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Footprint Catalysis. VIII.[1—7)]
Molecular Imprinting for Footprint Cavities on an Active Clay Surface

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Our molecular imprinting procedures were used for molecular footprint cavities formation on the surface of an amorphous clay mineral. The imprinting with a template, *N*-benzoylsulfonamide, generated footprint cavities on the surface of Japanese Active Clay (sulfuric acid-treated Japanese Acid Clay). The cavities showed specific catalysis toward transacylation of benzoic anhydride that served as a corresponding substrate. This finding provided an experimental clue to study the adsorption mechanism of the Active Clay surface that has hardly been defined so far. Additionally, our comments on the significance of footprint imprinting in chemical evolution are described briefly.

Molecular footprint are tailor-made cavities that our molecular imprinting procedures, using a template, mark on a surface of silica (alumina) gel (superficial silica-alumina gel).1—6) The cavities comprise complementary structures to the template molecules used during imprinting and a Lewis acid site within it. The cavities have molecular recognition capabilities base on the complementary structures.1,2) When a transition state analog or reactive intermediate analog as a template marks footprint cavities, the cavities reveal substrate-specific catalytic function, because the complementary structures can stabilize the species in the transition state or the reactive intermediate of the reaction to lower its activation energy.1,4) This specific catalysis can be referred to as the same as those of enzymes and catalytic antibodies.10,11) We have designed and imprinted various footprint cavities using several kinds of template molecules, and reported their unprecedented catalytic behavior, such as enzyme-like enantioselective catalyses6,7,9) and a feed-back regulating catalysis system.6) This molecular footprint imprinting requires conversion of a silica gel into silica (alumina) gel, because Lewis acid sites on gel surfaces are the requisite of the footprint cavity formation.7) Treatment of silica gel surface with concd hydrochloric acid and subsequent Al^{3+} ions doping cause isomorphic substitution of surface silicate with aluminate. It converts a silica gel into silica (alumina) gel loading Lewis acid sites on the surface. The surface of this silica (alumina) gel should be identical in nature with those of naturally occurring amorphous clay minerals. Therefore, similar footprint imprinting could be promising on such surfaces of amorphous clay minerals.

This paper deals with the footprint imprinting on a surface of Japanese Active Clay. Evidently footprint cavities were generated on the clay surface as well as on the silica gel surface.

Experimental

Materials. All chemicals were of the guaranteed grade of Nacalai Tesque Co., Ltd., if not specified.

Active Clay: "Standard Japanese Active Clay" was purchased from Wako Pure Chemical Industries, Ltd. Japan Oil Chemistry Society guaranteed quality of this clay preparation (Lot No. EPM 7199) as follows: Brownish grey powder, drying loss 16.0%, fineness (200 mesh passage) 88.0%, acid content was equivalent to 1.27 mg KOH per 1 g of the clay.

Template: *N*-Benzoylbenzenesufonamide1) (Ph–SO_2–NH–Bz). Mp 148 °C (lit, 147 °C); (Found: C, 59.51; H, 4.26; N, 5.37%).

Substrate: Benzoic anhydride was of Extra Pure Reagent grade from Nacalai Tesque Co., Ltd., and was recrystallized from benzene–petr. benzine. Mp 42 °C (lit, 43 °C).

Solvent: Acetonitrile, previously dehydrated over calcium chloride, was dried over phosphorus pentaoxide overnight. It was distilled using a Hempel fractionating column, Bp 81—82 °C. To the distillate was added calcium hydride, and repeating distillation gave water- and acidic impurity-free acetonitrile.

Nucleophile: Potassium 2,4-dinitrophenolate, prepared by neutralization of 2,4-dinitrophenol in methanol with concd aqueous potassium hydroxide, was recrystallized from hot water, and dried at 130 °C in vacuo.

Catalyst Preparation by Imprinting. Catalysts were prepared from the Active Clay by two imprinting procedures (**a**, **b**).

Imprinting a: This imprinting procedures were the same in principle as those for silica gel catalysts.7) Accordingly the Active Clay served as a starting material instead of silica gel as follows. The Active Clay (100 g) was refluxed with concd hydrochloric acid (500 cm^3) for 5 h. This activated the surface of the clay and also removed contamination of other metal ions (Fe^{3+}, Zn^{2+}, etc.) The clay sludge was then thoroughly washed with deionized water (200—300 cm^3, 15 times) by decatation till the supernatant became almost neutral (pH 6—7). Then the clay sludge was washed with dilute aq ammonia (pH 7—8, 200—300 cm^3, 3 times), and again washed with deionized water (300—500 cm^3, 3 times) to give "hydrochloric acid-treated clay". Repeated decantation during these washing procedures resulted in removal of very fine particles from the clay preparation. To sludge of the hydrochloric acid-treated clay, equivalent to 10 g of dry weight, was added $AlCl_3$ aq solution (0.2 mol dm^{-3}, 50 cm^3). The pH of the mixture was adjusted to 6.5 with dilute aq ammonia. Then the mixture was left at 80 °C for 3 h for Al^{3+} ions doping. A deposit of aluminium hydroxide was removed by decantation. Then the doped clay was washed with dilute hydrochloric acid (pH 4.0) three times for complete removal of aluminium hydroxide. "Al^{3+} ion doped clay" thus obtained was then subjected to imprinting with a template. The doped clay was suspended in a minimum amount of dilute hydrochloric acid (pH 4.0). To the suspension, was added an acetone solution of the template (2×10^{-3} mol, 520 mg in 5 cm^3 acetone) under vigorous shaking. The pH of the mixture was adjusted to 4.0 with diluted hydrochloric acid. Then the mixture was left at 80 °C for a week with occasional pH adjustment (pH 4.0) with dilute aq ammonia. The template immersed clay was collected by decantation and then washed with dilute hydrochloric acid (pH 4.0) three times to remove any aggregated deposit of excess template. The clay was collected by careful filtration so that its surface was kept still wet. Then it was air-dried on Petri dishes at room temperature (around 23 °C) till it reached a constant weight. Portions of the air-dried clay, required amounts for a subsequent study, were extracted with methanol using Soxhlet extractors before the use. The extractions were continued, the optical density being occasionally monitored, until the template was no longer observed. The extracted clay preparations were then gradually dried under atmospheric pressure and followed under weakly reduced pressure. This is because rapid evolution of methanol from the surface might destroy the fine structures of the clay surface. Finally, the clay preparations were exhaustively dried at 130—140 °C under reduced pressure (3 mHg) for 1 h. The dried preparations were immediately used for kinetic studies as "Catalyst **a**." "Blank **a**" lacked the Al^{3+} ions doping, which stemmed from the "hydrochloric acid-treated clay", and the Al^{3+} aq solution in doping procedures was replaced with water only. "Blank **a2**" lacked both the Al^{3+} ions doping and the imprinting with the template; only acetone was used instead the acetone solution of the template. "Control **a**" lacked the imprinting with the template, which stemmed from "Al^{3+} ions doped clay". The followed other procedures for them were precisely the same as those for Catalyst **a**.

Imprinting b: This imprinting omitted the surface activation by hydrochloric acid hydrolysis and Al^{3+} ions doping. Direct imprinting was done on the native surface of Acid Clay. The Active Clay (100 g) was thoroughly washed with deionized water (200—300 cm^3) and then dilute hydrochloric acid (pH 4.0, 200—300 cm^3) to remove very fine particles and acid-soluble contaminants. The "washed Active Clay" was imprinted with the template described above. The procedures were precisely the same as those for Catalyst **a**, which gave "Catalyst **b**." Catalyst **b** was different from Catalyst **a** in color and grain size. It was brown and contained finer particles; the Catalyst **a** was gray and coarse. "Control **b**," lacking the imprinting with the template and serving as a control for Catalyst **b**, came from the "washed Active Clay." The procedures were the same as those for Catalyst **b** except imprinting with the template.

Acidic Properties of Clay Preparations. An acid strength measurement was done by the method of Benesi[12] with Hammett indicators. Methyl Red, Oil Yellow AB, Methyl Yellow, and 4-phenylazodiphenylamine in dried benzene were used as the indicators. Lewis acid site detection was done with phenolphthalein in dried benzene by a method of Pines and Haag.[13]

Kinetic Measurement. The catalytic activities of the gel were measured by 2,4-dinitrophenolysis of benzoic anhydride. The procedures were the same as those previously reported.[3] To acetonitrile solutions of benzoic anhydride (49 cm^3, 0.9—4.5×10^{-3} mol dm^{-3}) equilibrated with a catalyst (50 mg) at 30 °C for 30 min, were added the nucleophile solution (1 cm^3, 1.5×10^{-2} mol dm^{-3}) to start the reactions. The catalyzed reactions were followed by triple-wavelength spectrophotometry. The decreases in optical density of the reaction mixtures at 400, 430, and 500 nm due to 2,4-dinitrophenolate were measured at proper intervals. In inhibition studies, the catalysts were equilibrated with an acetonitrile solution of an inhibitor for 1 h to gain homogeneous dispersion. Then they were equilibrated with the substrate solutions for 10 min more. Following procedures were the same as before. Pseudo-first-order rate constants, k_{obsd}, were calculated from linear part of semi-log plots of optical density vs time that was usually observed over at least 1 half life. The k_{obsd}s thus obtained obeyed Michaelis–Menten kinetics with respect to the substrate concentration. Kinetic parameters, K_ms (Michaelis constants), V_{max}s (maximum k_{obsd}s) were measured from the usual double reciprocal plots (Lineweaver–Burk plots), and k_{cat}s were calculated from V_{max} divided by catalytic sites molarity per gram.

Catalytic Sites Titration. Catalytic sites molarities were measured by the kinetic titration method previously reported.[3] To acetonitrile solutions of the substrate (benzoic anhydride, 10 cm^3, 1.5×10^{-2} mol dm^{-3}) and the gel catalyst (50 mg), were added specified amounts of pyridine in acetonitrile (5—15 cm^3, 5.0×10^{-5} mol dm^{-3}). Their volumes were made up to 49 cm^3 with acetonitrile. The mixtures were incubated at 30 °C for 1 h under gentle stirring to complete irreversible poisoning of the catalytic sites with pyridine. The nucleophile solution (1 cm^3, 1.5×10^{-2} mol dm^{-3}) was then added to the mixtures to start the catalyzed reaction by surviving catalytic sites. The following procedures were the same as those described above. The k_{obsd}s obtained were plotted against pyridine molarity. Extrapolation of a linear plot gave an intercept on the abscissa. The numerical value of the intercept showed directly the molarity of catalytic sites per 1 g of a catalyst, since pyridine in 50 cm^3 of the reaction mixture poisoned a catalyst of 50 mg under these conditions.

Results and Discussion

Footprint Imprinting: Japanese Active Clay served as a material for an amorphous clay mineral. This is because clay minerals of uniform qualities are hard to obtain. Since naturally occurring clay minerals are mixtures, their qualities often vary according to areas of their origin and means of purchase, but the Japanese Active Clay is an artificial clay widely used as a decoloring agent in the oil industry. It is manufactured from "Japanese Acid Clay" composed of mainly montmorillonite by sulfuric acid treatment (25—45% sulfuric acid at 80—105 °C for 6—12 h). A standard preparation of a quality quaranteed by the Japan Oil Chemistry Society is commercially available.

A template, *N*-benzoylsulfonamide, served in this study, because it is stable enough to withsatnd the severe imprinting conditions at 80 °C for a week, and because our imprinting studies used it so often that the kinetic measurement of catalytic activities was well established.[1—5)]

Two imprinting procedures were used. Imprinting **a** involved hydrochloric acid treatment and Al^{3+} ions doping before the imprinting with a template. It intended i) to exclude uncertain effects of contaminant metal ions included in the clay preparation (Fe^{3+}, Zn^{2+}, Mg^{2+}, etc.) on the cavity formation, and also ii) to confirm the rearrangement capability of the silicate matrix of the Active Clay surface, because the silicate matrix of the clay is necessarily the same as that of silica (alumina) gel. The former originates from degradation of montmorillonite of lattice structures, and the latter comes from Al^{3+} ions doping of amorphous silica gel by nature. Therefore, the imprinting **a** might serve as a control of the imprinting **b** that omits the hydrochloric acid treatment and Al^{3+} ions doping.

Characterization of the Clay Preparations: Table 1 shows that the acidic properties of Catalyst **a** and Control **a** resemble at glance those of silica-(alumina) gel preparations (superficial silica-alumina gel obtained by aluminium ions doping onto a silica gel).[4,8)] Both of them have catalytically active acid sites of the similar acid strength with those on the silica-(alumina) gels. These acid sites would be Lewis acid sites, since catalytically active acid sites on the silica-(alumina) gels were identified as Lewis acid sites.[1)] The Blank **a** and Blank **a2** lack the Lewis acid sites and catalytic activities, though they seem faintly positive to acid site detection with Hammett indicators. These findings show that conc hydrochloric acid treatment effectively eluted off almost all of the metal ions on the clay surfaces as metal chlorides that withstand the surfuric acid treatment. The complete removal of metal ions provided catalytically inactive Blanks **a** and **a2**. Al^{3+} ions incorporation into the silicate matrix can regenerate acid sites to give the Control **a**, which then lead to the Catalyst **a** by imprinting. Thus silicate matrix of the "hydrochloric acid treated clay" can play the equivalent role of a silica gel matrix in the imprinting procedures.

Figure 1 shows the titration plots of catalytic sites over Catalyst **a** and Control **a**. Both plots had fine linearity proportional to the pyridine concentration. This suggests that uniform catalytic sites, at least in sensitivity to pyridine poisoning, exist on the surface. These catalytic sites must be Lewis acid sites, not Broensted acid sites, because in a preliminary experiment, 2,6-dimethylpyridine showed no poisoning in contrast to pyridine and Catalyst **a** retained its activity. 2,6-Dimethylpyridine can neutralize the Broensted acid sites, but it cannot combine with Lewis acid sites due to steric hindrance of two methyl groups.[3)] Extrapolation of the two plots to the abscissa gave amounts of the catalytic sites; they were almost identical, 2.65×10^{-2} and 2.70×10^{-2} mol kg^{-1}, respectively. This finding means that Lewis acid sites generated by Al^{3+} ions doping were quantitatively changed to footprint cavities by the imprinting with the template. Figure 2 shows similar titration plots of Catalyst **b** and Control **b**. The plot of the Catalyst **a** is finely linear, and the titre is nearly identical with those of Catalyst **a** and Control **a**. It suggests that there are generated kinetically uniform acid sites that involve Al atoms within them, though the clay

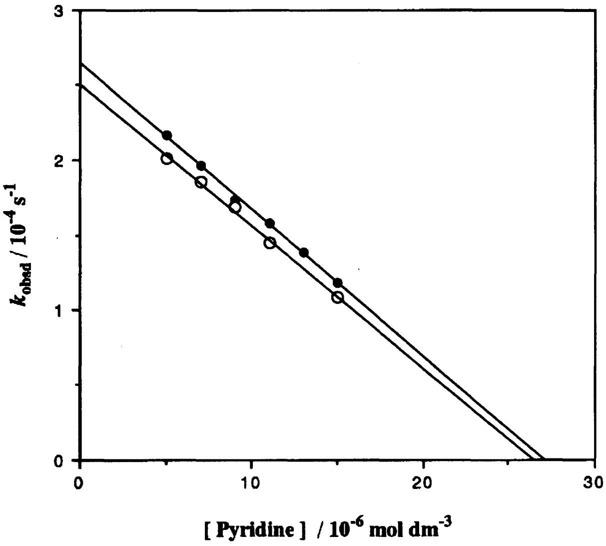

Fig. 1. Catalytic site titrations of Catalyst **a** and Control **a** by pyridine poisoning. The titration procedures are shown in Experimental. An intercept on abscissa gives the titer (See text). Open circles: Catalyst **a**, titre; 2.65×10^{-2} mol kg^{-1}. Closed circles: Control **a**, titre: 2.70×10^{-2} mol kg^{-1}.

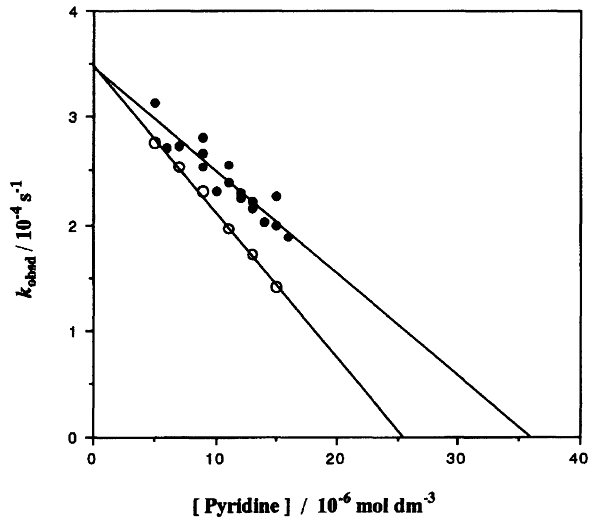

Fig. 2. Catalytic site titrations of Catalyst **b** and Control **b**. Open circles: Catalyst **b**, titre; 2.55×10^{-2} mol kg^{-1}. Closed circles: Control **b**, titer: 3.60×10^{-2} mol kg^{-1}.

Table 1. Acidic Properties of Footprint Cavities

Samples[a]	Acid sites above pK_a				Lewis acid sites[b]	Catalytic activities[c]
	+1.5[d]	+3.3[e]	+4.0[f]	+4.8[g]		V_{max}/mol^{-1}dm^{3}s^{-1}
Catalyst **a**[h]	++	++	++	++	+[i]	2.78×10^{-4}
Control **a**[h]	++	++	++	++	+	4.19×10^{-4}
Blank **a**[j]	+	+	+	+	−	0.00
Blank **a2**[h]	+	+	+	+	−	0.00
Catalyst **b**[k]	++	++	(+−)[l]	++	(+−)[m]	4.51×10^{-4}
Control **b**[k]	++	++	(+−)[l]	++	(+−)[m]	4.70×10^{-4}

a) Dried at 130—140 °C under reduced pressure (3 mHg) for 1 h. b) Detected with phenolphtalein. c) 50 mg catalyst. d) Determined with 4-phenylazodiphenylamine in benzene. e) With Methyl Yellow. f) With Oil Yellow AB. g) With Methyl Red. h) Coloration is much clearer than those of Blank **a** and Blank **a2**. i) Purple coloration is positive. j) Coloration is faint. k) Coloration is much clearer than those of Catalyst **a** and Control **a**. l) Determination is difficult due to brown color of the sample. m) Coloration is not purple but pink.

preparation contains several metal ions. However, the data points on the plot of Control **b** are evidently dispersed. It indicates that a native Active Clay surface likely holds catalytic acid sites of much quantity that are less stable or "demanding." This demanding character could be due to heterogeneity or to unstability of the acid sites. Such character might be, however, common to catalysis of native (non-imprinted control silica (alumina) catalysts as has been observed.

Interestingly, the acid sites amounts on the Catalyst **a**, **b**, and the Control **a** ($2.55—2.70\times10^{-2}$ mol kg^{-1}) are close to the guaranteed acid content (KOH mg g^{-1}, 1.27; 2.26×10^{-2} mol kg^{-1}). This may imply that the acid sites or potential sites changeable to acid sites on an Active Clay might be definite.

Footprint Cavities and Their Catalytic Behavior: Figure 3 shows the Lineweaver–Burk plots of the Control **a** with and without the template molecules. The two plots are almost identical; the addition of the template compound caused no inhibitory effect at all. It means that there is no space around the Lewis acid sites for a template molecule to bind on the surface of Control **a**. Figure 4 shows the Lineweaver–Burk plots of Catalyst **a** with and without the template compound. Three plots make almost identical intercepts on the vertical axis; they have a typical competitive inhibition pattern. A competitive inhibition constant of 10^{-6} mol dm^{-3} order (see Table 2) was calculated. This very strong competitive inhibition clearly proves the successful formation of footprint cavities on the clay surface. Also, fine linearities of these plots means that kinetically uniform catalytic sites were generated. Figure 5 shows the Lineweaver–Burk plots of Control **b** with and without the template compound. The results were the same as those for Control **a**. No inhibitory effect of the template compound was observed; no cavity or space for the template was present on the native Active Clay surface. Figure 6 also shows the Lineweaver–Burk plots for Catalyst **b**. They had fine linearities the same as those of Catalyst **a**, and a typical competitive inhibition pattern. The similar strong competitive inhibition of the magnitude of 10^{-6} mol dm^{-3} was observed. It undoubtedly proved that direct imprinting on a native Active Clay surface generated footprint cavities. Their kinetic parameters are summarized in Table 2, in which those of two footprint cavities on silica(alumina) gel (**1**, **2**) are cited for comparison. Examination of these parameters showed that three of the four imprinted catalysts (Catalysts **a**, **b**, and Silica gel **2**) resemble each other as far as compared by K_ms, k_{cat}s and k_{cat}/K_m values. They are also similar to each other in molecular recognition capabilities (K_is, $-\Delta G_0$s). The exception of Silica gel **1** might be due to its extraordinarily fine imprinting by the severe imprinting conditions at 75 °C for a week. However, Silica gel **2**, imprinted at room temperature for a week, showed the usual catalytic behavior and molecular recognition capabilities. This Silica gel **2** seemed to correspond with Catalysts **a**, and

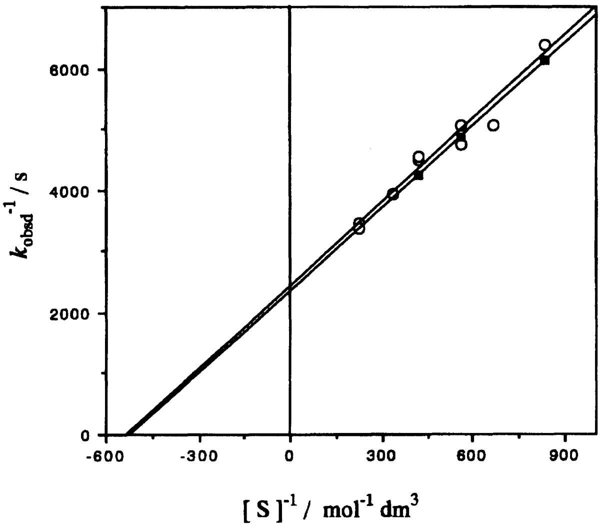

Fig. 3. Lineweaver–Burk plots for Control **a**. No competitive inhibition. Open circles: Catalyzed reaction without the template compound as an inhibitor. Close circles: Catalyzed reaction with the inhibitor; [I]$=2.0\times10^{-5}$ mol dm^{-3}.

Table 2. Kinetic Parameters

Catalysts	K_m	$V_{\max}$ a)	Acid sites	k_{cat}	k_{cat}/K_m	K_i	$-\Delta G_0$ b)
	10^{-4}M c)	10^{-4}M^{-1}s^{-1}	10^{-2}mol kg^{-1}	s^{-1}	10^{-5}M^{-1}s^{-1}	10^{-6}M	kJ mol^{-1}
Catalyst **a**	4.44	2.78	2.65	210.0	4.73	2.93	32.10
Control **a**	19.84	4.19	2.70	309.6	1.56	—	—
Catalyst **b**	9.54	4.51	2.55	354.5	3.71	1.02	34.75
Control **b**	8.99	4.70	3.60	261.1	2.90	—	—
Silica gel **1** d)	0.79	5.90	1.95	603.0	76.4	0.05	42.35
Silica gel **2** e)	3.78	4.69	2.87	326.8	8.64	2.22	32.08

a) $V_{\max}=k_{\text{obsd.max}}$. b) Molecular recognition capability defined as $-\Delta G_0=RT\ln(K_i^{-1})$. c) M=mol dm^{-3}. d) Silica(alumina) gel catalyst imprinted at 75 °C for a week. See Ref. 8. e) Imprinted at room temperature for a week. See Ref. 4.

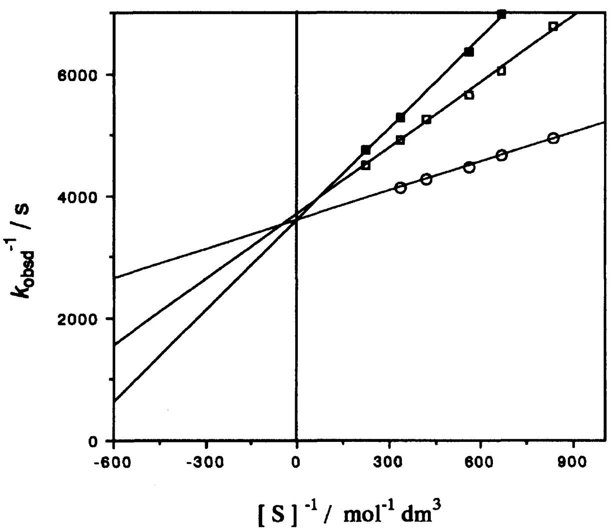

Fig. 4. Lineweaver–Burk plots for Catalyst **a**. Competitive inhibition. Open circles: Catalyzed reaction without the inhibitor. Open squares: With the inhibitor, [I]$=4.0\times10^{-7}$ mol dm^{-3}. Closed squares: [I]$=2.0\times10^{-5}$ mol dm^{-3}. $K_i=2.93\times10^{-6}$ mol dm^{-3}.

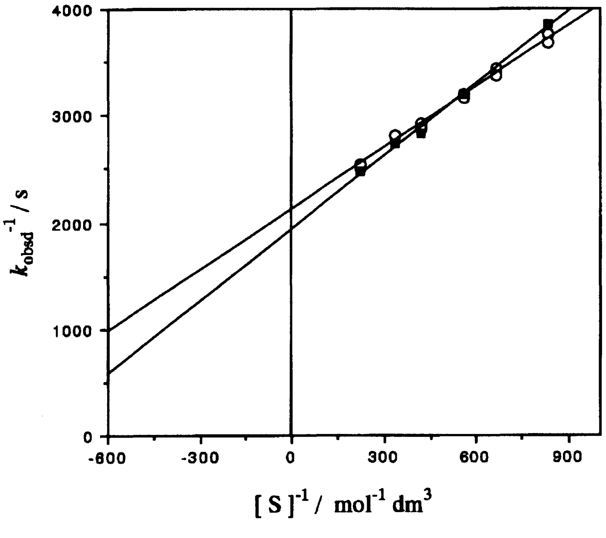

Fig. 5. Lineweaver–Burk plots for Control **b**. No competitive inhibition. Open circles: Catalyzed reaction without the inhibitor. Closed squres: With the inhibitor; [I]$=2.0\times10^{-5}$ mol dm^{-3}.

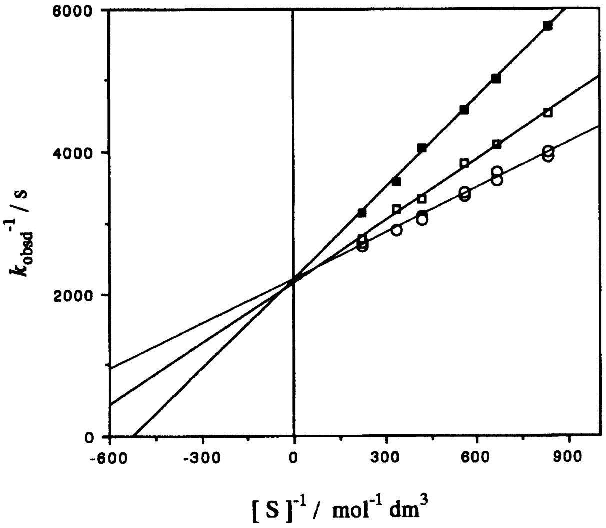

Fig. 6. Lineweaver–Burk plots for Catalyst **b**. Competitive inhibition. Open circles: Catalyzed reaction without the inhibitor. Open squares: With the inhibitor, [I]$=4.0\times10^{-7}$ mol dm^{-3}. Closed squares: [I]$=2.0\times10^{-5}$ mol dm^{-3}. $K_i=1.02\times10^{-6}$ mol dm^{-3}.

b, which are severely imprinted at 80 °C for a week. Therefore, a silica (alumina) gel surface is likely more susceptible to imprinting than the Active Clay surface. The similarities in catalytic properties and molecular recognition capabilities, however, strongly suggest that the identical footprint cavities in nature and structure would be generated on the both surfaces. At the end, a silica matrix around Lewis acid sites of the Active Clay evidently can be rearranged to form footprint cavities in the same manner as does a silica matrix of a silica (alumina) gel.

Concluding Remarks: The successful imprinting would provide a clue to understanding the adsorption mechanism on the Active Clay surface that has not been well defined. That is to say, it confirms that the surface structures are clearly rearranged to form complementary structures toward adsorbates, since such a rearrangement is a requisite of footprint formation. Such an adoptive rearrangement should explain the strong adsorptive capabilities of the Active Clay surface and also those of any amorphous clay surface. Then, the specific catalytic activities of footprint cavities could be an experimental tool for evaluation of adsorptive characteristics of amorphous clay minerals.

These footprint cavities imprinted on the clay minerals would be very significant from the standpoint of chemical evolution. If one would define life as efficient and self-replicating metabolic systems, all materials that constitute such systems should be accumulated on the earth in a highly concentrated state before life evolved. Accumulation of organic compounds at random would be insufficient to evolve life, because such a soup of labile organic compounds easily lead to tar. The prebiotic "metabolites" should be assembled into a state of "pre-metabolism." There must be a certain order and proper constituents of reactions. Such mixtures could make some self-regulating systems with mutual interactions, interconversions, and equilibrium, etc. These states might resemble the present metabolic system where one enzyme corresponds to one metabolite, catalyzing and regulating specifically. Each such an enzyme and metabolite sum up to make a finely order metabolic map. This scenario postulates numerous inorganic catalysts with enzyme-like functions, "prebiotic enzymes." The cavities imprinted on amorphous clay minerals would be the most promising candidates for the prebiotic enzymes. Since cavities on a silica (alumina) surface had several enzyme-like functions with information carrying characteristics, such as substrate specificities,[1,3,4] enantioselective catalyses with an enzyme-like mechanism,[6,8,9] and self-regulating feed back mechanism,[6] cavities on amorphous clay surfaces must function similarily. Thus, various footprint cavities could be imprinted with metabolite relating compounds; they could correspond specifically to various metabolites. This footprint hypothesis would be only way to explain how fewer inorganic compounds can correspond to numerous organic compounds that newly evolved. It may extend the hypothetical roles of clay minerals in the evolution of life proposed originally by J. D. Bernal[14] and developed by many researchers.[15]

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