Be Careful When You Want to Use Buffers in Aqueous Solutions of Cyclodextrins. Effect of Buffers on the Formation Constants of 3-Hydroxy-2-Naphthoic Acid with β-Cyclodextrin

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Formation constants of 3-hydroxy-2-naphthoic acid with β-cyclodextrin were determined in aqueous solutions without and with almost all the buffers usually used by steady-state fluorescence Benesi-Hildebrand method. The results show that buffers have influence on the formation constants and we suggest that buffers should not be used in aqueous solutions of cyclodextrins unless the experimental error is unacceptable.

Cyclodextrins(CDs) can include various organic molecules and some inorganic anions.[1-5] Usually the formation constants of the inclusion compounds have been determined in aqueous solutions and salts are added to control the ionic strength and pH values. Thus it's of significant importance to study the effect of these salts on the formation constants of CDs with guest molecules. It has been reported that[3-6] salts may affect the inclusion equilibrium in following ways: (1) Salts change the structure and activity of water, which has effect on the hydrophobic interaction between gust and cyclodextrins. And also, water itself may take part in the inclusion reactions. (2) Salts change the activities of the free and complexed gust. (3) Some salts are trapped within the cavity of CDs, competing with guests for the binding site. (4) Some anions may form ternary complex with CDs and guest through hydrogen bonding. Although the influence of some anions such as ClO_4^-,Cl^-,SCN^-, NO_3^-, etc. on the formation constants of CDs inclusion complexes has been studied extensively,[2-5] few data are known about the effect of buffers on them. Recently M.D.Johnson and J.G.Bernard [6] showed that some buffers dramatically influence the magnitude of cyclodextrin inclusion of transition metal complexes. It is explained by assuming the formation of a ternary complex composed of cyclodextrin, metal complex, and buffer held together through hydrogen bonding. However, Y. Matsui, et al.[5] reported that the addition of KF, K_2SO_4, KH_2PO_4, K_2HPO_4 and $KHCO_3$ caused no or small upfield shifts of C(5)-H of CDs in ^{1}HNMR signal and they suggested that these salts be used to adjust the ionic strength and pH values of CD solutions without any interference of gust inclusion within the CD cavity. Who is true?

In the present work, we measured formation constants of 3-hydroxy-2-naphthoic acid (3H2NA) with β-CD in aqueous solutions at quite a lot pH values without and with buffers respectively by steady-state fluorescence Benesi-Hildebrand method.[7] We didn't add salts to control the ionic strength in the determination of formation constants because we found that they do have influence on the formation constants(see Table 1). In our experiments, the concentration of 3H2NA is 1.8×10^{-5} M (1 M = 1 mol/L). At such low concentration, the dimerization of 3H2NA may be ignored [8] and we didn't observe the excimer fluorescence of 2:2 inclusion complex of 3H2NA with β-cyclodextrin.

Table 1. The formation constants (K) of 3H2NA with β-CD in aqueous solutions without and with several ionic strength adjusters (C=0.1 mol/L, pH=5.0, T=25 °C)

salt	None	$NaClO_4$	KF	KCl	K_2SO_4
K(L/mol)	1083±20	264±15	1235±35	1260±50	1251±66

From Table 1, we can learn that the experimental error is quite small without salts to control the ionic strength and there is no improvement upon the addition of inorganic salts. Furthermore, K value is greatly decreased in 0.1 M $NaClO_4$, which may caused mainly by the including of ClO_4^- within the β-CD cavity. Meanwhile, K values are increased in the presence of 0.1 M KF, KCl and K_2SO_4 respectively. Since these salts caused no or slight shifts of C(5)-H of β-CD and they aren't included in the CD cavity,[5] the increase of K values are probably due to the structure and activity change of water, free guest and complexed guest.[3,4]

Table 2 shows the effect of buffers on the formation constants of 3H2NA with β-CD in aqueous solutions. From Table 2 we can see that: (1) After adding buffers, the experimental error have no virtual improvement except for 0.1 M $NaHC_4H_4O_6$ at pH 3.8. (2) K values are different from that of K_{buff} in most buffers. With 0.05 M $NaHC_2O_4$ (pH=1.7), 0.1 M $C_2H_4(OH)COOH$ + NaOH (pH=5.0), 0.16 M HAc-1.5 M NaAc (pH=5.7), 2 M NH_4Ac (pH=7.0), 0.5 M NaAc (pH=8.5) and 0.1 M $NaHCO_3$ (pH=8.6), K_{buff} is much larger than corresponding K. Probably this is mainly due to the formation of ternary complexes of buffers with β-CD and guests through hydrogen bonding, for these buffers are all able to serve as proton donors or acceptors or both. However, with 0.05 M $KH_2C_6H_5O_7$ (pH=3.8), 0.05 M $KHC_8H_4O_4$ (pH=4.0) and 0.1 M NaH_2PO_4 (pH=4.5), K_{buff} is much smaller than corresponding K. Maybe this is chiefly caused by the inclusion of anions within the β-CD cavity, especially for potassium dihydrogen citrate and potassium hydrogen phthalate whose anions present large hydrophobicity. Of course, the change of structure and activity of water, free guests and complexed guest may also affect the formation constants. (3) The effect of buffers on K is related to the concentration of the salts. For example, at pH 8.1 the increase of K value upon the addition of 0.1 M NaAc is 108 L/mol, but at pH 8.5 and 5.7, in the presence of 0.5 M NaAc and 0.16 M HAc-1.5 M NaAc, the increase of K value is 240 and 393 L/mol respectively. This indicates that the lower the concentration of salts, the smaller the effect of buffers on the formation constants.

Table 2. The formation constants of 3H2NA with β-CD in aqueous solutions at different pH values without (K) and with buffers (K_{buff}) respectively (T=25 °C)

pH [a]	K(L/mol)	buffer [a]	K_{buff} (L/mol)
1.7 [b]	2063±185	0.05 M $NaHC_2O_4$	3513±281
3.8	1250±111	0.05 M $KH_2C_6H_5O_7$	793±65
		0.1 M $NaHC_4H_4O_6$	1116±27
4.0	1244±107	0.05 M $KHC_8H_4O_4$	500±30
4.5	1115±98	0.1 M NaH_2PO_4	868±65
5.0	1083±20	0.1 M $C_2H_4(OH)COOH$	1346±111
5.7	1153±80	0.16 M HAc -1.5 M NaAc	1546±111
7.0	1154±9	2 M NH_4Ac	1464±25
7.6	1052±42	0.04 M NH_3-2.2 M NH_4Cl	1126±83
		0.05 M $(CH_2OH)_3$ CNH_2	1114±83
8.1	1107±81	0.1 M NaAc	1215±70
8.5	1157±56	0.5 M NaAc	1397±58
8.6	1140±44	0.1 M $NaHCO_3$	1340±33
9.5	1145±73	0.1 M Na_2HPO_4	1234±98
10.0	1031±20	0.025 M $NaHCO_3$	1124±20
11.2 [b]	970±88	0.02 M $NaCO_3$	962±86

[a] NaOH or HCl were added to obtain the pH values if needed. [b] This is an apparent formation constant for at pH 1.7 and 11.2, 3H2NA (pK_{a1}=2.6) [9a] and β-CD (pK_a =12.2) [9b] partly dissociate respectively.

From what has been discussed above, we may learn that buffers or ionic strength adjusters have influence on the formation constants of 3H2NA with β-CD in aqueous solutions. Some of them increase the K values and some decrease them. So we suggest that: (1) Be careful not to use buffers and ionic strength adjusters in aqueous solutions of cyclodextrins unless the experimental error is unacceptable. (2) Before adding salts to adjust the pH values and ionic strength, please find out the best salts that have no or slight effect on the formation constants. (3) What has been suggested above may apply to other host-guest systems.

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