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Footprint Catalysis. I. A New Method for Designing "Tailor-Made" Catalysts with Substrate Specificity: Silica (Alumina) Catalysts for Butanolysis of Benzoic Anhydride

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The design of tailor-made specific catalysts for a given organic reaction was investigated. Dibenzamide or *N*-benzoylbenzenesulfonamide, transition state analogs of benzoic anhydride on transacylation, was found to act as a template upon aluminium ion-doped silica gel and to imprint specific adsorption sites, "footprints," on the surface. The footprints were particular Lewis acid sites with a complementary structure to the template. They demonstrated an enzyme-like specific catalytic function on the butanolysis of benzoic anhydride through their specific affinities for substrate molecules in the transition state.

Several kinds of enzyme-simulating catalysts consisting of a binding site and catalytic functional group(s) have been extensively investigated, and fair success has been reported.[1-4] However, there remain some problems,[5] and their catalytic features might seem, to date, somewhat unlike those of real enzymes. This is mainly because the present synthetic means encounters much difficulty in preparing so highly organized catalytic sites as those of natural enzymes and, consequently, the catalytic sites of such enzyme mimics cannot effectively used the non-covalent binding energy of E–S complexes to lower the activation energy barrier to a reaction as do the active sites of natural enzymes in their activities.[6-8]

Another approach to enzyme mimics, however, might be possible if the competitive inhibition mechanism for enzymes by transition state analogs, proposed by Wolfenden,[9] is applicable to designing enzyme-like catalytic sites. According to this mechanism, transition state analogs are specifically adsorbed on the active sites of enzymes much more tightly than the substrates themselves. Since these strong bonding in E–I complexes are similar in kind to those in E–S complexes, such a large bonding energy in E–I complexes can be applicable to the design of catalysts. If adsorption sites of any kind are available that possess complementary structures to the transition state analogs and, thereby, have a specific affinity for them, the sites might show a catalytic function when they bind the substrate molecules of the reaction. This is because the sites might misuse their specific affinity for the substrate molecules in a transition state to stabilize them and to lower the activation energy barrier of the reaction, which is, say, a reversed application of the inhibition mechanism by transition state analogs[9] to catalysis.

Such specific adsorption sites can be prepared on the surfaces of appropriate materials by rather easy imprinting procedures using chemically stable transition state analogs as template molecules. Thus, how to design a specific catalyst for a given reaction becomes directly how to design a specific adsorbent for a transition state analog of the substrate for the reaction. One of the present authors has found a method for imprinting specific adsorption sites for Methyl Red on the surface of silica(alumina) gels,[10,11] by a similar procedure as that described by Dickey.[12] These adsorption sites, regarded as "footprints" of Methyl Red, possess a Lewis acidic nature, keeping a complementary structure to the template molecules. This leads to a possibility of their use as an acid catalyst with substrate specificity.

The present paper reports that the "footprints" could be marked on the surface of commercially available silica gel by surface modification using aluminium ions and transition state analogs, e.g., dibenzamide or *N*-benzoylbenzenesulfonamide[†], and that the "footprints" revealed unusual and specific catalytic behaviors on butanolysis of benzoic anhydride.

Experimental

Materials and Apparatus. All materials, if not specified, were of guaranteed grade of Nacalai Tesque Co. Ltd., and were used without further purification.

Silica gel; Merck Kieselgel 60, art. no. 7754, particle size 0.06—0.20 mm, mesh 70—230.

Dibenzamide (Bz–NH–Bz); prepared from benzonitrile.[13] Mp 145 °C (lit, 148 °); (Found: C, 74.81; H, 4.88; N, 6.18%).

N-Benzoylbenzenesulfonamide (Ph–SO_2–NH–Bz); prepared by usual pyridine-assisted benzoylation of benzenesulfonamide. Mp 148 °C (lit, 147 °C); (Found: C, 59.51; H, 4.26; N, 5.37%).

Dibenzoylmethane; recrystallized from petroleum benzine. Mp 74.5 °C (lit, 77.5—78 °C).

Benzoic anhydride; recrystallized from benzene–petroleum benzine. Mp 42 °C (lit, 42 °C).

Phthalic anhydride; recrystallized from benzene. Mp 130 °C (lit, 138.8 °C).

[†] In the strict sence, this compound is not a true transition state analog, but a tetrahedral intermediate analog as shown in Scheme 1. Its action on catalysis, however, nearly the same as a transition state analog according to Hammond rule.

Acetone; purified by distillation after refluxing with potassium permanganate.

1-Butanol; purified by distillation.

Benzene; purified by distillation over sodium metal.

Acetonitrile; purified by distillation after drying with calcium sulfate, and phosphorus pentoxide.

Anhydrous barium perchlorate; obtained by dehydration of barium perchlorate (3—4 H_2O) at 140 °C in vacuo.

pH-meter; Toa Electronics Ltd. HM-5B with a glass electrode GC-125.

Preparation of Catalysts. Kieselgel (100 g) was refluxed with concd hydrochloric acid for 4 h to release free surface silanol groups according to Fritz et al. and King et al.[14,15] The gel was throughly washed with water and, successively, with dil. aqueous ammonia till pH of supernatant reached 6.0—7.0. The gel was collected by filtration and pressed on filter papers. The "wet" gel, thus obtained, (equivalent to 10 g of dry weight), was added to 0.2 mol·l^{-1} aluminium chloride aqueous solution (50 cm^3) and the pH of the supernatant was adjusted to 7.0—8.0 with dil. aqueous ammonia. The mixture was then allowed to stand for one or two days. The precipitated aluminium hydroxide was removed off by decantation, and the silica(alumina) gel was washed three times with dil. hydrochloric acid (pH 4.0). To this gel, was added dibenzamide (450 mg) (or *N*-benzoylbenzenesulfonamide) in aqueous ammonia (40 cm^3) or in a minimum amount of acetone in order to dissolve the templates immediately. The supernatant was acidified to pH 4.0 quickly, and the mixture was allowed to stand for one or two days with an occasional pH adjustment. The gel was collected by filtration, and added to dil. hydrochloric acid (50 cm^3, pH 4.0) for washing, and collected by filtration and again washed on filter paper with the same hydrochloric acid. It was then air-dried at room temperature for 2—5 days to reach constant weight. The dried gel was subjected to methanol extraction by the use of a Soxhlet extractor untill no more absorbance at 243 nm could be observed. After extraction, the gel was quickly transfered into a desiccator over calcium chloride and dried under atmospheric pressure for one day and then under reduced pressure (25 mHg[††]) for a further one or two days. Finally, it was dried at 120—140 °C under reduced pressure (3 mHg) to give a sample ("imprinted") silica(alumina) gel catalyst preparation. A blank gel catalyst which omitted aluminium ions and templates, and a control gel catalyst which omitted only templates were prepared, respectively, by quite the same procedure as the sample gel catalyst preparation (always in parallel). All final gel preparations were carefully stored in tightly stoppered vinials for protection against moisture. The gel catalysts, inactivated by moisture, could be re-activated by repeated azeotropic dehydration with 2-propanol (20 cm^3) and benzene (80 cm^3) for 1 h.

Acidic Properties of Gel Catalysts. An acid strength determination was carried out by a method of Benesi with Hammett indicators,[16] and Lewis acid site detection was made with phenolphthalein according to a method of Pines and Haag.[17]

Kinetic Measurements. The reaction conditions for the butanolysis of benzoic anhydride was the same as that of phthalic anhydride described by Tarama et al.[18] To a mixture of benzene (70 cm^3) and 1-butanol (30 cm^3), was added a weighed amount of catalysts; the mixture was equilibrated at 55 °C for 1 h. In inhibition studies, an inhibitor was added 40 min later, and the mixture was kept at 55 °C for a further 20 min. Under vigorous stirring with a magnetic stirrer, an exactly weighed quantity of benzoic anhydride (2.262 g) was added to the mixture in order to initiate the reaction. Aliquots of 5 cm^3 were taken out at proper intervals in order to analyze the benzoic acid formed by the method of Greenhow,[19] as follows. To acetonitrile (10 cm^3) containing anhydrous barium perchlorate (0.225 g), was added an aliquot of the reaction mixture; the resulting solution was subjected to potentiometric titration with a 0.01 M[†††]-tripropylamine acetone solution using a glass electrode. Time courses of the butanolyses were practically linear up to 120 min and V_{obs}s were obtained from the slope. $V=V_{obs}-V_{uncat}$, where V_{uncat} was V_{obs} of catalyst amount extrapolated to zero. Kinetic parameters, K_ms and V_{max}s, were obtained from the usual Lineweaver-Burk plots, and activation parameters were calculated from the V_{max} values obtained at 50 °C, 55 °C, and 62 °C, respectively, where $\ln V_{max}$ vs. T^{-1} plots were finely linear (Fig. 3). Since the catalysts varied in activity by preparation lots and were very susceptible to moisture during storage, the kinetic parameters of catalysts of the same lots and of the same determination were always compared for a meaningful discussion of the catalytic behaviors of the gels.

Results

Table 1 demonstrates the acidic properties of gels, and the catalytic activities observed thereof. The purple coloration of sample (imprinted) gels by phenolphthalein for Lewis acid sites was immediately lost by an addition of the original template molecules. Table 2 shows that inactivated catalysts by moisture were regenerated by azeotropic dehydration. Figure 1 (A, B, C) displays typical Lineweaver-Burk plots for the catalytic butanolysis by the sample (imprinted) catalysts and the control catalyst, suggesting that the catalyzed reaction follows Michaelis-Menten kinetics with respect to the benzoic anhydride concentration in the range of 0.5—5.5 M of 1-butanol. Figure 2 shows that the initial velocity is nearly linear with respect to 1-butanol concentration below 0.8 M and, thereafter, leveled off. The rate of the catalyzed reaction can be expressed as follows:

$$\text{rate} = \frac{V_{max}[\text{benzoic anhydride}][\text{1-butanol}]}{K_m + [\text{benzoic anhydride}]} \qquad (1)$$

In Table 3, are shown the kinetic parameters, and in Table 4, the activation parameters calculated from data shown in Table 3 and Fig. 3. In Figs. 4 and 5 are shown competitive inhibition plots by the original templates, and in Fig. 6, those plots by dibenzoylmethane, for sample (imprinted) gels-catalyzed butanolysis, respectively. The inhibition constants, K_is, are

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[††] 1 mmHg≈133.322 Pa.

[†††] 1 M=1 mol dm^{-3}.

Table 1. Acidic Properties and Catalytic Activity

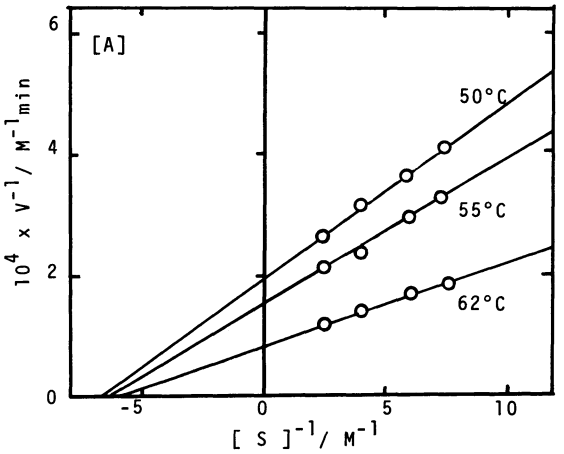
Catalyst	Acid site above pK_a; +1.5[b]	+4.8[c]	+6.8[d]	Lewis acid site[e]	Activity[a] $10^4 \times V$/M min^{-1}
Sample (footprint) gel imprinted by dibenzamide					
not dried	+	+	+	−	0.00
dried[f]	+	+	+	+[g]	1.24
Control gel					
not dried	+	+	+	−	0.00
dried[f]	+	+	+	+	0.35
Blank gel					
dried[f]	−	−	−	−	0.00

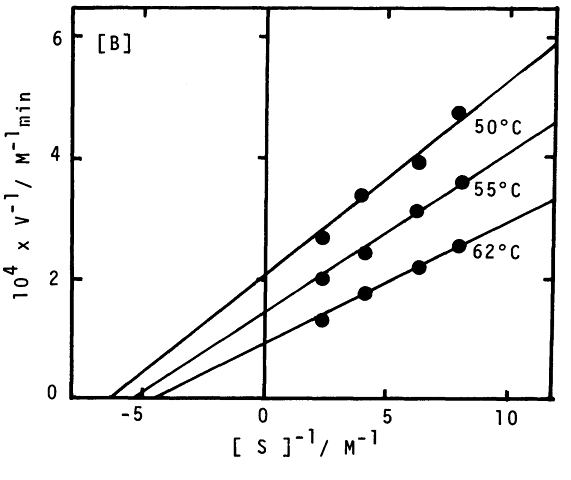
a) Per 300 mg of catalysts. b) Determined with 4-(phenylazo)diphenylamine. c) With Methyl Red. d) With Neutral Red. e) Detected with phenolphthalein. f) Dried in vacuo at 120—140 °C. g) Decolorized by dibenzamide addition.

Table 2. Regeneration of Catalytic Activity

Catalyst[a]	Activity: $10^4 \times V$/M min^{-1} 300 mg	500 mg	700 mg
Original	1.2	2.2	3.0
Inactivated[b]	—	—	0.0
Regenerated[c]	—	1.1	1.9
Regenerated[d]	—	0.7	1.1

a) Imprinted by dibenzamide. b) Allowed to stand for one day toward room humidity. c) Azeotropically dehydrated with 2-propanol-benzene (20:80 v/v), 2 times. d) Another catalyst, dehydrated 4 times.





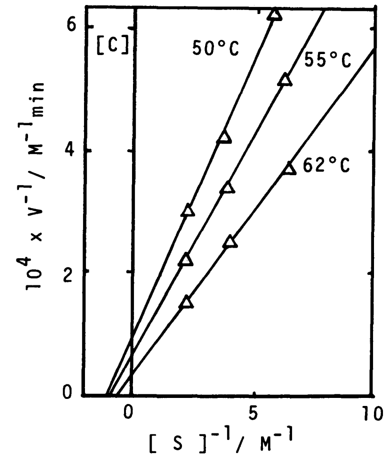


Fig. 1. Linewever-Burk plots for butanolysis of benzoic anhydride catalyzed by silica (alumina) gel catalysts.

(A): Catalyst imprinted by Bz-NH-Bz; 700 mg. (B): Catalyst imprinted by Ph-SO_2-NH-Bz; 700 mg. (C): Control catalyst; 700 mg. [S]: Benzoic anhydride concentration. $V = V_{\text{observed}} - V_{\text{uncatalyzed}}$.

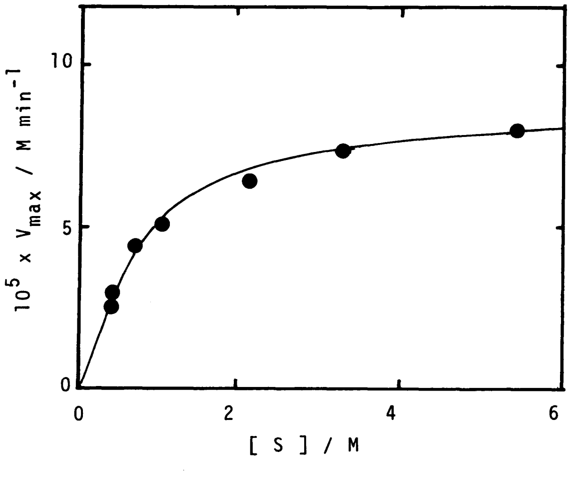


Fig. 2. Relationship between maximum velocity and 1-butanol concentration.

Catalyst imprinted by Ph-SO_2-NH-Bz; 700 mg: [S]: 1-Butanol concentration.

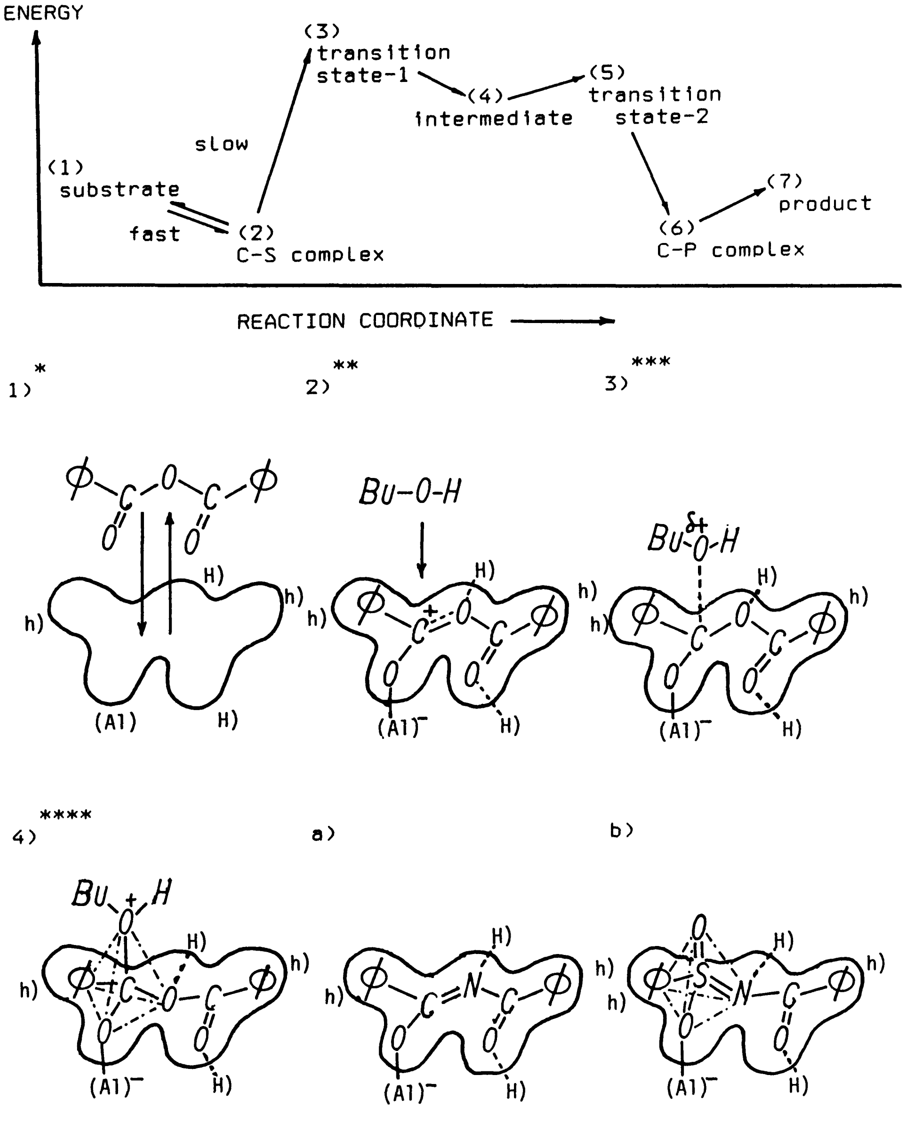
shown in Table 5. No competitive inhibition by the templates (Bz-NH-Bz, Ph-SO_2-NH-Bz, 2.24×10^{-3} M) was observed on Lineweaver-Burk plots (not shown) for the control gel-catalyzed butanolysis. Lineweaver-Burk plots (not shown) for the sample (imprinted) gels and the control gel-catalyzed butanolyses of phthalic anhydride are almost identical, and the kinetic parameters are shown in Table 6.

Discussion

The butanolysis of benzoic anhydride, a water-free esterification, was selected as a catalysis assay system because water was known to be poison for silica alumina catalysts, and benzoic anhydride was preferable to phthalic anhydride because its related derivatives for further studies were more easily available.

The linear relationship between the amounts of the sample (imprinted) and the control catalysts and the increase in reaction rates comfirms that the butanolyses are catalyzed reactions.

As shown in Table 1, the catalytic activities of the sample (imprinted) gel and the control gel are evidently caused by Lewis acid sites on the silica



Scheme 1. Speculated catalytic mechanism for butanolysis of benzoic anhydride upon a footprint catalytic site.

* Substrate and footprint, a shallow hollow, imprinted by Bz-NH-Bz. (Al): Lewis acid site at bottom of the hollow. h): Hydrophobic subsite. H): Hydrogen bond donor.

** Adsorbed substrate on a catalytic site, carbocation.

*** Transition state. Bu-OH: 1-butanol as nucleophile.

**** Tetrahedral intermediate for transacylation.

a) Analog for the transition state (3), dibenzamide (Bz-NH-Bz), bound onto the footprint. b) Analog for the tetrahedral intermediate (4), *N*-benzolybenzenesulfonamide (Ph-SO_2-NH-Bz), bound onto the footprint.

(alumina) gels, since both the blank gel lacking all kinds of acid sites and the "not dried" gels possessing acid sits, but lacking Lewis acid sites, are fully inactive. Furthermore, Lewis acid sites, not Brϕnsted acid sites, are assured to participate in the catalysis on the "imprinted" catalytic sites for following reasons: 1) Only such catalyst preparation as are positive (purple) to phenolphthalein for Lewis acid sites and lose immediately the purple collor upon the addition of templates showed the characteristic catalytic behaviors of "imprinted" catalytic sites, as mentioned below. 2) The catalytic activities were strongly affected by a Lewis base, such as water. 3) Dibenzoylmethane showed a competitive inhibition effect (Fig. 6) which could bind only onto Lewis acid sites through its enol-form but not to Brϕnsted acid sites.

The rate law of Eq. 1 for the butanolysis suggests that the reaction proceeds through a Rideal-Eley mechanism in which benzoic anhydride molecules initially adsorb onto the catalytic sites to activate carbonyl groups for the rate-limitting nucleophilic attack of 1-butanol in solution, as shown in Scheme 1.

As shown in Table 3, the K_m values of "imprinted" catalytic sites of the sample gels are clearly smaller than those of the corresponding control catalysts. Repeated the preparation of catalysts demonstrated that these difference in K_ms were reproducible: The K_ms observed on several sample (imprinted) catalysts laid between 0.13—0.28 M, and those of control catalysts laid between 1.25—2.31 M. Such differences in the K_ms indicate that the "imprinted" catalytic sites of the sample gels always possess about a 10-times stronger affinity ($1/K_m$) for benzoic anhydride than those of the control gels. An exact comparison of the substrate specificity (V_{max}/K_m) of the catalytic sites between the two catalysts is impossible, since amounts of the catalytic sites are unkown here. However, the number of "imprinted" catalytic sites of a sample catalyst is assumed to be nearly same, or less than those of the corresponding control catalyst, since the two catalyst have been prepared in parallel from the same aluminium ion-doped silica gel preparation. Therefore, the "imprinted" catalytic sites of sample catalysts

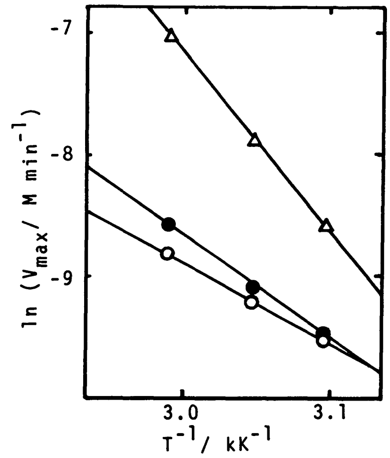


Fig. 3. Arrhenius plots for the catalyzed butanolyses. --○--: catalyst imprinted by Bz-NH-Bz, --●--: catalyst imprinted by Ph-SO$_2$-NH-Bz, --△--: control catalyst.

Table 3. Kinetic Parameters for Butanolysis of Benzoic Anhydride

Catalyst[a] imprinted by:	T	K_m	$10^5 \times V_{max}$	$10^5 \times V_{max}/K_m$
	°C	M	M min^{-1}	min^{-1}
Bz-NH-Bz[b]	50	0.14	4.8	34.3
	55	0.16	6.8	42.5
	62	0.18	11.2	62.2
Ph-SO$_2$-NH-Bz	50	0.16	5.1	31.2
	55	0.20	7.5	37.5
	62	0.33	12.5	37.9
Control	50	1.25	13.8	11.0
	55	1.67	22.7	13.6
	62	2.50	62.5	25.0
Bz-NH-Bz[c]	55	0.13	6.6	50.8
Control[f]	55	1.25	7.9	6.3

a) 700 mg. b) Bz: benzoyl. c) A set of another catalyst preparation.

Table 4. Activation Parameters for Butanolysis of Benzoic Anhydride

Catalyst imprinted by:	E_a	ΔH^*	ΔS^*
	kJ deg^{-1} M^{-1}	kJ M^{-1}	kJ deg^{-1} M^{-1}
Bz-NH-Bz[a]	63.2	60.7	−137.2
Ph-SO$_2$-NH-Bz	66.5	64.0	−126.4
Control	113.0	110.5	23.8

a) Bz-: benzoyl.

are assured to be more "specific" (with larger V_{max}/K_m) than the "native" catalytic sites of control catalysts.

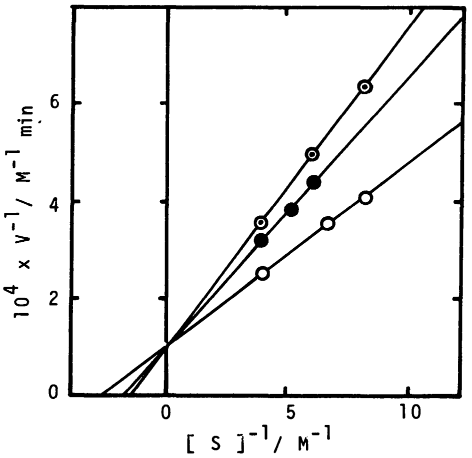


Fig. 4. Inhibitory effect of template molecules on footprint catalyst: Competitive inhibition.
Catalyst imprinted by Bz-NH-Bz; 700 mg: inhibitor; Bz-NH-Bz:
--○--: [I]=0, --●--: [I]=2×10^{-4} M, --⊙--: [I]=3×10^{-4} M.

The "imprinted" catalytic sites can also be characterized by the activation parameters, shown in Table 4. There is a distinct difference in the E_a values between the "imprinted" and the "native" catalytic sites, which confirms that the former are more effective catalytic sites, and supports the idea that an increase in the specificity of the former are caused by not only binding steps (K_m), but also by catalytic steps (V_{max}). The difference in $\Delta S^{\neq}$ values suggests that substrate molecules in transition states on the "imprinted" catalytic sites are assumed to be more firmly restricted than on the "native" catalytic sites of the control gel.

The other characteristic of the "imprinted" catalytic sites are their unusual behaviors toward the inhibitory effect by the template molecules. As shown in Figs. 4 and 5, markedly strong competitive inhibitions have been observed in catalysis on the "imprinted" catalytic sites by action of the templates used for imprinting, where the ratio of K_m/K_i is 2765 in one case. On the other hand, absolutely no inhibition by the templates has been found on Lineweaver-Burk plots (not shown) for a catalyzed reaction on "native" catalytic sites.

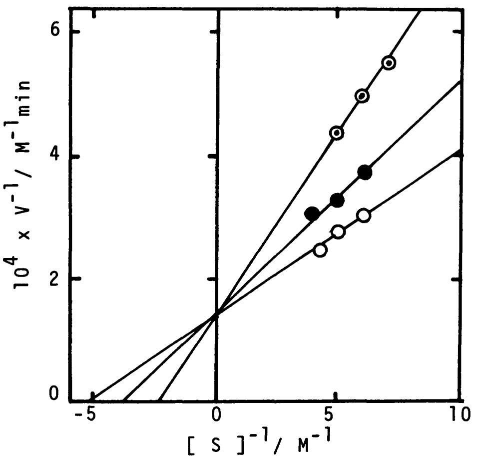


Fig. 5. Inhibitory effect of template molecules on footprint catalyst: Competitive inhibition.
Catalyst imprinted by Ph-SO_2-NH-Bz; 700 mg: inhibitor; Ph-SO_2-NH-Bz:
--○--: [I]=0, --●--: [I]=2×10^{-4} M, --⊙--: [I]=3×10^{-3} M.

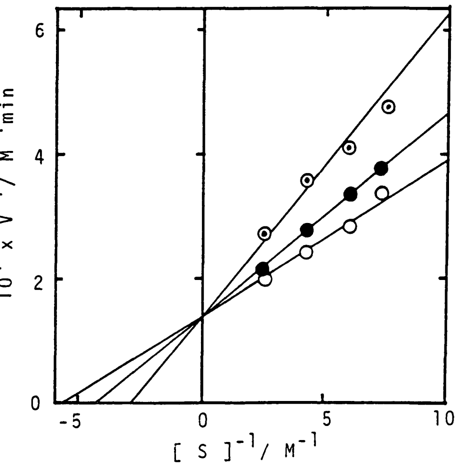


Fig. 6. Inhibitory effect of dibenzoylmethane on footprint catalyst: Competitive inhibition.
Catalyst imprinted by Bz-NH-Bz; 700 mg: inhibitor; dibenzoylmethane:
--○--: [I]=0, --●--: [I]=1.26×10^{-3} M, --⊙--: [I]=8.93×10^{-3} M.

Table 5. Inhibition Constants for Butanolysis of Benzoic Anhydride

Catalyst imprinted by:	Inhibitor:	$10^4 \times K_i$	K_m	K_m/K_i
		M	M	
Bz-NH-Bz[a]	Bz-NH-Bz	0.47	0.13	2765
Bz-NH-Bz[b]	Bz-NH-Bz	2.50	0.50	520
Bz-NH-Bz	Dibenzoylmethane	33.70	0.16	48
Ph-SO_2-NH-Bz	Ph-SO_2-NH-Bz	1.95	0.19	974
Control	Bz-NH-Bz	No inhibition	1.54	—
Control	Ph-SO_2-NH-Bz	No inhibition	1.54	—

a) Bz-: benzoyl. b) Another catalyst preparation.

Table 6. Kinetic Parameters for Butanolysis of Phthalic Anhydride

Catalyst[a] imprinted by:	K_m(K_m[b])	$10^4 \times V_{max}$	$10^4 \times V_{max}/K_m$
	M	M min^{-1}	min^{-1}
Bz-NH-Bz	0.45 (0.16)	1.67	3.75
Ph-SO_2-NH-Bz	0.45 (0.20)	1.67	3.75
Control	0.45 (1.67)	1.67	3.75
Bz-NH-Bz[c]	0.40 (0.13)	1.79	4.48
Control[c]	0.40 (1.25)	1.79	4.48

a) 500 mg. b) K_m for benzoic anhydride. c) A set of another catalyst preparation.

Furthermore, butanolysis with another substrate, phthalic anhydride,[18] was examined in order to characterize the "imprinted" catalytic sites. No difference in Lineweaver-Burk plots (not shown) was observed between the "imprinted" and the "native" catalytic sites. As can be seen from the kinetic parameters in Table 6, the "imprinted" catalytic sites show no particular affinity for phthalic anhydride at all and simply serve as usual acidic catalytic sites.

These unusual behaviors of the "imprinted" catalytic sites cannot be attributed merely to their acidic nature, since no difference in the acidic character was detected between the two catalysts, as shown in Table 1. Therefore, it is necessary to assume the presence of particular adsorption sites of Lewis acidic nature like "footprints" of the templates used for imprinting, as illustrated in Scheme 1. The following speculation is probable regarding the formation and molecular recognition capability of the "footprints".

Isomorphic substitutions of surface silicate by aluminate can form potential Lewis acid sites which coordinate to the conjugate bases of template molecules to yield surface acid-base complexes. Among some models of Lewis acid sites of silica alumina gels reported thus far, the model proposed by Tamele[20] is the most favorable in this case, since the "imprinted" catalytic sites have been formed by surface modification in mild conditions.

The acid-base complexes must make maximal interaction, such as hydrogen bonding and hydrophobic bonding, etc., with surrounding silicates throughout a continual and reversible rearrangement being subjected to thermodynamic control, which gives rise to most energetically stable surface complexes. A subsequent repeated extraction with hot methanol forces the removal of template molecules from stable acid-base complexes; the resulting decomposition of the complexes leaves energetically unstable particular sites, "footprints", on the surface with "complementarity" toward the templates. The term "complementarity" has dual meaning, i.e., "geometric" and "electronic".[21] The latter affords the footprints "electronic strain", a situation of high energy, postulated by Blow and Steiz[21] for the active sites of enzymes. The "electronic strain" arises from an unpaired lone-pair acceptor (Lewis acid), unpaired hydrogen bond donor(s) and/or acceptor(s), and so on toward even weaker forces, as can be seen in Scheme 1. This may provide a driving force for the molecular recognition capability to the footprints. This must be an origin of the enzyme-like "specific" Lewis acid catalysis on "footprint" catalytic sites.

Since the net structure of bulk silica gel must remain unchanged and shrinking never occurs during drying, unlike Dickey's silica gel,[12] the destruction of a surface structure can be prevented and a reproducible preparation of catalytic sites can be possible.

The "footprint" catalysis reported here has unprecedented features, such as substrate specificities, turnover capability, and easy and "tailor-made" preparability, etc., which are of greater advantage than any other stoichiometric synthetic reactions using template effects on surfaces of synthetic polymers recently reported,[22] and further studies on the "footprint" catalysis are in progress.

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