formation. Figure 2 shows the non-linear dependences of the

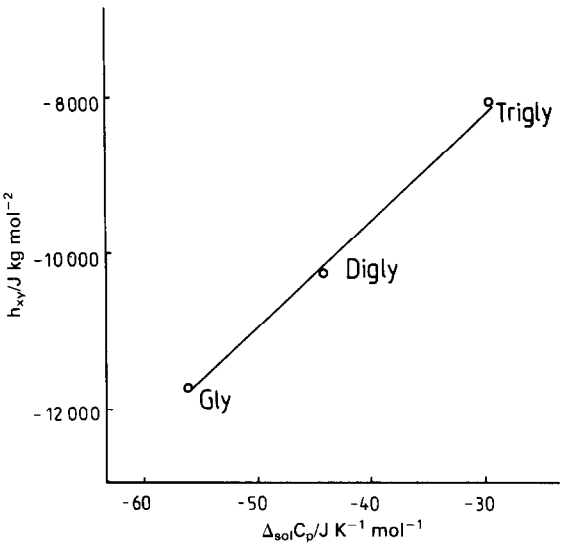

Fig. 3. Cross interaction coefficients for the systems containing glycyl peptides and 18-crown-6 versus the number of glycyl residues.

cross interaction coefficients h_{xy} versus the self interaction coefficients h_{xx} of the crown ethers. The linear dependence between h_{xx} and $\Delta_{solv}H$ has been previously established for crown ethers [24]. These values are characteristic for solute–solute and solute–solvent interactions. Figure 2 suggests that in this case the solvation state of crown ethers does not determine the entire change of the enthalpy of an interaction with dipeptides. The size of the macrocycle is not significant because a considerable rise in the negativity of h_{xy} values is observed for the 18-crown-6/peptide interaction.

The analysis of the solvation effect of the peptide guest molecule on the intermolecular peptide–crown interaction can be performed using the glycine oligomer data. The results presented in Table 2 and Fig. 3 show clearly that as the number of glycine residues increases, the enthalpic virial coefficients h_{xy} become less negative in an approximately linear way, i.e. the interaction of glycine with 18-crown-6 is thermochemically more favourable. Because glycyl peptides have no apolar side groups and the electrostatic contribution depends inversely on the peptide size, then the additive specific contribution from the increasing molecular length determines this dependence. The heat capacity of the solution characterizes the specificity of solvation of the peptide in water [32, 33]. The correlation between h_{xy} and $\Delta_{sol}C_p$ (Fig. 4) shows the additivity of these values which is caused by the origins depending on each other. The strong specific interaction of α-amino acids and peptides with 18-crown-6 must be accompanied by a significant desolvation process of the guest molecule. The exothermic effect of hydration of the peptides, as has been shown [34–36], increases with the increase

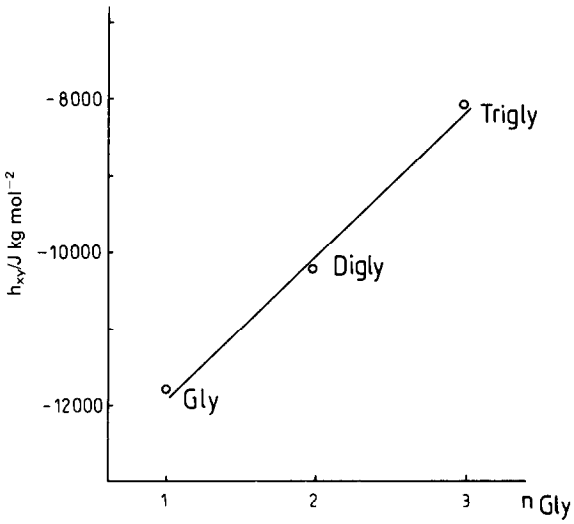

Fig. 4. Cross interaction coefficients for the systems containing glycyl peptides and 18-crown-6 versus the heat capacity of solution $\Delta_{sol}C_p$ of the peptides in water.

in amino acid residues, which results in the opposite endothermic desolvation process. Therefore, assuming that the desolvation contribution of the macrocycle is constant, the greater the endothermic desolvation of the longer glycyl peptides during their interaction with 18-crown-6, the less negative the h_{xy} value induced. As a result, the interaction between the NH_3^+ group and the donor atoms of the ligand becomes less enthalpically favourable over the series glycine > diglycine > triglycine. Therefore, the specific solvation of glycyl peptides influences the change in the cross coefficient values in the interaction with 18-crown-6. This conclusion confirms the concept that much of the amino acid molecule is exposed to the reaction medium [12].

Analysing the values of the triplet cross coefficients, it should be noted that the peptide/18-crown-6 interaction of 2:1 type is more favourable than that of 1:2. The presence of methyl side groups and lengthening of the peptide molecules is followed by a decrease in the values of the h_{xxy} and h_{xyy} coefficients in the peptide/18-crown-6 interaction, except for the h_{xxy} coefficient of the 18-crown-6/diglycine pair.

In conclusion, the effect of solvent on the properties of the peptide–crown interactions should be emphasized. The enthalpies of melting decomposition of crystalline complexes $\Delta_{fus}H$ characterize the energetics of the binding of host and guest molecules in the crystals. From the data obtained previously [13] and from those presented in this work (Table 2), it can be seen that the differences between the $\Delta_{fus}H$ values for the 18-crown-6/diglycine (139 kJ mol^{-1}), 18-crown-6/dialanine (140 kJ mol ^{1}), 18-crown-6/triglycine (184 kJ mol^{-1}) and 18-crown-6/glycine (129 kJ mol^{-1}) complexes

are less remarkable than those for the h_{xy} cross interaction coefficients of the corresponding pairs in water. Because the coefficient h_{xy} determines the enthalpy of the pair-wise interaction in the solvent, it can be concluded that the effect of the solvent makes the peptide–crown recognition process enthalpically more selective.

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