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SHORT COMMUNICATION

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Surfactant-modified zeolites as a drug carrier and the release of chloroquin

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Abstract The adsolubilization of chloroquin (CQ) by complexes of zeolites with hexadecyl-, tetradecyl-, and dodecyltrimethylammonium bromides was determined by spectrophotometry. The zeolites used were P-type zeolite (ZP) with a sodium counterion and X-type zeolites with sodium (NX) or calcium (CX) counterions. ZP adsorbed CQ without surfactant, but the ZP surfactant complexes enhanced the adsorption of CQ. Without surfactant, NX and CX did not adsorb CQ, but the surfactant complexes induced the adsorption of CQ. Since the surfactants and CQ were cationic under the experimental conditions, the enhanced CQ incorporation was ascribed to the adsolubilization of CQ by the zeolite/surfactant complexes. The NaCl concentration in the eluant controlled the rate of CQ elution from the complexes. The examination of the surfactant elution proved that the elution of CQ was dependent on the residual surfactant content of the zeolite/surfactant complexes. Sodium chloride affected the release of both surfactant and CQ from the complexes.

Key words Adsolubilization · Drug carrier · Zeolite · Cationic surfactant · Chloroquin

Introduction

A specific property of zeolites is their variation in pore size, which leads to selectivity for guest molecules. Zeolites with small pores, however, are often useless for chemical reactions or as molecular sieves for large guest molecules. Best-fit molecules or groups are preferentially incorporated into porous zeolites and this incorporation sometimes activates the molecule for subsequent chemical reactions. The adsorption of surfactant on various solid surfaces is reported to induce or enhance the coadsorption of dyes below the critical surfactant micelle concentration [1–8]. Probe studies of surfactant adsorption on solid surfaces have revealed the formation of surfactant aggregates in hemimicelles or admicelles on various solid particles in aqueous suspensions [1, 9–30]. The enhanced coadsorption of different organic molecules on surfactant/solid complexes is ascribed to the partition of organic solutes between the aqueous bulk phase and admicelles on the solid surface and has been termed surface solubilization or adsolubilization [1, 31–33]. These observations suggest that zeolite/surfactant complexes are capable of incorporating hydrophobic compounds, such as surfactant micelles, to solubilize water-insoluble compounds in the hydrophobic core. Indeed, Esumi and coworkers [5, 33] found that hexanol was incorporated in alumina/surfactant complexes. This adsolubilization effect has been found in mixed suspensions of surfactant and fine particles [6, 32, 34–38]. We infer that the formation of admicelles on zeolite may lead to the incorporation of hydrophobic compounds, independent of the zeolite pore size. Our previous fluorescence probe study demonstrated the cooperative adsorption of cationic surfactant and proved that a hydrophobic domain formed on P-type zeolite (ZP) [29]. These results imply the formation of admicelles and lead

us to expect the efficient adsolubilization of drugs by zeolite/surfactant complexes. The adsolubilization of drugs may lead to potential new uses, such as new drug delivery systems and controlled-release agricultural chemicals. We are not aware of any combined studies of adsolubilization and elution in zeolite/surfactant complexes.

In this study, we examined the incorporation and elution of the drug chloroquin (CQ) by zeolite/surfactant complexes. The cationic surfactants used were hexadecyl-, tetradecyl-, and dodecyltrimethylammonium bromide (HTAB, TTAB, and DTAB, respectively). We found that the zeolite/surfactant complexes incorporated more CQ than zeolite alone and that the elution rate depended on the length of the surfactant chain and the ionic strength of the eluate.

Experimental

Materials

ZP, which was synthesized in a hydrothermal reaction from *shirasu* (an ancient pyroclastic flow deposit), was a kind gift from Sankei Chemical Co. It had a Si/Al molar ratio of 2.0, an ionic exchange capacity of 4.1 $mEqg^{-1}$ for ammonium cation, a specific surface area of 65.3 m^2g^{-1}, and a pore size of 0.35 nm. Porosimetry using a Shimadzu-Micromeritex Assap 2400 surface area porosimeter showed that it had a mesopore 7.5 nm in diameter. The two X-type zeolites, Zeoster CX and NX, with calcium and sodium counter ions, respectively, were obtained from Nippon Kagaku Kogyo. The specific surface areas of NX and CX were determined to be 830 and 850 m^2g^{-1}, respectively. NX and CX both had a Si/Al molar ratio of 1.3, the pore size was 0.9 nm for NX and 0.8 nm for CX, and the ionic exchange capacity was 2.5 mEq/g for NX and 2.6 mEq/g for CX. The zeolites were thoroughly washed in doubly distilled water and were dried under reduced pressure. They were dried for an additional 2 h at 100 °C before use. The surfactants, DTAB, TTAB, and HTAB (GR from TCI, Tokyo), were recrystallized twice from acetone. CQ was used as received; the solubility was determined to be 32.2 g in 100 g water at room temperature.

Measurements

Suspensions (15 ml) including 1.0 g zeolite, surfactant, and CQ were shaken for 9 days at 25 °C. The solution pH was adjusted to 6.8 using 2.5 mM phosphate buffer solution. Equilibration was reached within 2 days, but a very slow increase in surfactant adsorption was sometimes observed after the initial rapid 90% adsorption. After equilibration, the surfactant concentration in the supernatant was determined by potentiometry with a surfactant ion-selective electrode and the CQ concentration was determined by spectrophotometry. Since the molar absorbance of CQ depends on the pH, the absorbance was measured at 330 nm after a given amount of supernatant had been diluted in a pH 2 buffer solution prepared from 0.08 M HCl and 0.2 M KCl. The molar absorbance at 330 nm and pH 2 was 16,000 mol^{-1} dm^3 cm^{-1}. The equilibrium for CQ incorporation was determined.

Solid complexes consisting of ZP, surfactant, and CQ were separated by centrifugation, rinsed lightly with distilled water and dried. The surfactant and CQ content of the complexes was determined after liberation into the aqueous bulk phase with excess salt. Prepared dry complexes were suspended in aqueous eluates with a fixed NaCl concentration, put in vials and shaken for at least 1 day at 25 °C. The concentrations of surfactant and CQ liberated into the eluate were determined. The solid was removed and resuspended in fresh eluate and the process was repeated several times to monitor the elution of both CQ and surfactant.

Results and discussion

Incorporation of CQ by surfactant-modified zeolites

The CQ adsorption isotherms are shown in Fig. 1. These plot the amount of CQ (X_{CQ}) adsorbed on zeolite as a function of the equilibrium concentration of CQ in the absence of surfactant. CQ is adsorbed on ZP, and the amount adsorbed becomes saturated at 50 μmol dm^{-3} free CQ. Analysis of the isotherm with the Langmuir equation gives $X_{max} = 0.18$ μmol dm^{-3} and the adsorption constant $K = 0.15 \times 10^6$ M^{-1} for the ZP/CQ system. These parameters match the actual data well, as shown by the solid curve in Fig. 1. The value obtained for X_{max} is much less than the cation-exchange capacity of ZP, suggesting adsorption on the outer surface. On the other hand, only a little CQ is adsorbed on NX and CX even at 50 μmol dm^{-3} free CQ. The strong adsorption by ZP is partly ascribed to the hydrophobic properties of ZP and indicates a larger second-order binding constant for TTAB than for DTAB [29].

The dependence of X_{CQ} on the TTAB concentration in shown in Fig. 2. The CQ adsorption increases with the surfactant concentration. CQ was not adsorbed on NX alone, but a remarkable increase in X_{CQ} on NX was observed in the presence of TTAB (Fig. 1). Since CQ and TTAB are both cationic, this enhanced CQ

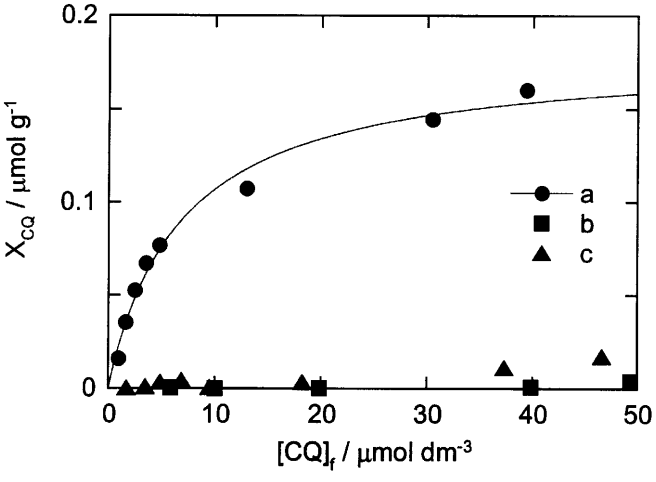


Fig. 1 Adsorption isotherms of chloroquin (*CQ*) by zeolites at 25 °C; *a* P-type zeolite with a sodium counterion (*ZP*), *b* X-type zeolite with a sodium counterion (*NX*), and *c* X-type zeolite with a calcium counterion (*CX*). The *solid line* indicates a simulation curve calculated using the Langmuir equation

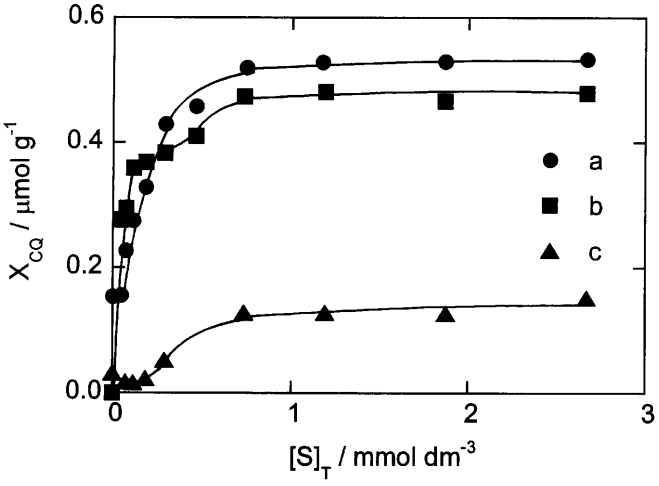


Fig. 2 Dependence of CQ adsorption by zeolite on tetradecyltrimethylammonium bromide (*TTAB*) concentration in aqueous solutions including 50 mM CQ. *Symbols* correspond to those in Fig. 1

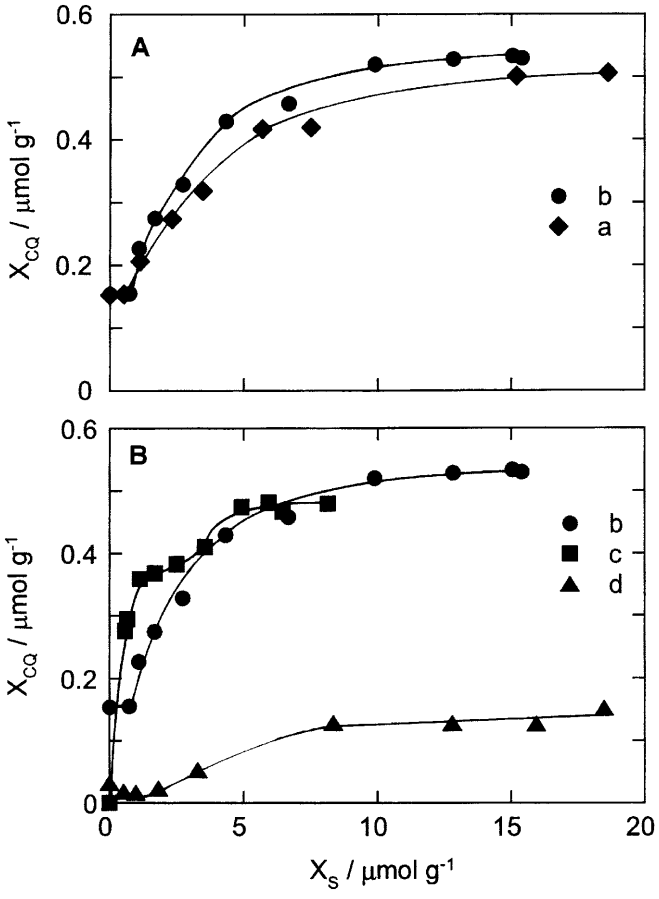


Fig. 3A, B Dependence of CQ adsolubilization on surfactant content in zeolite/surfactant complexes. **A** Surfactant chain length dependence and **B** zeolite dependence. *a* ZP/dodecyltrimethylammonium bromide (*DTAB*), *b* ZP/TTAB, *c* NX/TTAB, and *d* CX/TTAB complexes

adsorption may be ascribed to the adsolubilization of CQ with the ZP/TTAB complex. If CQ and TTAB compete for adsorption at anionic sites, X_{CQ} should decrease as the TTAB concentration increases.

If the coadsorption of CQ is due to adsolubilization by surfactant aggregates on the zeolite surface, the amount of CQ adsorbed is expected to depend on the amount of surfactant adsorbed (X_S). The amount of surfactant adsorbed was determined by potentiometry using a surfactant ion-selective electrode.

In the presence of TTAB, the amount of CQ adsorption was determined as a function of the amount of surfactant adsorbed at a constant total CQ concentration of 50 μmol dm^{-3}. The amounts of CQ incorporated on ZP complexes using two surfactants with different chain lengths are compared in Fig. 3A. The surfactant adsorption on ZP is much greater with TTAB than with DTAB [29]. Compared to the ZP/DTAB complex, the ZP/TTAB complex shows a similar CQ incorporation for the adsorbed quantities of surfactant.

The dependence of X_{CQ} on X_S for complexes of TTAB with ZP, NX, and CX is shown in Fig. 3B. The formation of a zeolite/surfactant complex induces a remarkable increase in CQ incorporation, especially with NX, which does not adsorb CQ unless TTAB is present, as shown in Fig. 1. The CX/TTAB complex incorporates much less CQ than the other two complexes, although TTAB is adsorbed on CX. The calcium counterion may induce this result, but the reason is unclear and further study is needed. Although CQ is incorporated into ZP without surfactant, the adsorption of TTAB on ZP enhances the incorporation of CQ, as shown in Fig. 1. For example, 0.53 μmol g^{-1} CQ is incorporated into the ZP/TTAB complex with a 15 μmol g^{-1} TTAB content, which is 3.5 times more CQ than is adsorbed on the bare ZP surface.

Elution of CQ

Solid complexes consisting of CQ, zeolite, and surfactant were suspended in NaCl solution and the amount of CQ released into the eluant was determined. The elution of CQ from the ZP/DTAB complexes is represented in Fig. 4. The smooth curves obtained at different time intervals (1–3 days) suggest that desorption equilibrium was achieved and was not affected by a light rinse. The esidual amount of CQ (X_{CQ}) decreased each time the eluant was refreshed. The elution rate was slow in the absence of NaCl, but it increased with NaCl concentration. CQ was completely released from the ZP/DTAB complexes after the eluant containing NaCl had been refreshed several times, while a little CQ still remained

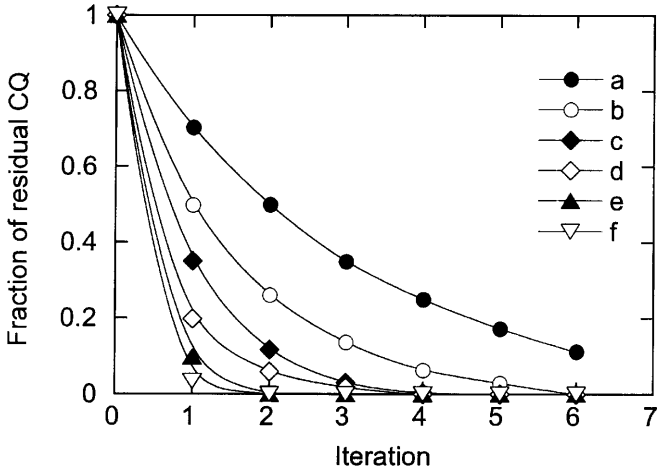


Fig. 4 Elution of CQ from ZP/DTAB complexes into NaCl solutions. The iteration number indicates the number of sequential elution runs. NaCl concentration: *a* 0, *b* 2.5, *c* 5.0, *d* 10, *e* 20, and *f* 50 mM

after the sixth elution with the ZP/TTAB and ZP/HTAB complexes.

The amount of CQ released from the complex in the first elution experiment is plotted as a function of the NaCl concentration in Fig. 5. This indicates that CQ was rapidly released from the zeolite/surfactant complexes as the NaCl concentration increased. This means that the ionic strength of the eluate may control the rate of elution of CQ from zeolite/surfactant complexes, suggesting an electrostatic contribution for the interaction between the CQ and the ZP/surfactant complex or between CQ/surfactant complex and ZP. A comparison of the three curves in Fig. 5A indicates that the ZP/DTAB complex released CQ more quickly than the other two complexes.

The CQ elutions from the ZP/TTAB, NX/TTAB, and CX/TTAB complexes are compared in Fig. 5B. Since the CX/TTAB complex had a small capacity for adsolubilization of CQ, very little CQ was released, even in 50 mM NaCl. In the absence of NaCl, more CQ was released from the NX/TTAB complex (0.1 μmol g^{-1}, Fig. 5B, curve d) than from the ZP/TTAB complex (0.05 μmol g^{-1}, Fig. 5B, curve b); however, more CQ was released from the ZP/TTAB complex than from the NX/TTAB complex in 50 mM NaCl. This is ascribed to the fact that more CQ is adsolubilized into the ZP/TTAB complex than into the other X-type zeolite/TTAB complexes.

It is believed that surfactant desorption is responsible for the release of CQ. The residual fraction of surfactant in the zeolite/surfactant complexes after dissolution into the first elution run is shown as a function of NaCl concentration in Fig. 6. Surfactant desorption was clearly indicated, but the residual amounts were still high, even in 50 mmol dm^{-3} NaCl. This surfactant

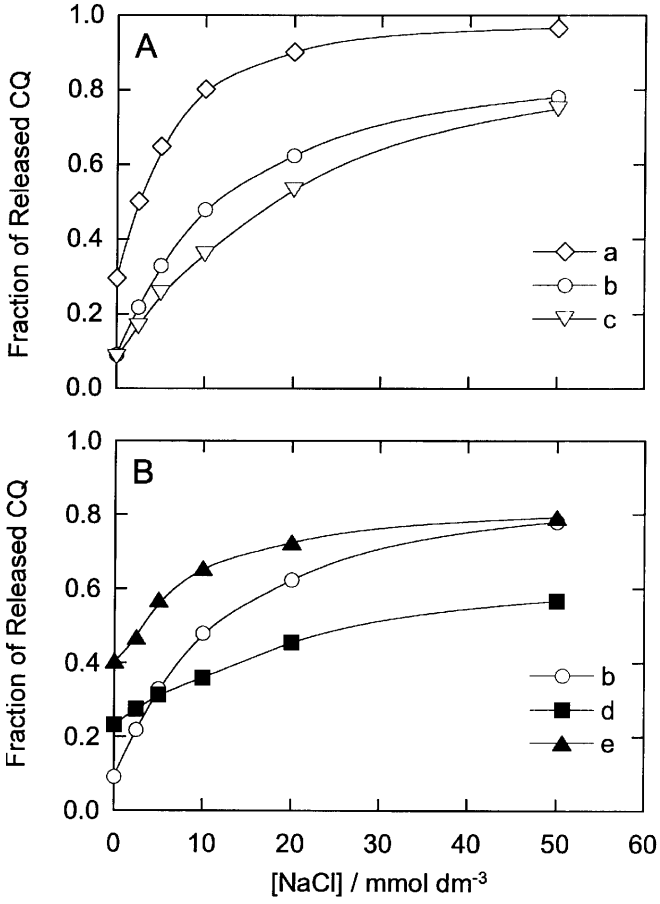


Fig. 5A, B Dependence of elution of CQ on NaCl concentration in eluants. **A** Variation of surfactant chain length and **B** variation of zeolite. *a* ZP/DTAB, *b* ZP/TTAB, *c* ZP/hexadecyltrimethylammonium bromide, *d* NX/TTAB, and *e* CX/TTAB. The initial amounts of CQ bound are 0.461 μmol/g for *a*, 0.555 μmol/g for *b*, 0.584 μmol/g for *c*, 0.457 μmol/g for *d*, and 0.163 μmol/g for *e*

desorption is ascribed to the weakened electrostatic contribution for the surfactant adsorption on the anionic outer zeolite surface. Since the ZP/TTAB complex includes 11 μmol g^{-1} TTAB after the first elution run in 50 mM NaCl, we infer from Fig. 3 that 0.5 μmol g^{-1} CQ could be adsolubilized. In fact, 0.4 μmol g^{-1} CQ was released and only 0.12 μmol g^{-1} CQ remained in the ZP/TTAB complex. This observation suggests that there is a discrepancy between the adsolubilization and elution equilibria.

Dependence of X_{CQ} on X_S in both the coadsorption and elution experiments

The surfactant content in each eluant was determined potentiometrically and the residual surfactant content (X_S) was calculated. The X_{CQ} versus X_S plots for the elution of CQ from the ZP/DTAB, ZP/TTAB,

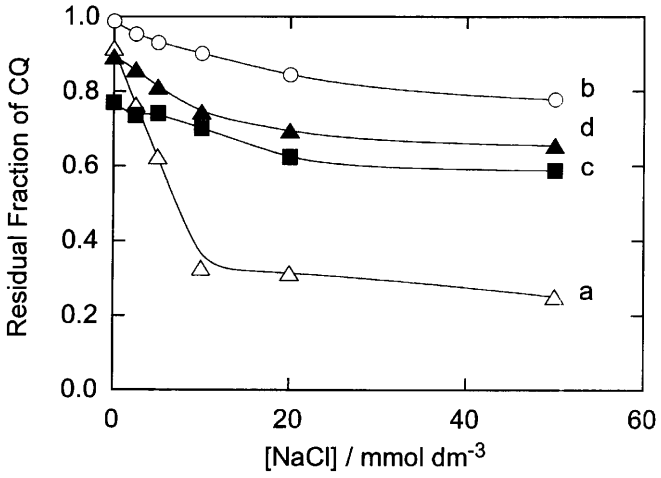
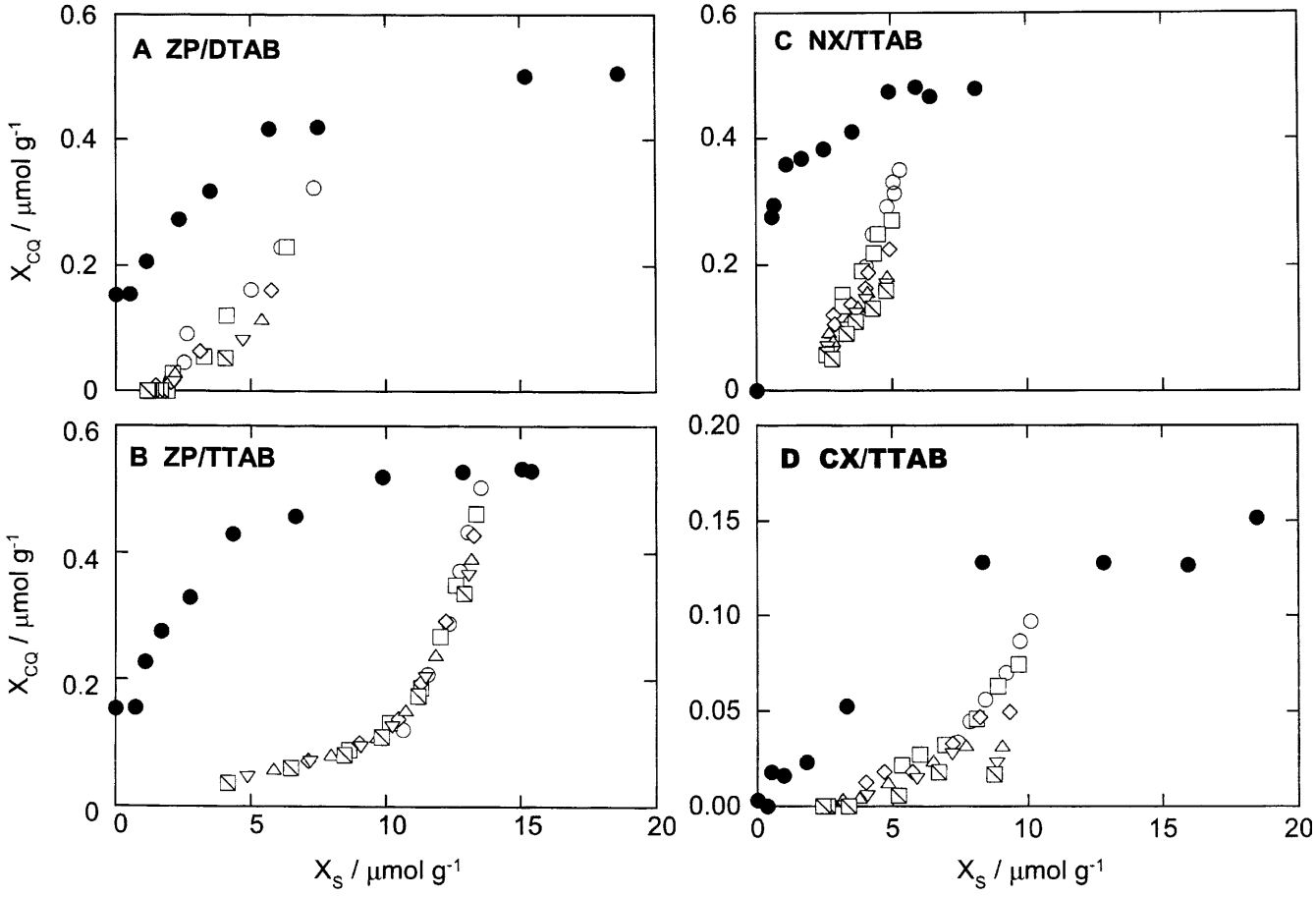


Fig. 6 Elution of adsorbed surfactant. *a* ZP/DTAB, *b* ZP/TTAB, *c* NX/TTAB, and *d* CX/TTAB. The initial amounts of surfactant adsorbed are 8.01 μmol/g for *a*, 13.7 μmol/g for *b*, 6.90 μmol/g for *c*, and 11.3 μmol/g for *d*

NX/TTAB, and CX/TTAB complexes are shown in Fig. 7. A single curve fits the plots (Fig. 7B is a typical example), indicating no dependence on the NaCl concentration or the number of elution runs. This also indicates that desorption equilibrium is achieved. This figure clearly indicates that the residual amount of adsolubilized CQ depends only on the amount of surfactant adsorbed; therefore, the observed effect of NaCl on the rate of elution of CQ (Fig. 5) is ascribed to the weakened electrostatic contribution for the cationic surfactant binding by zeolite.

Figure 7 also shows that the X_{CQ} versus X_S plots for the elution experiments clearly differ from those for the adsolubilization experiments. The elution measurements revealed the complete release of CQ, even in the presence of residual adsorbed surfactant, while the adsolubilization measurements indicated the enhancement of CQ incorporation with the adsorption of a small amount of surfactant. We infer that CQ was adsolubilized in the surfactant aggregates on the outer surface of the zeolite/surfactant complexes, while some of the surfactant was adsorbed on the inner surface of the zeolite and

Fig. 7A–D Dependence of adsorbed or residual CQ amounts on content of surfactant in zeolite/surfactant complexes. *Filled circle:* adsolubilization measurements; *open symbols*: elution measurements. Each different open symbol corresponds to a different NaCl concentration in the eluants. **A** ZP/DTAB, **B** ZP/TTAB, **C** NX/TTAB, and **D** CX/TTAB



did not contribute to the adsolubilization of CQ. The second type of surfactant was not desorbed into the aqueous eluant.

Summary

Zeolite/surfactant complexes enhance the adsolubilization of CQ. The enhancement depends on both the surfactant chain length and the zeolite species. The CX complex had a weak adsolubilization capacity for CQ. The adsolubilization capacity depends principally on the amount of surfactant adsorbed. The amount of CQ eluted from the zeolite/surfactant complexes suggests that desorption depends on the NaCl concentration in the eluant, but it is ascribed to the dependence of surfactant desorption on the NaCl concentration. In comparing the adsolubilization and elution experiments, hysteresis was observed in plots of X_{CQ} versus X_S.

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