Continuous Chemoselective Methylation of Functionalized Amines and Diols with Supercritical Methanol over Solid Acid and Acid−Base Bifunctional Catalysts

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Abstract: The selective N-methylation of bifunctionalized amines with supercritical methanol (scCH$_3$OH) promoted by the conventional solid acids (H-mordenite, β-zeolite, amorphous silica−alumina) and acid−base bifunctional catalysts (Cs−P−Si mixed oxide and γ-alumina) was investigated in a continuous-flow, fixed-bed reactor. The use of scCH$_3$OH in the reaction of 2-aminoethanol with methanol (amine/CH$_3$OH = 1/10.8) over the solid catalysts led to a significant improvement in the chemoselectivity of the N-methylation. Among the catalysts examined, the Cs−P−Si mixed oxide provided the most efficient catalyst performance in terms of selectivity and reactivity at 300 °C and 8.2 MPa; the N-methylation selectivity in the products reaching up to 94% at 86% conversion. The present selective methylation was successfully applied to the synthesis of N-methylated amino alcohols and diamines as well as O-methylated ethylene glycol. Noticeably, ethoxyethylamine was less reactive, suggesting that the hydroxy group of the amino alcohols is a crucial structural factor in determining high reactivity and selectivity, possibly because of the tethering effect of another terminus, a hydroxo group, to the catalyst surface. The magic-angle-spinning NMR spectroscopy and X-ray diffraction analysis of the Cs−P−Si mixed oxide catalyst revealed that the acidic and basic sites originate from P$_2$O$_5$/SiO$_2$ and Cs/SiO$_2$, respectively, and the weak acid−base paired sites are attributed to three kinds of cesium phosphates on SiO$_2$. The weak acid−base sites on the catalyst surface might be responsible for the selective dehydrative methylation.

Introduction

The use of supercritical fluids (SCFs) as reaction media for homogeneous molecular catalysts or compressed carrier media for heterogeneous catalysts can offer a great opportunity to manipulate the outcome of the reactions in terms of the reactivity and selectivity.[1] Since the early 1990s, great efforts have been extended to homogeneous catalysis in scCO$_2$,[2] and the area of catalysis in the SCF homogeneous phase has gained attention significantly because of the intrinsic properties of SCFs including high miscibility of the gaseous reactants, favorable mass transfer, weakened solvation, and tunable solvent power. SCFs are now realized to be promising reaction media for environmentally benign chemical processes. However, difficulties in separation and recovery of the homogeneous catalysts and

products have remained unresolved except for recent advances in reaction and extraction techniques or multiphasic catalysis systems including a SCF phase.[3]

When one performs heterogeneous catalysis over solid catalysts under supercritical conditions, one can not only control the product selectivity by tuning the reaction temperatures and pressures of the media, but one can also achieve good separation of the catalyst and product thanks to the liquidlike solubility and gaslike diffusivity of SCFs.[4−6] The high solubilizing power of SCFs compared to that of gas phase allows a significant improvement in the catalyst lifetime and activity by precluding the deposition of higher-molecular weight products in the catalyst pores or on the catalyst surface. The enhanced diffusivity of solid organic compounds in SCFs can allow the effective

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removal of the reaction products from the catalyst surface. An increase in the solubility of the gaseous reactants such as alkenes or H_2 in $scCO_2$ causes a significant improvement in the selectivity of heterogeneously catalyzed reactions.[5,6] Furthermore, the favorable heat-transfer properties of SCFs can remove heat generated by highly exothermic hydrogenation, leading to facile manipulation of the reactivity and selectivity in the reaction.

In fact, Poliakoff has demonstrated a highly efficient Friedel–Craft alkylation of aromatic compounds with propene or 2-propanol over polysiloxane-based solid acid catalysts under supercritical conditions[5c,d] or hydrogenation of unsaturated compounds over the heterogeneous Pd and Pt catalysts supported on polysiloxane in $scCO_2$[5a,b] leading to the desired products in a selective manner. Additionally, Baiker has reported that control of the pressure of $scNH_3$ caused a marked increase in the selectivity of the amination of diols or amino alcohols to diamines with $scNH_3$ over a solid Co–Fe catalyst.[4] Thus, heterogeneous catalysis in SCFs has attracted considerable attention by attaining highly chemoselective molecular transformations using unique properties of SCFs. We have recently reported preliminary results on the selective N-methylation of 2-aminoethanol (**1**) with $scCH_3OH$ over a solid acid–base catalyst, where $scCH_3OH$ acts as a methylating agent and a reaction medium.[7] Changing the pressure of $scCH_3OH$ resulted in a marked increase in product selectivity.

For the transformation of **1** with CH_3OH to industrially useful common chemicals, the product distribution is highly influenced by the reaction phases as well as the catalysts used, as illustrated in Scheme 1. For example, the vapor-phase reaction of **1** over the conventional solid acid catalyst, H-β zeolite, provides

Scheme 1

R = H, CH₃, CH₂CH₂OH
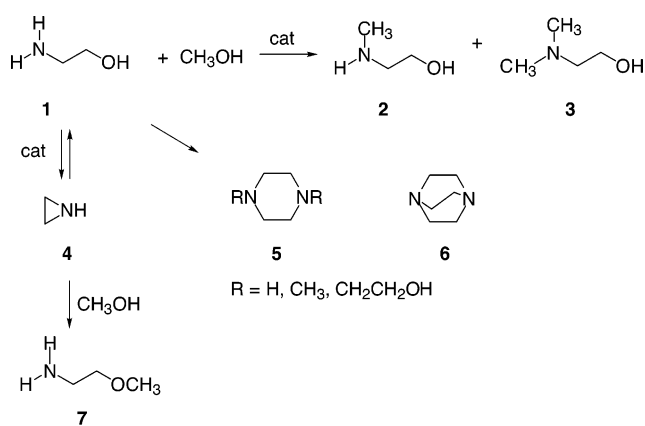
predominantly intermolecular dehydration products, piperazine (**5**) or triethylenediamine (**6**), in addition to N-methylated products, *N*-methylaminoethanol (**2**) and *N,N*-dimethylaminoethanol (**3**). At higher temperatures, the alkaline earth metal–Si or alkali metal–P–Si oxides in the gas phase selectively afford the intramolecular dehydration product, ethyleneimine (**4**), instead of the intermolecular dehydration products, **2** or **3**.[8,9] Thus, the N-alkylation of **1** with methanol under gas-phase conditions over solid catalysts proceeds in a nonselective manner, leading to various side reactions such as cyclization, oligomerization, and decomposition through C–N bond cleavage. Therefore, the N-methylation of functionalized amines is carried out by means of reductive amination under the pressurized hydrogen gas through imine formation using formaldehyde or selective alkylations using alkyl halides or diazomethane in the solution phase.[10] These conventional methods, however, are far from the ideal greener synthetic routes because of the formation of undesired byproducts derived from dehydrogenated products, aldehydes, or a large amount of inorganic salts as wastes. Therefore, the development of environmentally more benign direct N-methylation processes by means of dehydrative methylation of functionalized amines with methanol is highly desirable.

N-Methylation of aromatic amines with methanol over solid catalysts has been studied in a great detail and has been proved to proceed by two possible mechanisms: (i) dehydrogenation of methanol to formaldehyde, leading to an imine which is hydrogenated with pressurized H_2 and (ii) direct methylation via methyl cation generated on the acid catalyst surface. In contrast to the reaction of aromatic amines, alkylation of functionalized amines has been limited to reductive alkylation

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of ammonia or alkylamines with alcohol and H_2 over solid catalysts such as copper chromite.

In this report, we will describe the details of the chemoselective methylation of 2-aminoethanol as well as functionalized amines over solid acid−base catalysts with $scCH_3OH$ using a continuous-flow fixed-bed, tubular reactor. Solid NMR studies of the catalyst and experimental results as well as kinetic simulation provide a deeper insight into the reaction mechanism of the selective N-methylation of functionalized amines. The use of $scCH_3OH$ as a reactant and reaction medium will allow for a new alternative synthetic process for selective N-methylation of amines with the formation of only water as the coproduct over suitable solid catalysts, which exhibit environmentally benign and elongated catalyst lifetimes under this unique reaction media.

Experimental Section

SAFETY WARNING: Operators of high-pressure equipment should take proper precautions to minimize the risk of personal injury.

Materials. Spherical silica beads of 10−20 mesh size (CARiACT Q-30, Fuji Silysia Chemical Ltd.), mordenite with a Si:Al atomic ratio of 9:1 (HSZ640HOA, proton form, Tosoh Corporation), zeolite beta with a Si:Al atomic ratio of 12:1 (CP811E-22, proton form, Zeolyst International), silica−alumina with a $SiO_2:Al_2O_3$ molar ratio of 11:1 (N632L, Nikki Chemical), γ-alumina (N612N, Nikki Chemical), sodium nitrate (99.9%, Wako Pure Chemical Industries, Ltd.), potassium nitrate (99.9%, Wako Pure Chemical Industries, Ltd.), cesium nitrate (99.9%, Wako Pure Chemical Industries, Ltd.), and ammonium dihydrogenphosphate (>99%, Wako Pure Chemical Industries, Ltd.) were used for a catalyst or its precursor. Methanol (>99.8%), 2-aminoethanol (>99%), *N,N*-dimethylaminoethanol (>99%), *n*-butylamine (>98%), 2-pyrrolidone (>98%), ethylenediamine (>99%), *N,N*-dimethylethylenediamine (>97%), 1,3-propanediamine (>97%), 1,4-butanediamine (>98%), 2-(2-aminoethoxy)ethanol (>95%), and ethylene glycol (>99.5%) were supplied by Wako Pure Chemical Industries, Ltd. *N*-Methylaminoethanol (>99%), *N*-isopropylaminoethanol (>99%), 3-aminopropanol (>98%), 4-aminobutanol (>98%), 5-aminopentanol (>95%), 1,5-pentanediamine (>95%), 1,6-hexanediamine (>99%), 1,7-heptanediamine (>98%), and ethoxyethylamine (>99%) were supplied by Tokyo Kasei Kogyo Co., Ltd. Aniline (>99%), *N*-ethylaminoethanol (>98%), and distilled water (for preparative liquid chromatography grade) were supplied by Kanto Kagaku Co., Inc. All materials were used without further purification.

Catalyst Preparation. Cs−P−Si Ternary Mixed Oxide Catalyst. The Cs−P−Si mixed oxide catalyst was prepared using the following procedure. Silica beads (60.1 g, 1 mol) were impregnated with an aqueous solution of cesium nitrate (39.0 g, 200 mmol) and ammonium dihydrogenphosphate (18.4 g, 160 mmol). The crude mixture was then dried at 120 °C and calcined at 500 °C for 2 h in air. A Cs:P:Si atom ratio in the catalyst was 1:0.8:5, and the specific surface area was 7 m^2/g. The Cs−P−Si catalyst was found to have only macropore, approximately 50 nm diameter determined by the measurement of mercury porosimeter and N_2 adsorption isotherm analysis.

K−P−Si Ternary Mixed Oxide Catalyst. The K−P−Si mixed oxide catalyst was prepared using the following procedure. Silica beads (60.1 g, 1 mol) were impregnated with an aqueous solution of potassium nitrate (20.2 g, 200 mmol) and ammonium dihydrogenphosphate (18.4 g, 160 mmol). The crude mixture was dried at 120 °C and calcined at 500 °C for 2 h in air. The K:P:Si atom ratio in the catalyst was 1:0.8:5, and the specific surface area was 5 m^2/g.

Cesium on Silica Catalyst (Binary Oxide). The cesium on silica catalyst was prepared using the following procedure. Silica beads (60.1 g, 1 mol) were impregnated with an aqueous solution of cesium nitrate (39.0 g, 200 mmol) without ammonium dihydrogenphosphate. The

crude mixture was the dried at 120 °C and calcined at 500 °C for 2 h in air. The Cs:Si atom ratio in the catalyst was 1:5, and the specific surface area was 2 m^2/g.

Phosphorus on Silica Catalyst. The phosphorus on silica catalyst was prepared using the following procedure. Silica beads (60.1 g, 1 mol) were impregnated with an aqueous solution of ammonium dihydrogenphosphate (18.4 g, 160 mmol) without cesium nitrate. The crude mixture was dried at 120 °C and calcined at 500 °C for 2 h in air. The P:Si atom ratio in the catalyst was 0.8:5, and the specific surface area was 80 m^2/g.

Other catalysts used here were compressively pelletized to 0.3−0.8 mm and calcined at 550 °C for 3 h in air.

The Continuous-Flow, Fixed-Bed Reactor System for N-Methylation of Amines with $scCH_3OH$. The continuous-flow, fixed-bed reactor system consists of five components as follows (see Supporting Information): (i) the equipment for feeding of the methanol solution of amine (PU1580 HPLC pump, Jasco Corporation), (ii) a preheating coil (SUS 316 tube, 1/16 in. × 1 mm × 1.0 m) in a GC oven (GC14B, Shimadzu Corporation), (iii) a high-pressure, tubular reactor (SUS316 reactor with Swagelok VCR joint, 1/2 in. × 10 mm × 135 mm) in the previously described oven, (iv) an automatic back-pressure regulator (880-81, Jasco Corporation), and (v) pressure gauge attached to upper and lower pressure limiters with automatic power breakers (GL Sciences Inc.) and pressure release valves (R3A, Nupro). Because the critical data of pure methanol are T_c = 239.5 °C, P_c = 8.1 MPa and ρ_c = 0.273 g/cm^3, a tubular reactor has a maximum operating temperature and pressure of 537 °C and 24.1 MPa, respectively.

Catalytic N-Methylation of Amines with $scCH_3OH$. The N-methylation reaction of amines in the gas or supercritical phase was isothermally carried out in a continuous up-flow tubular reactor (see Supporting Information). The tubular reactor loaded with catalyst particles was placed in an air-oven. The temperature controller of the oven controlled the reaction temperature, and the temperature in the catalyst bed was also monitored during the reaction. A mixture of amine and methanol was introduced into the reactor through the preheating coil with an HPLC pump. The pressure in the reaction system was controlled by the automatic back-pressure regulator at between 0.1 and 15 MPa. Standard reaction conditions for the N-methylation of **1** were the following: 5.0 mL of catalyst, the reaction temperature and pressure of 300 °C and 8.2 MPa, respectively, a molar ratio of methanol to amine of 10.8:1 or 20:1, and the space velocity as normal liquid flow rate of a mixed solution of reactants, LHSV (mL-liquid/mL-cat h) 5 h^{-1}.

The reaction products were identified by GC−MS analysis (Agilent 5973N-6890N, Agilent Technologies). The selectivity and chemical yield of the products were determined by GC analysis (GC-17A, Shimadzu Co.; FID detector and DB-1 capillary column, J&W). Conversion of amines X_a, yield Y_n, and selectivity S_n of methylated products **2, 3**, and **n** were defined as

$$X_a = (F_{a(ini)} - F_a)/F_{a(ini)} \times 100 \ (\%)$$

$$Y_n = F_n/F_{a(ini)} \times 100 \ (\%)$$

$$S_n = Y_n/X_a \times 100 \ (\%)$$

where $F_{a(ini)}$ and F_a represent molar flow rates of reactant amine at the reactor inlet and outlet, respectively, and F_n represents that of the methylated product **n** at the reactor outlet.

During the reaction, no degradation products of methanol such as dimethyl ether, carbon monoxide or methane were detected. Methanol was only consumed as a reactant in the N-methylation reaction.

Visual Inspection of the Phase Behavior. A visual inspection of the inside of a 10-mL high-pressure vessel equipped with sapphire windows (TSC-W, Taiatsu Techno Corporation) confirmed that the reactants and possible main reaction products are all dissolved into

Table 1. Reaction of **1** with Methanol over Various Solid Catalysts in Both Gas and Supercritical Phases[a]

entry	catalyst	T, °C/ P, MPa	W/F	conv, %	yield, % 2	yield, % 3	selectivity, % 2+3	selectivity, % 4	selectivity, % 5+6
1	H-mordenite	300/0.1	111	0	0	0	0	0	0
2	"	300/15	111	26	12	4	61	0	0
3	H-β zeolite	250/0.1	55	18	2	1	17	0	46
4	"	250/15	55	32	12	8	63	0	0
5	SiO₂−Al₂O₃	300/0.1	66	34	7	2	26	0	0
6	"	300/8.2	66	77	15	10	32	0	10
7	"	300/15	66	81	15	13	35	0	8
8	γ- Al₂O₃	300/0.1	79	21	12	3	71	tr	9
9	"	300/8.2	79	48	24	9	69	0	3
10	"	300/15	79	48	26	10	75	0	1
11	P on SiO₂	300/8.2	55	100	0	5	5	0	3
12	Cs on SiO₂	300/8.2	55	7	2	0	29	0	0
13	K−P−Si oxide	300/8.2	55	74	35	12	64	0	0
14	Cs−P−Si oxide	300/0.1	55	12	6	1	58	37	4
15	"	300/8.2	55	71	51	16	94	0	1
16	"	300/8.2	133	79	48	24	91	0	0
17	"	300/8.2[b]	26	54	38	13	94	0	tr
18	"	300/8.2[b]	133	86	48	33	94	0	tr
19	"	300/8.2[c]	133	85	42	35	91	0	0

[a] Conditions: The reaction was conducted in a fixed-bed, tubular reactor with an amine to CH₃OH molar ratio of 1:10.8 and at a contact time of amine to catalyst W/F of g cat·h/mol amine = 26−133. The product ratio was determined by GC after the reaction condition became steady state for 1 h. [b] Amine:CH₃OH = 1:20. [c] Amine:CH₃OH = 1:40.

scCH₃OH to make a single phase under the reaction conditions examined here.

The Magic-Angle-Spinning NMR Measurements. The NMR spectra were measured by the use of a Bruker AVANCE 400 spectrometer, whose ^{133}Cs and ^{31}P resonance frequencies were 52.49 and 161.97 MHz, respectively. The chemical shifts of ^{133}Cs and ^{31}P were determined using 1.0 mol/L aqueous CsCl solution and 85% H₃-PO₄ as standards.

Results and Discussion

N-Methylation of 2-Aminoethanol (1) over Various Solid Acid and Base Catalysts under Supercritical Conditions. Various solid acid and base catalysts were screened for the reaction of **1** with scCH₃OH by using a continuous-flow fixed-bed tubular reactor at 250−400 °C and a pressure range of 0.1−15 MPa. The outcome of the reaction of **1** with methanol is highly influenced by the reaction conditions as well as the catalysts used. Table 1 summarizes some representative experimental results. As shown in Scheme 1, the reaction of **1** with methanol provides several different products including the desired products, *N*-methylaminoethanol (**2**) and *N,N*-dimethyl-aminoethanol (**3**) and the intra- or intermolecular dehydration products **4** or **5**, and **6**, respectively, as byproducts. Ethylene-imine **4** is known to readily react with methanol to give the O-methylated compound, 2-methoxyethylamine (**7**).[11] When the reaction was performed in the gas phase over solid acid catalysts, such as H-mordenite, H-β zeolite, amorphous silica−alumina or phosphorus oxide on silica, and the solid base catalyst such as cesium on silica in addition to slightly weak acid−base bifunctional catalysts, M−P−Si ternary mixed oxide (M = K or Cs), the desired products, **2** and **3**, could not be obtained, as summarized in Table 1. However, only the γ-alumina catalyst with moderate acid and base bifunctionality afforded the desired N-methylated products, **2** and **3**, in moderate yield and selectiv-
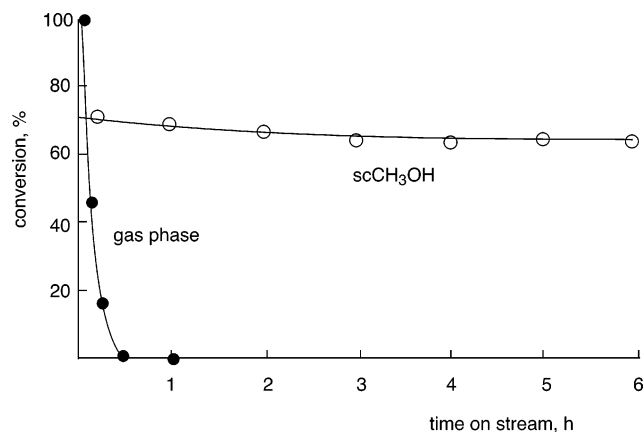
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Figure 1. Reaction of N-methylation of **1** with CH₃OH in vapor and supercritical phase over H-mordenite catalyst.

ity, 15 and 71%, respectively. The H-β zeolite catalyst afforded the intermolecular condensation products, **5** and **6**, in 46% cumulative selectivity, and the Cs−P−Si catalyst gave the intramolecular dehydration product **4** with a moderate selectivity, 37%, and a small amount of **5** and **6** in the gas phase.

In contrast to the gas-phase reaction, all catalysts tested have proven to effect the N-methylation of **1** under supercritical conditions to give predominantly N-methylation products, **2** and **3**, in good to excellent yields as listed in Table 1. A marked increase in the reactivity and the chemical yield of N-methylation products by using supercritical conditions are possibly attributed to the unique properties of SCFs. The effective desorption of N-methylation products from the catalyst surface might be enhanced by the condensed carrier medium, scCH₃OH, because of its strong ability to dissolve the reaction products. The solvation or local clustering around amino functional group in **1** with CH₃OH molecules might hinder the intermolecular condensation, leading to the cyclic byproducts discussed later.

Catalyst deactivation due to the coking of the heavier products can be suppressed using a scCH₃OH carrier possibly because of the efficient removal of the condensates from the surface or protecting the strong acid site on the catalyst surface with a large amount of CH₃OH. In fact, H-mordenite in the gas-phase reaction was immediately deactivated by the exothermic coking process, while it maintained its activity under supercritical conditions at 300 °C and 15 MPa, resulting in a significant improvement in the catalytic activity as shown in Figure 1. In addition, under supercritical conditions, the zeolite catalyst surface may be stabilized by the formation of methylsilicate species from the reaction of acidic silanol units with methanol, as observed in the vapor-phase Beckmann rearrangement reaction over high silica MFI zeolite.[12] The formation of the stable catalyst species might be responsible for the significant improvement in the catalyst lifetime under scCH₃OH conditions.

The screening tests of the effective catalysts as listed in Table 1 revealed that among the most efficient catalysts for chemoselective N-methylation in scCH₃OH are the M−P−Si (M = K

(12) (a) Kitamura, M.; Ichihashi, H. *Stud. Surf. Sci. Catal.* **1994**, *90*, 67−70. (b) Sato, H.; Kitamura, M.; Hirose, K.; Ishii, N. *Sumitomokagaku* **1995**, *I*, 19. (c) Ichihashi, H.; Kitamura, M.; Kajikuri, H.; Tasaka, E. U.S. Patent 5,354,859, 1994. (d) Ichihashi, H. In *Science and Technology in Catalysis 2002*; Anpo, M., Onaka, M., Yamashita, H., Eds.; Kodansha-Elsevier: Tokyo, 2003; pp 73−78.
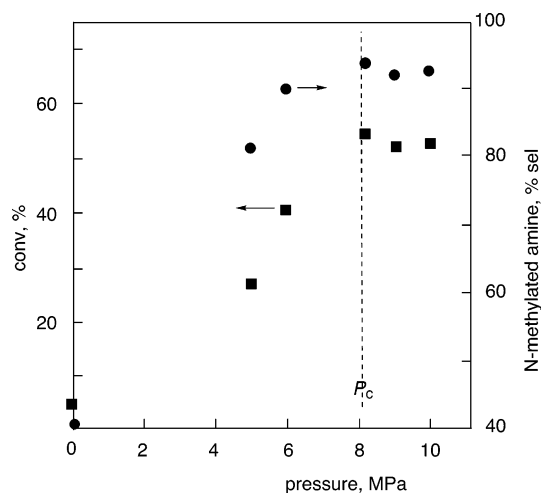
Figure 2. Pressure effect on the conversion and N-methylation selectivity. Conditions: 300 °C amine: CH_3OH = 1:20, the contact time of amine to catalyst, W/F of g-cat·h/mol-amine = 26
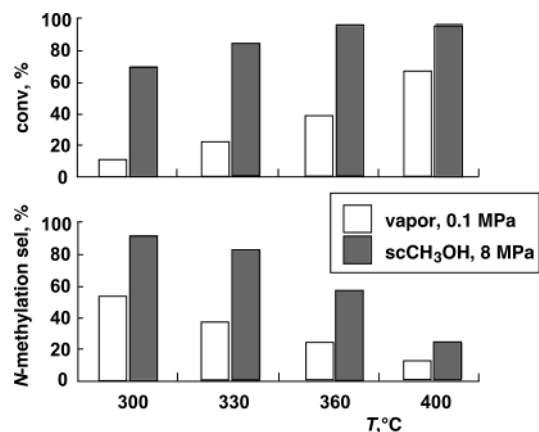

Figure 3. Effect of the reaction temperature on the conversion and N-methylation selectivity under both vapor and supercritical phase. Conditions: cat, Cs−P−Si mixed oxide, W/F (g-cat h/amine mol) = 55, CH_3-OH:amine = 10.8:1.

or Cs), which both have very weak acidic and basic sites.[13] In particular, the Cs−P−Si catalyst exhibited an excellent N-methylation selectivity, 94% at 71% conversion at 300 °C and 8.2 MPa. Noticeably however, dimethyl ether and O-methylated product, **7**, were not obtained. The mixed oxide catalyst was stable for several days under supercritical conditions. Binary oxide catalysts, P_2O_5 on silica and Cs on silica, gave unsatisfactory results, suggesting that this ternary mixed oxide catalyst including K or Cs−P−Si is a crucial structural factor for determining the catalyst performance in terms of the reactivity and selectivity. The γ-alumina catalyst also effected the reaction of **1** at 300 °C and 15 MPa to give the desired products, **2** and **3**, in 75% cumulative selectivity, at 48% conversion.

Catalyst Performance of the Cs−P−Si Ternary Mixed Oxide Catalysts in the Supercritical Phase: The Effect of the Temperature and Pressure. The catalyst performance of the ternary Cs−P−Si mixed oxide catalyst bearing both weak acidic and basic sites[8,13] is strongly affected by the reaction conditions as shown in Table 1 and Figures 2, 3. As discussed above, the gas-phase reaction under otherwise identical conditions at 300 °C provided unsatisfactory results with 58% selectivity of N-methylated products at 12% conversion, while at 400 °C, ethyleneimine **4** was obtainable as a major product with 72% selectivity. It has been reported that the ethyleneimine formation under the gas-phase condition proceeds reversibly via intramolecular dehydration of **1** by aid of the acid−base bifunctional synergetic effect on this ternary catalyst system.[8] The forward dehydration of **1** to **4** and H_2O is preferably occurring under the reduced pressure condition at 400 °C because of thermodynamic reasons.

The use of scCH$_3$OH caused a significant improvement in the productivity of N-methylation mainly because of the lower reaction temperature and an increased concentration of CH_3-OH on the catalyst surface. Since an intramolecular dehydration of **1** to **4** was strongly suppressed due to the lower temperature of 300 °C, an intermolecular dehydration of **1**, with scCH$_3$OH,

proceeded predominantly to form the desired N-methylated products. The pressure of CH_3OH over the Cs−P−Si mixed oxide catalyst under conditions with a W/F (contact time of amine, g-cat h/mol-amine) of 26 g-cat h/mol amine and a molar ratio of CH_3OH to **1**, 20:1, at 300 °C, strongly influenced the product distribution as shown in Figure 2. On increasing the pressure of CH_3OH from 0.1 to 10 MPa, a marked increase in the conversion and the selectivity for the N-methylated products was observed with a significant decrease in the formation of **4** and its derivatives such as **7**, acetaldehyde, ethylamine, and acetonitrile. Noticeably, pressures around the critical pressure, P_c = 8.1 MPa, gave the optimum yield and selectivity of N-methylated products. Above the critical pressure but at the same temperature, the outcome of the reaction does not largely change with increasing pressure.

When the reaction was performed with a W/F (contact time of amine, g-cat h/mol-amine) of 133 and an CH_3OH:amine molar ratio of 20:1 at 300 °C under conditions otherwise identical to those described in Table 1, the yield of the N-methylated products increased to the maximum yield, 81% and 94% cumulative selectivity at 86% one-pass conversion. An increase in the temperature from 300 to 400 °C in scCH$_3$-OH caused a serious drop in the selectivity to 25% although there was high conversion of **1**, as shown in Figure 3. At 400 °C, the supercritical phase reaction gave a complicated mixture of **4**, O-methylated compound, **7**, and some other degradation compounds.

The Effect of Water on N-Methylation of 1 in scCH$_3$OH over the Cs−P−Si Catalyst. The N-methylation reaction of **1** with CH_3OH proceeds via a formally intermolecular dehydration to give the desired products and H_2O as a concomitant product. Therefore, the influence of the generated water on the reaction might be inevitable. However, the reverse reaction of the N,N-dimethylated product, **3**, with an equimolar amount of H_2O in scCH$_3$OH under conditions similar to those described above did not give the demethylation products **1** and **2**, at all.[14] Similarly, the reaction of N-methylaminoethanol, **2**, with scCH$_3$OH in the presence or absence of added water provided only the forward

(13) The acid and base strength of the Cs−P−Si mixed oxide catalyst has been determined by the Hammet indicator method to be weaker than +6.3 [Ho] and +8.3 [H−], respectively. Moreover, NH_3 and CO_2 chemisorption at room temperature did not occur in the temperature-programmed desorption (TPD) method indicating that this catalyst has only very weak acid and base sites (ref 8).

(14) The reaction of **3** without water in scCH$_3$OH over the Cs−P−Si catalyst afforded a complicated degradation mixture of **3** at 300 °C, 8.2 MPa, 20/1 molar ratio of **3** to CH_3OH, and W/F = 80, which consisted of 2-methoxyethanol, monoethylene glycol, 2-methoxyethylamine, N,N'-dimethylpipirazine etc., at 42% conversion.

Table 2. Effect of Added Water on the Reactions of Amines with ScCH$_3$OH

amine	added H$_2$O, equiv	conv, %
HOCH$_2$CH$_2$NH$_2$	0	63[a]
	1	26[a]
HOCH$_2$CH$_2$NH(CH$_3$)	0	47[b]
	1	9[b]
HOCH$_2$CH$_2$N(CH$_3$)$_2$	0	0
	1	0

Conditions: 300 °C, W/F(g-cat.·h/mol-amine) = 38, CH$_3$OH:amine:water = 20:1:1. [a] The reaction product, a mixture of **2** and **3**. [b] The reaction product, **3**.

reaction product, *N,N*-dimethylated product, **3**, without formation of **1**. Furthermore, in the reaction that used *N*-ethylaminoethanol as a starting material with scCH$_3$OH under conditions otherwise identical to those described in Table 1, disproportionation products such as *N,N*-diethylaminoethanol, vide infra were not produced. However, water generated in the reaction has been proven to have an inhibiting effect on the forward reaction. In fact, an addition of an equimolar amount of water to **1** or **2** caused a serious drop in the catalytic activity from 63% conversion of **1** to 26% conversion as shown in Table 2. In addition, when the reaction was performed at high-dilution conditions, a molar ratio of CH$_3$OH to **1** of 20:1 or 40:1, with the W/F = 133, the conversion and the yield of the dimethylated product **3** were markedly improved as listed in Table 1. These results indicate that the N-methylation of **1** or the intermediate **2** with scCH$_3$OH irreversibly proceeds and that water does not participate in the reverse reaction or the disproportionation of N-methylated amino alcohols under these conditions but strongly inhibits N-methylation possibly because of the interaction of water with active sites on the catalyst that is relatively stronger than that of methanol.[15] The use of scCH$_3$OH might allow the effective desorption of the generated water from the catalyst surface.

The Effect of the Structures of *N*-Alkylaminoethanol on N-Methylation over the Cs–P–Si Catalyst. The product distribution in the N-methylated products, **2** and **3**, was strongly affected by a change in the pressure, the temperature, and the contact time, suggesting that the methylation with scCH$_3$OH proceeds from **1** through the monomethylated product, **2**, to the dimethylated product, **3**. It should be noted that the reaction of **1** with scCH$_3$OH was about two times faster than that of **2**, possibly because of steric reasons. The marked steric effect of the alkyl substituents on the amino group was demonstrated by the decrease in the reactivity in the order of H > CH$_3$ > C$_2$H$_5$ ≫ CH(CH$_3$)$_2$ as alkyl substituents. Noticeably, the methylation of *N*-alkylaminoethanol with scCH$_3$OH predominantly gave *N*-methyl-*N*-alkylaminoethanol without formation of any alkyl group scrambling products, indicating that the disproportionation reaction of alkylamines does not occur under the conditions tested as discussed in the previous section.

Scope and Limitation of N-Methylation over the Cs–P–Si Mixed Oxide. N-Methylation of functionalized amines over the Cs–P–Si mixed oxide catalyst is applicable to the synthesis of N-methylated functionalized amino alcohols, as listed in Table 3. The reaction of various functionalized amines smoothly proceeded to provide the corresponding N-methylated products

(15) N-Methylation of ammonia with methanol to methylamines in vapor phase over a solid acid catalyst is known to be a reversible reaction (Segawa, K.; Tachibana, H. *J. Catal.* **1991**, *131*, 482–490 and references therein).

Table 3. N-Methylation of Various Amines over the Cs–P–Si Catalyst in ScCH$_3$OH[a]

entry	amine	conv, %	N-methylation products sel, %	cyclic amines sel, %
1	HO(CH$_2$)$_2$NH$_2$	90	94	1
2	HO(CH$_2$)$_3$NH$_2$	81	93	1
3	HO(CH$_2$)$_4$NH$_2$	87	12	87
4	HO(CH$_2$)$_5$NH$_2$	51	80	20
5	HO(CH$_2$)$_2$O(CH$_2$)$_2$NH$_2$	71	87	13
6	HO(CH$_2$)$_2$NHCH$_3$	76	88	0.1
7	HO(CH$_2$)$_2$NHC$_2$H$_5$	45	82	0.5
8	HO(CH$_2$)$_2$NHCH(CH$_3$)$_2$	24	78	1
9	*n*-C$_4$H$_9$NH$_2$	18	94	–
10	C$_6$H$_5$NH$_2$	15	94	–
11	2-pyrrolidone	16	88	–
12	C$_2$H$_5$O(CH$_2$)$_2$NH$_2$	11	98	–

[a] Conditions: The reaction was conducted over the Cs–P–Si catalyst at 300 °C in a fixed-bed tubular reactor with an amine to CH3OH molar ratio of 1:20 and at contact time of amine to catalyst W/F of g-cat·h/mol-amine = 140.

with high regioselectivity. Noticeably, the product distribution was found to be influenced by the structures of the amines tested. An increase in the number of the methylene units in the amino alcohols caused a remarkable decrease in the reactivity on the order of 2-aminoethanol > 3-aminopropanol > 5-aminopentanol, although 4-aminobutanol exhibited good reactivity but gave predominantly the cyclization product, pyrrolidine, in 87% selectivity, possibly because of thermodynamic reasons. Diglycolamine with a structure similar to that of 5-aminopentanol provided N-methylated products along with morpholine as a byproduct.

In sharp contrast to the reactivity of bifunctionalized amines, simple amines such as *n*-butylamine or aniline and an amide, 2-pyrrolidone, were less reactive, giving N-methylated products with excellent selectivity regardless of their structures, but with low conversion (10–20% for the amines). These results strongly suggested that the hydroxy group on the other terminus in the functionalized amines is a crucial structural factor to attain high reactivity and selectivity. In fact, ethoxyethylamine bearing no hydroxy group was far less reactive than **1**, and its reactivity was close to that of simple amine, *n*-butylamine, suggesting that the hydroxy group might interact with the acid–base pair sites on the catalyst surface as a tethering on the catalyst surface, which will be discussed later.

In a similar manner, the reaction of ethylenediamine with scCH$_3$OH has been proven to proceed smoothly to give *N*-methylethylenediamine as a main product in addition to *N,N*-dimethylethylenediamine in a good total yield as listed in Table 4. Noticeably, no reaction product was obtained under the gasphase condition at 300 °C or even at the high reaction temperature of 400 °C. Above the critical pressure, however, the yield of the N-methylation product reached a maximum (with 95% selectivity), and an increase in the reaction temperature from 300 to 400 °C at 8.2 MPa caused an increase in the conversion but a decrease in the N-methylated product selectivity. Symmetrically substituted *N,N′*-dimethylethylenediamine was formed, and some decomposition products were formed at the higher temperature. Moreover, the reactivity of the diamines decreased with an increase in the distance between the two amino groups of the diamines, on the order of 1,2-ethylenediamine > 1,3-propanediamine > 1,5-pentanediamine > 1,6-hexanediamine > 1,7-heptanediamine. 1,4-Butanediamine gave the

Table 4. N-Methylation of Various Diamines over the Cs−P−Si Catalyst in ScCH$_3$OH[a]

entry	amine	T, °C/ P, MPa	conv, %	selectivity, %		
				N-CH$_3$	*N,N*-CH$_3$)$_2$	*N,N'*-(CH$_3$)$_2$
1	H$_2$N(CH$_2$)$_2$NH$_2$	300/0.1	0	0	0	0
2	"	300/8.2	70	83	12	5
3	"	330/8.2	79	71	16	9
4	"	360/8.2	88	61	21	12
5	"	400/0.1	0	0	0	0
6	"	400/8.2	94	43	28	14
7	H$_2$N(CH$_2$)$_3$NH$_2$	300/8.2	48	80	10	4
8	H$_2$N(CH$_2$)$_4$NH$_2$	300/8.2	52	71	10	4
9	H$_2$N(CH$_2$)$_5$NH$_2$	300/8.2	31	80	8	3
10	H$_2$N(CH$_2$)$_6$NH$_2$	300/8.2	25	78	7	3
11	H$_2$N(CH$_2$)$_7$NH$_2$	300/8.2	25	83	10	4

[a] Conditions: The reaction was conducted over the Cs−P−Si catalyst at 300 °C in a fixed-bed tubular reactor with an amine to CH$_3$OH molar ratio of 1:20 and at contact time of amine to catalyst *W/F* of g-cat·h/mol-amine = 140.

cyclization products, *N*-methylpyrrolidine and *N*-vinyl ethyl-eneimine, respectively. 1,6-Hexanediamine and 1,7-heptanedi-amine have low reactivities similar to that of *n*-butylamine.

It should be noted that the formation of symmetrically substituted *N,N′*-dimethylethylenediamine was also observed as only a minor product in the reaction of 1,2-ethylenediamine with scCH$_3$OH. In the liquid-phase reaction of ethylenediamine with methanol over the CuO−ZnO−Al$_2$O$_3$ catalyst under a pressur-ized dihydrogen atmosphere the symmetrical *N,N′*-dimethyl-ethylenediamine was obtained as the main product.[16] A separate experiment showed that the N-methylation of *N,N*-dimethyl-ethylenediamine was very slow, under the same reaction conditions as are described in Table 4, and provided only 6% conversion. These results indicate that the terminal NH$_2$ function in the diamine is also crucial in determining the reactivity of the diamines as observed in the reaction of 2-aminoethanol.

O-Methylation of Ethylene Glycol with Methanol over Cs−P−Si Mixed Oxide. The selective methylation bifunctional compounds based on the tethering effect can be successfully applied to mono-O-methylation of ethylene glycol **8** with scCH$_3$-OH under supercritical conditions. The O-methylation of **8** with CH$_3$OH to monomethylated product 2-methoxyethanol **9** was carried out over the Cs−P−Si catalyst at a temperature range of 300−400°C and a pressure range of 0.1−12 MPa. The reaction pathways of **8** with methanol were also highly dependent on the reaction conditions, as illustrated in Scheme 2. The use of the supercritical conditions caused a significant increase in the formation of monomethylation product **9** reaching the maximum 76% at 300 °C and 12 MPa as summarized in Table 5. The intramolecular dehydration, dimerization, and cyclization of **8**, which were favored in a vapor phase, could be suppressed under the supercritical conditions. In fact, the vapor-phase reaction of **8** with methanol over the Cs−P−Si catalyst selectively afforded a mixture of dehydration product, acetaldehyde **13**, and its condensation product, **14**, aldols in 58% yield, in addition to diethylenglycol **11** and a small amount of 1,4-dioxane **12** in 31 and 1%, yield, respectively (Table 5).[17]

It should be noted that the dimethylated product, dimethyl ethyleneglycol **10**, was not obtained under both the vapor nor

(16) Göbölös, S.; Margitfalvi, J. L. *Prog. Catal.* **1997**, *6*, 123−134.
(17) Similarly, the reaction of 1,2-propyleneglycol at 300 °C and 8.2 MPa gave only monomethylation products with 78% selectivity (1-methyl-:2-meth-ylpropyleneglycol = 2.25:1), although at 11% conversion.

Table 5. O-Methylation of Ethylene Glycol over the Cs−P−Si Catalyst in ScCH$_3$OH[a]

entry	diol	T, °C/P, MPa	conv, %	selectivity, %		
				9	11+12	13+14+15
1	HO(CH$_2$)$_2$OH	300/0.1	46	10	32	58
2	"	300/5	44	50	35	15
3	"	300/10	31	68	23	4
4	"	300/12	23	76	21	3

[a] Conditions: The reaction was conducted over the Cs−P−Si catalyst in a fixed-bed tubular reactor with a diol to CH$_3$OH molar ratio of 1:20 and at contact time of amine to catalyst *W/F* of g-cat·h/mol-amine = 150.
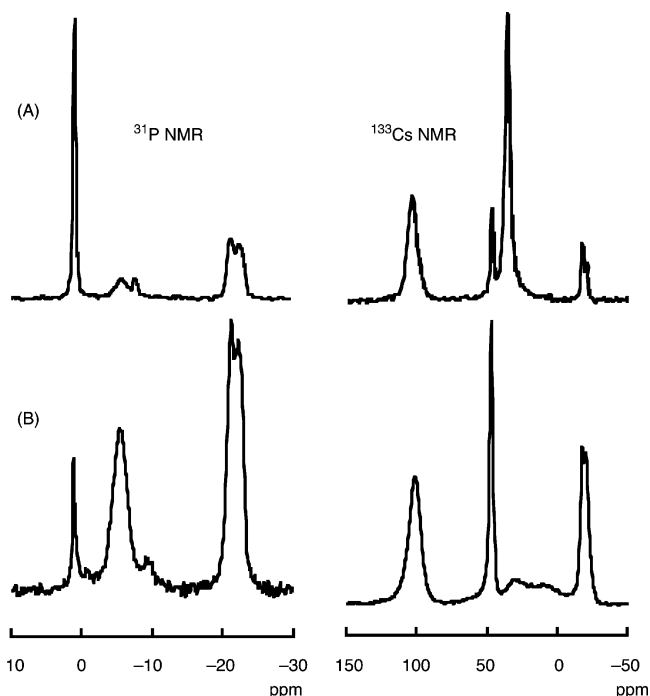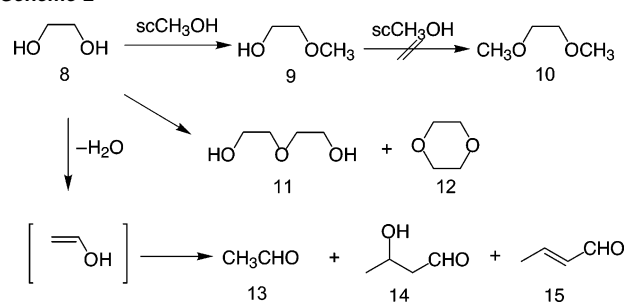

Figure 4. ^{133}Cs NMR and ^{31}P NMR spectra of the Cs−P−Si mixed oxide catalyst calcined at 500 °C (A) and 400 °C (B).

Scheme 2

supercritical phase over the Cs−P−Si catalyst, suggesting that the hydroxy group might interact with the acid−base pair sites on the catalyst surface as a tethering on the catalyst surface, as discussed in the reaction of aminoethanol. In addition, the reaction of 2-propanol with scCH$_3$OH gave a trace amount of isopropyl methyl ether and propene as major product but with low yield. No acetone formation was observed. These results strongly indicate that the Cs−P−Si catalyst does not promote dehydrogenation of alcohol but accelerates the dehydrative methylation of 2-aminoethanol and diols.

Characterization of Cs−P−Si Mixed Oxide by Solid ^{133}Cs and ^{31}P Magic-Angle-Spinning NMR Spectroscopy. Although the ternary mixed oxide catalyst, Cs−P−Si, which is the most

efficient known catalyst in scCH₃OH, is known to have both very weak acidic and basic sites, no detailed information on the intrinsic nature of the active sites for the methylation reaction is available. Valuable information on the solid catalyst was provided by the solid MAS NMR spectroscopy on the Cs−P−Si synthesized from the reaction of silica beads and CsNO₃ with [NH₄][H₂PO₄], followed by calcination at 500 °C. As shown in Figure 4, both ^{133}Cs and ^{31}P NMR spectra of the Cs−P−Si catalyst exhibit the presence of at least five different species. A ^{31}P NMR spectrum of the catalyst displays a sharp signal at $\delta = 1$ ppm due to the P₂O₅ on the silica,[18] which virtually disappeared in the proton cross-polarization (CP-MAS) measurement. On the other hand, the ^{133}Cs NMR spectra indicated that two signals due to the cesium on silica were observed at $\delta = -17$ and -19 ppm, which are indicative of the presence of the Cs−O−Si bond by comparison to that of the authentic sample prepared impregnated with CsNO₃ calcined at 500 °C. These results confirm that the origins of the both acidic and basic sites in the Cs−P−Si oxide are at least the P₂O₅ and Cs on SiO₂, respectively. However, these binary catalysts, P₂O₅ on SiO₂ and Cs on SiO₂, did not show activity for the N-methylation reaction (entries 11 and 12 in Table 1).

Besides these binary moieties, the existence of three kinds of cesium phosphate species including monophosphate (orthophosphate), diphosphate (pyrophosphate), and multicondensed cesium phosphate (metaphosphate) could be confirmed by the X-ray diffraction analysis. The ^{133}Cs spectrum of the catalyst shows that a signal at $\delta = 47$ ppm was assigned to the monocesium orthophosphate by comparison of the NMR spectra of the authentic samples prepared from CsOH with [NH₄][H₂PO₄]. In a similar way, ^{31}P NMR signals at -6 ppm can be assigned to orthophosphate species.[19] X-ray diffraction patterns of the catalyst supported the structure of the catalyst.

Unfortunately, the pure samples of cesium pyrophosphate and cesium metaphosphate could not be synthesized because these compounds are easily hydrolyzed to the orthophosphate by the moisture under the synthetic conditions. However, valuable information on these two phosphate compounds was obtained by changing the calcination temperature. X-ray diffraction analysis of the Cs−P−Si mixed oxide prepared after calcination at 400 °C showed that this authentic sample consisted of only ortho- and metaphosphate units. The ^{31}P NMR spectrum of the compound displayed signals at -21 to -22 ppm in addition to a signal due to orthophosphate at -6 ppm and a signal due to P₂O₅ on SiO₂ at 1 ppm. Similarly, the ^{133}Cs spectrum of this sample showed three signals at 104 ppm in addition to the signal due to orthophosphate and Cs on SiO₂ as shown in Figure 4. Therefore, the two ^{133}Cs signals at 36 and 104 ppm and two ^{31}P signals at -8 and -21 to -22 ppm are assignable to the cesium pyrophosphate and metaphosphate species, respectively.[19] These MAS NMR studies on the ternary mixed oxide Cs−P−Si catalyst confirm that the distinct acidic and basic sites originated from P₂O₅/SiO₂ and cesium/SiO₂, respectively, in addition to the weak acid−base paired sites originating from
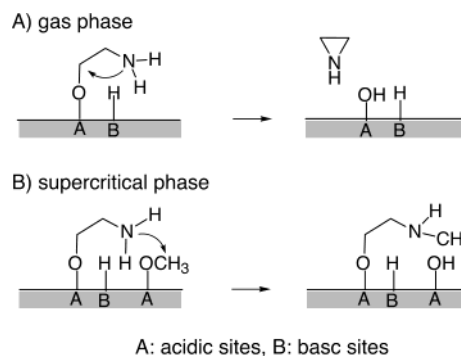
(18) Two different methods were used to prepare the authentic sample of phosphorus oxide on silica: (i) by impregnation with an aqueous solution of P₂O₅ followed by drying at 120 °C for 5 h in air and (ii) by impregnation with NH₄H₂PO₄ followed by calcination at 500 °C for 2 h in air.
(19) Hayashi et al. previously investigated the ^{31}P MAS NMR of various alkali phosphates. They reported that the ^{31}P chemical shift of Cs₃PO₄ was $\delta = -3$ to -7 ppm, and shifted to a higher magnetic field with higher condensation of phosphates (Hayashi, S.; Hayamizu, K. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 3061−3068).

Figure 5. Schematic diagrams of the acid−base synergetic effect for dehydration of **1** on the catalyst surface of the Cs−P−Si catalyst in the gas phase and supercritical phase based on the experimental data as well as reported works.[8]

three kinds of cesium phosphates on SiO₂. These weak acidic−basic sites on the catalyst surface are possibly responsible for the selective N-methylation reaction with scCH₃OH.

A Possible Reaction Mechanism over Cs−P−Si Mixed Oxide. For N-methylation of aromatic and alkylamines with methanol over solid acid catalysts in the gas phase, two possible mechanisms have been proposed: reductive alkylation over the supported metal through dehydrogenation of methanol to formaldehyde, followed by formation of an imine which is hydrogenated by H₂, and electrophilic substitution of methyl cation generated from methanol with the help of acidic sites on the acidic catalyst surface.[20] Recently, ^{13}C MAS NMR investigations of methylation of aniline with methanol over zeolite revealed that the N-methylation proceeds through the formation of methoxy groups on the surface, followed by electrophilic substitution of methyl cation.[21] As mentioned above, the ternary mixed oxide Cs−P−Si catalyst possesses the distinct acidic and basic sites, in addition to the weak acid−base paired sites on the surface.

On the basis of the present results as well as the previously reported results in the ethyleneimine formation from **1** over M−P−Si analogues,[8] the plausible reaction pathways can be envisaged. In ethyleneimine formation in the gas phase, 2-aminoethanol was reported to interact with the acid−base paired site on the surface to form 2-aminoethyl phosphate or silicate as the tethers, in which the dehydration possibly proceeds by aid of the acid−base bifunctional synergetic effect. The formation of these phosphate or silicate esters may be a crucial step for selective N-methylation in the supercritical phase. The amino group in the 2-aminoethyl ester moieties would exclusively attack the methyl carbon of the neighboring methyl ester species on the surface because of the high concentration of methanol on the catalyst surface as depicted in Figure 5. In fact, the reaction of 2-ethoxyethylamine with CH₃OH over Cs−P−Si mixed oxide catalyst was strongly retarded under the same reaction conditions. It has also been reported that liquid-phase N-alkylation of polyfunctional amines with alcohols over SrH-

(20) (a) Narayanan, S.; Deshpande, K. *Appl. Catal., A* **2000**, *199*, 1−31 and references therein. (b) Pouilloux, Y.; Doidy, V.; Kervennal, J.; Barrault, J. *Stud. Surf. Sci. Catal.* **1997**, *108*, 139−147.
(21) (a) Wang, W.; Seiler, M.; Ivanova, I. I.; Sternberg, U.; Weitkamp, J.; Hunger, M. *J. Am. Chem. Soc.* **2002**, *124*, 7548−7554. (b) Wang, W.; Buchholz, A.; Seiler, M.; Hunger, M. *J. Am. Chem. Soc.* **2003**, *125*, 15260−15267.

PO$_4$ catalyst proceeds via the nucleophilic substitution of phosphate ester with reactant amine to form N-alkylated amine products.[22]
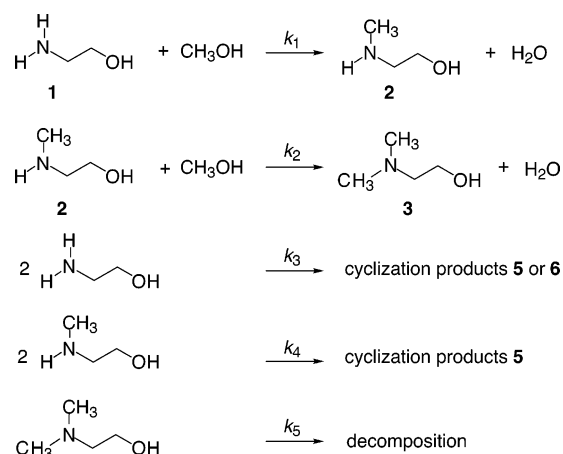
The use of supercritical conditions makes it possible to use the lower reaction temperature of 300 °C. Therefore, intramolecular ethyleneimine formation was significantly suppressed for kinetic reasons, and higher pressures over the critical pressure resulted in the thermodynamic equilibrium shift to the formation of intermolecular methylation in accordance with Le Chatelier's principle. In addition to the remarkable effects of the supercritical conditions, the N-methylated aminoethanol moieties bonded to the surface might be effectively removed via esterexchange with a large amount of CH$_3$OH under the reaction conditions. Since cyclization to **4**, **5**, and **6** via the intermolecular dehydration of 2-aminoethyl species might proceed thermally, a low concentration of CH$_3$OH and a high reaction temperature favor the formation of thermodynamically stable cyclization products.

As shown in Table 4, the reaction of ethylenediamine with scCH$_3$OH provided unsymmetrically substituted *N*-methyl- and *N,N*-dimethylethylenediamine as major products with a good total yield, indicating that the Cs−P−Si catalyst might be able to interact not only with the hydroxy group but also the amino group as an anchor on the catalyst surface under high-pressure conditions. However, no reaction of diamines with CH$_3$OH proceeds in the gas phase possibly due to minimal adsorption of ethylenediamine on the surface;[23] the reactivity difference between amino alcohols and diamines suggests that the adsorption through the hydroxy group might be stronger than that through the amino group.

Valuable information for the reaction mechanism was provided by the methylation of diol and 2-propanol with scCH$_3$-OH under conditions giving only monomethylated ethylene glycol and propene, respectively. These experimental results strongly indicate that the Cs−P−Si ternary oxide does not serve as solid basic catalyst but as an acidic catalyst for the dehydrative methylation of functional amines and alcohols.

A Simulation of Reaction Kinetics by Langmuir−Hinshelwood Model. For further clarification about the reaction mechanism, the kinetic simulation of N-methylation was carried out using the Langmuir−Hinshelwood model for the competitive adsorption mechanism and the experimental results obtained here. As discussed above, the methylation of **1** with CH$_3$OH irreversibly proceeds to the desired N-methylated products, in which monomethylated product **2** does not disproportionate under the reaction conditions. The coproduced water may inhibit the reaction possibly by competitive adsorption with reactants on the catalyst surface (Table 2). However, data are not available for the adsorption equilibrium constants of the substrates, including water in scCH$_3$OH, or for the kinetic rate constant; as a result, the Runge−Kutta curve-fitting analysis was conducted using several parameters for the reaction sequences (Scheme 3) as well as experimental data, including the conversion, the yield of each product represented by the partial pressure (MPa), the contact time ranging from 0 to 1600 (t, g-cat min/

(22) Labadie, J. W.; Dixon, D. D. *J. Mol. Catal.* **1987**, *42*, 367−378.
(23) In the vapor phase adsorption study at 50 °C, very weak signals at 2230 cm,$^{-1}$ possibly due to the surface primary ammonium species of ethylenediamine, were observed by infrared spectroscopy. It is assumed that ethylendiamine might adsorb on the surface acidic site in an ionic manner in scCH$_3$OH, forming a 2-aminoethylammonium moiety, which might be a relatively weak interaction.
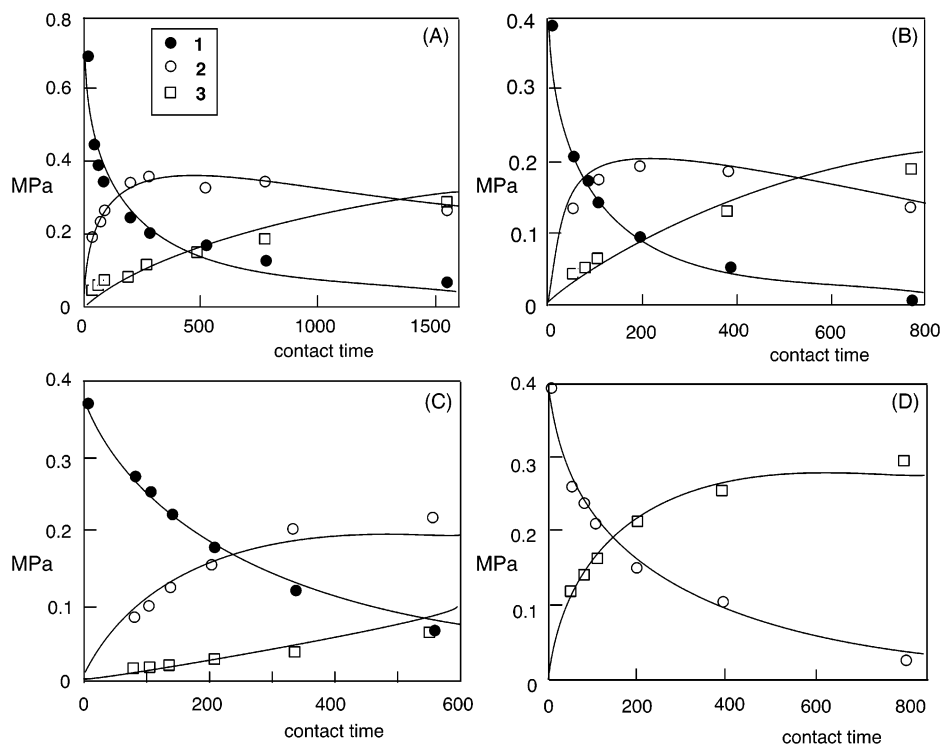
Scheme 3

mol), and the molar ratio of substrate to methanol ranging from 1:10.8 to 1:20 at 300 °C and 8.2 MPa.

Figure 6 shows the agreement between the observed and simulated results for the N-methylation of **1**. Table 6 summarizes the reaction parameters. Representative calculation results are as follows: the rate constant of monomethylation, $k_1 = 0.142$, the rate constant of dimethylation, $k_2 = 0.068$, and the adsorption equilibrium constant of **1**, $K_1 = 1.20$. The Langmuir−Hinshelwood competitive adsorption model can convincingly explain actual experimental results. In fact, we found that water interacts with the catalyst surface much more strongly than **1** and CH$_3$-OH under these conditions and the adsorption equilibrium constant (K) of water is much larger than that of **1** and CH$_3$-OH: $K_{methanol}/K_1 = 0.05$ and $K_{water}/K_1 = 5$. The ratio of the reaction rate of **2** to **3** vs **1** to **2** determined experimentally is 0.48, and it is almost the same as the ratio of calculated rate constants, k_2/k_1, 0.48. Thus, this competitive adsorption mechanism can interpret the catalysis inhibition by generated water and the steric effect of the substituent on the amino group.

Conclusions

We have demonstrated the first examples of continuous chemoselective N-methylation of bifunctional amines with CH$_3$-OH over the solid acid catalysts as well as the solid acid−base bifunctional catalysts under supercritical conditions, in which scCH$_3$OH can be used as a methylating agent and a condensed carrier medium. Among the catalysts examined, the Cs−P−Si mixed oxide provided the most efficient catalyst performance in terms of selectivity and reactivity at 300 °C and 8.2 MPa, the N-methylation selectivity in the products reaching up to 94% at 86% conversion. The selective N-methylation of aminoethanol was successfully applicable to the synthesis of N-methylated amino alcohols and diamines. In sharp contrast to the reactivity of bifunctional amines, ethoxyethylamine bearing no free hydroxy group was less reactive, suggesting that the hydroxy group of the amino alcohols is a structural factor crucial to determining the high reactivity and selectivity, possibly because of the tethering effect of another terminus of these amines to the catalyst surface. The selective dehydrative methylation was also applicable to O-methylation of diols. The magic-anglespinning NMR spectroscopy and X-ray diffraction analysis of the Cs−P−Si mixed oxide catalyst revealed that the acidic and basic site originated from P$_2$O$_5$/SiO$_2$ and Cs/SiO$_2$, respectively, and the weak acid−base paired sites are attributed to three kinds

Figure 6. Curve-fitting calculation for the reaction of **1** with scCH₃OH under supercritical condition. A molar ration of CH₃OH /**1**/water (A)10.8/1/0, (B) 20/1/0, (C) 20/1/1, and (D) N-methylation of **2** to **3** in 20/1/0 molar ratio. Symbols represent observed data. Lines represent simulated data.

Table 6. Calculation Results of Reaction Parameters

parameter	value in minimum error
k_1	0.142
k_2	0.068
k_3	0.010
k_4	0.000
k_5	0.020
K_1	1.20
K_2	1.01
K_3	1.01
K_5	0.06
$K_{methanol}$	0.06
K_{water}	6.02

of cesium phosphates on SiO_2. The weak acid−base sites on the catalyst surface might be responsible for the selective N-methylation. The Langmuir−Hinshelwood competitive adsorption mechanism can interpret the experimental data including catalysis inhibition by generated water and the steric effect of the substituent on the amino group. Thus, the continuous

N-methylation of 2-aminoethanol to *N*-methylaminoethanol and *N,N*-dimethylaminoethanol over Cs−P−Si ternary mixed oxide catalyst using supercritical methanol is an attractive alternative as an environmentally benign chemical process. Only water as a wasted coproduct was generated during the methylation reaction.

Supporting Information Available: Experimental procedures, results of N-methylation of 2-aminoethanol with scCH₃OH, the reaction equipment, and simulated results. This material is available free of charge via the Internet at http://pubs.acs.org.

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