Scheme I

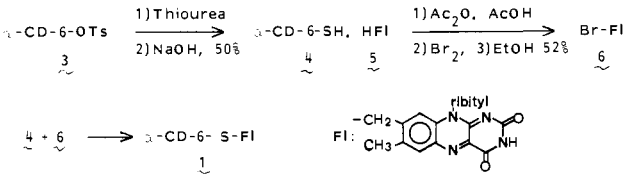

Table I. Association Constants and Rate Constants for the Reduction of Natural and Artificial Flavoenzyme

flavin	reductant	K_a (M^{-1})	k_2 (s^{-1})	$k_2 \cdot K_a$ (M^{-1} s^{-1})
NADH FMN oxidoreductase[a]	NADH	21000	15.5	326000
8α-S-flavopapain (7)[b]	benzyl-NAH	10300	0.0054	56
8α-S-flavoCD (1)[c]	*n*-hexyl-NAH	2500	0.5	1200
	isopropyl-NAH	260	0.36	94
	benzyl-NAH	1050	0.06	63

[a] 23 °C, pH 7.0, ref 9b. [b] 25 °C, pH 7.5. [c] 25 °C, pH 7.4. Rate constant for 8α-S-substituted riboflavin obtained (ca. 50 M^{-1} s^{-1}) by the Hammett extrapolation from substituted Fl's.

25 °C. The reaction was nearly quantitative as determined by electronic spectroscopy when an excess (at least 10-fold) of RNAH was used. The rates of the electron transfer from RNAH to the flavin moiety of the flavo-CD (eq 1) were measured by following

$$1 + \text{RNAH} \overset{K_a}{\rightleftharpoons} 1\cdot\text{RNAH} \xrightarrow[H^+]{k_2} \text{RNA}^+ + 1\cdot\text{H}_2 \qquad (1)$$

the characteristic absorption of the flavin at 450 nm by using a stopped-flow apparatus. As shown in Table I, flavo-CD **1** has reasonably large association constants of 1050, 260, and 2500 M^{-1} for benzyl-, isopropyl-, and *n*-hexyl-NAH, respectively, although smaller than 8α-S-flavopapain.[4a] The natural NADH·FMN oxidoreductase[9a] has an even larger association constant (ca. eightfold greater) for NADH which has much more extensive recognition site than RNAH. It is noteworthy that simple CD cavity confers almost the same degree of recognition as the natural enzyme.

The most interesting feature of compound **1** is the large rate constant for the electron transfer (Table I). Although the natural NADH dependent flavoprotein exhibits a 30-fold larger rate constant than **1**, the "structurally related flavopapain" **7**[4a] has a much smaller (by a factor of 90) rate constant than **1**. This suggests that the spacial arrangement of the flavin moiety relative to the bound dihydronicotinamide is much better in **1** than the flavopapain, since the latter probably has an Fl-NAH edge–edge distance of 4–14 Å, depending on the flavin internal rotation based on the X-ray crystallographic analysis of unmodified papain.[9b]

The overall efficiencies of dihydroflavin production for **1** (eq 1), expressed by $k_2 \cdot K_a$, are 63, 94, and 1200 M^{-1} with benzyl-, isopropyl-, and *n*-hexyl-NAH, respectively, larger than 56 for 8α-S-flavopapain[4a] with benzyl-NAH but smaller than 1.64×10^6 for the sterically less hindered and more electron deficient flavopapain with *n*-hexyl -NAH.[10]

Furthermore, according to our preliminary experiments, **1** exhibited efficient catalytic activities for the electron transfer from RNAH to metalloporphyrins, which are important steps in respiration and the reduction of cytochrome P-450. A typical example is the electron transfer from *n*-hexyl-NAH to TPPS·Mn^{III} catalyzed by **1** with the observed catalytic constant of 200 M^{-1} s^{-1} at 25 °C in pH 7.4 aqueous solution. The catalytic efficiency of **1** was 5.5-fold higher than FMN (see Table II). According to our preliminary experiments, artificial Fl-CD can be a good model of Fl-protein (e.g., P-450 reductase).

Table II. Rates of Flavin-Catalyzed Reduction of Mn^{III}·Porphyrin

Mn^{III} porphyrin[a]	flavin[a]	k_2[b] (M^{-1} s^{-1}) MeNAH	k_2[b] (M^{-1} s^{-1}) *n*-hexyl-NAH
MnTPPS		0.2	0.2
MnTPPS	FMN	36	31
MnTPPS	**1**	22	200
cytochrome *c*	**7**	56 (benzyl-NAH)[c]	

[a] 8×10^{-6} M. [b] $v = k[Mn^{III}TPPS][RNAH]$, H_2O, 25 °C, pH 7.4. [c] Reference 4 and 10.

The present observations of excellent RNAH binding and efficient electron transfer may give a promise for versatile application of flavocyclodextrin to a variety of biomimetic chemistries.

Acknowledgment. This research was supported by Grant-in-Aid 61065003, Japan Ministry of Education.

Bifunctional Activation of Ketone with Rhodium(III) Porphyrin. Efficient Cooperation of Metal and Intramolecular Base

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The enolization of carbonyl compounds is an essential process in many organic and biological reactions. The generation of enolates as reactive intermediates in organic synthesis usually requires strongly basic conditions.[1-3] On the other hand, the enolization catalyzed by metalloenzymes such as aldolases involves an efficient cooperation of metal ion (as a Lewis acid) and a basic amino acid residue (as a Brønsted base) under neutral conditions.[4] Such a concerted acid–base cooperation, although not readily accessible by using synthetic systems,[5] is significant for the development of catalytic organic reactions under mild conditions. Now, we wish to report here that simple ketones such as acetone undergo novel bifunctional activation (enolization) with Rh(III) porphyrins having suitably located intramolecular bases.

Chlororhodium(III) complexes of *trans*- and *cis*-5,15-bis(2-hydroxy-1-naphthyl)octaethylporphyrin (**1a**-*trans* and **1a**-*cis*)[6]

(9) (a) Jablonski, E.; DeLuca, M. *Biochemistry* **1977**, *16*, 2932. (b) Matthews, B. W. In *The Proteins*, 3rd ed.; Newrath, H., Hill, R. L., Boeder, C.-L., Eds.; Academic Press: New York, 1977; Vol. 3, p 527. (c) Levine, H. L.; Kaiser, E. T. *J. Am. Chem. Soc.* **1978**, *100*, 7670.

(10) Radziejewski, C.; Ballow, D. P.; Kaiser, E. T. *J. Am. Chem. Soc.* **1985**, *107*, 3352. Reported k_2/K_m for 8α-S-acetylflavopapain + *n*-hexyl-NAH is 1.64×10^6 M^{-1} s^{-1}.

(1) (a) House, H. O. *Modern Synthetic Reactions*; W. A. Benjamin: Menlo Park, CA, 1972. (b) d'Angelo, J. *Tetrahedron* **1976**, *32*, 2979–2990. (c) Mundy, B. P. *Concepts of Organic Chemistry*; Marcel Dekker: New York, 1979; Chapter 9.

(2) (a) Review: Kuwajima, I.; Nakamura, E. *Acc. Chem. Res.* **1985**, *18*, 181–187. (b) Mukaiyama, T.; Banno, K.; Narasaka, K. *J. Am. Chem. Soc.* **1974**, *96*, 7503–7509.

(3) For enolization reagents working under more neutral conditions, see: (a) Mukaiyama, T.; Inoue, T. *Chem. Lett.* **1976**, 559–562. (b) Mukaiyama, T.; Saigo, K.; Takazawa, O. *Ibid.* **1976**, 1033–1036. (c) Inoue, T.; Uchimaru, T.; Mukaiyama, T. *Ibid.* **1977**, 153–154.

(4) (a) Scrutton, M. C. In *Inroganic Biochemistry*; Eichhorn, G. L., Ed.; Elsevier: Amsterdam, 1973; Vol. 1, Chapter 14. (b) Kluger, R. In *Bioorganic Chemistry*; van Tamelen, E. E., Ed.; Academic Press: New York, 1978; Vol. 4, Chapter 9. (c) Kaiser, E. T.; Sugimoto, T. *J. Am. Chem. Soc.* **1978**, *100*, 7750–7751.

(5) For the bifunctional catalysis of some primary–tertiary diamines in the α-hydrogen isotope exchange reactions of ketones, see: Hine, J.; Miles, D. E.; Zeigler, J. P. *J. Am. Chem. Soc.* **1983**, *105*, 4374–4379, and references cited therein.

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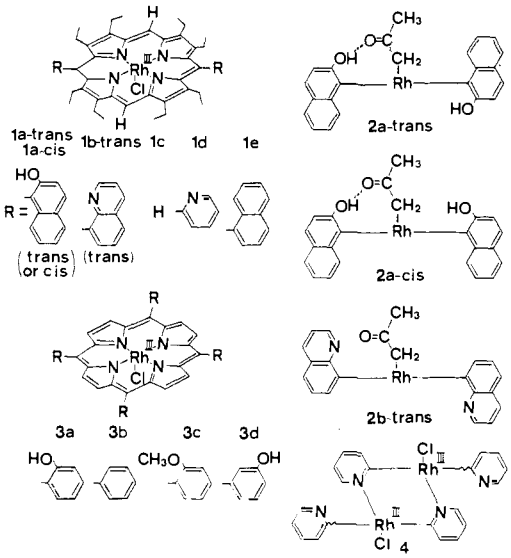
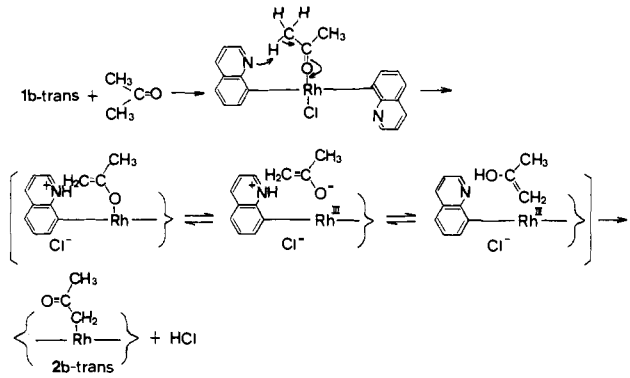


reacted with acetone at 50 °C for 6 h to give the α-metalation products **2a**-*trans* and **2a**-*cis* (in a schematic form),[7] which were identified on the basis of spectroscopic evidence in a similar manner as the corresponding rhodium–acetone complex of octaethylporphyrin (OEP) (**2c**).[8] The ^{1}H NMR and IR spectra of **2a**-*trans*[7] showed nonequivalent OH proton resonances at δ 5.58 (1 H) and 7.58 (1 H) and ν_{CO} at 1660 cm^{-1} as compared respectively with the OH proton resonances for the free base porphyrin at 5.23 (2 H)[6a] and ν_{CO} for **2c** at 1675 cm^{-1}.[8] A large (~2 ppm) downfield shift of one OH proton and a shift to lower wavenumber by 15 cm^{-1} in ν_{CO} are consistent with an intramolecular hydrogen bonding between CO and nearby OH groups in **2a**-*trans*. The metalation product with **1a**-*cis* (**2a**-*cis*) showed a single OH proton resonance at 6.18 (2 H) and ν_{CO} at 1660 cm^{-1} indicative of hydrogen-bonding interaction,[9] thus suggesting that the alkylation

Scheme I



took place only at one side of the porphyrin plane having the OH groups. Acetone was metalated also with tetrakis(2-hydroxyphenyl)porphyrin complex (**3a**).[6,10] Chlororhodium(III) complex of *trans*-5,15-di(8-quinolyl)OEP (**1b**-*trans*)[6] reacted with acetone even at 25 °C for 24 h to give the corresponding metalation product (**2b**-*trans*).[11] The presence of phenolic hydroxyl or quinolyl nitrogen is essential for the present metalation of acetone since OEP (**1c**), tetraphenylporphyrin (TPP, **3b**), and (5,15-dinaphthyl)OEP (**1e**)[6] complexes lacking these groups show no reactivity at all toward acetone unless the coordinating chloride ions are removed from the rhodium centers by use of $AgClO_4$.[8]

The general mechanism for α-substitution reactions of ketone involves preenolization of substrate ketone. This suggests that the role of essential phenolic OH or quinolyl nitrogen is that of a Brønsted base to promote enolization of acetone in cooperation with the central Rh(III) as a Lewis acid as shown in Scheme I for the conversion of **1b** to **2b**. The role of phenolic OH might be that of an acid. This is, however, not the case; tetramethoxy derivative (**3c**)[6] was found to be still active in the metalation of acetone, although its reactivity is significantly smaller than that of **3a**. Control runs showed that no metalation of acetone with **1c** took place in the presence of an equimolar amount of **1a**-*trans* (which itself was converted to **2a**-*trans*) or free base porphyrin of **1a** or **1b**. These results, taken in conjunction with the side-selective alkylation of **1a**-*cis* to give **2a**-*cis*, indicate that the cooperation of basic and metal centers with acetone between them is an intramolecular event (Scheme I). Examination of the CPK molecular models suggests that such an arrangement is feasible for **1a**, **1b**, and **3a** but not for tetrakis(3-hydroxyphenyl)porphyrin complex (**3d**),[6] in which the basic and metal centers are too remote. In accord with this, **3d** showed no reactivity toward acetone at all. If there is no steric restraint, on the other hand, the acid and base fragments readily combine with each other to give a neutralization product in which the individual reactivities are lost; e.g., intermolecular reaction of **1c** or **3b** and pyridine readily gave the corresponding pyridyl–rhodium(III) complex, which showed no reactivity in the metalation of acetone. 5,15-Di(2-pyridyl)OEP complex (**1d**)[6] provides another case of deactivation via neutralization; **1d** seemed to be closely related to **1b**, but it showed little reactivity toward acetone. A difference in **1b** and **1d** lies in the direction of lone-pair electrons of the quinolyl and pyridyl nitrogen. In **1d** they are directed "upward", and it has been shown that **1d** forms an intermolecular dimer (**4**, in a schematic representation).[6b] In **1b**, on the other hand, the direction of nitrogen lone-pair electrons and the axial coordination axis are perpendicular to each other, allowing neither intramolecular nor intermolecular coordination interaction. In fact, the electronic spectra of **1a**, **1b**, and **1e** were essentially identical,[6] and the ^{1}H NMR

(6) Prepared by rhodium incorporation ($[Rh(CO)_2Cl]_2$/benzene or $[Rh(CO)_2Cl]_2/CH_3CO_2Na/CH_3CO_2H$) into the corresponding free base porphyrins followed by oxidation of the resulting Rh(I) complexes and purified by means of chromatography (cf. Aoyama, Y.; Yoshida, T.; Sakurai, K.; Ogoshi, H. *Organometallics* **1986**, *5*, 168–173): yield, R_f (silica TLC) (eluant; DCM = CH_2Cl_2 and EA = $CH_3CO_2C_2H_5$), λ_{max} (CH_2Cl_2) are 48%, 0.09 (DCM), 417, 531, 564 nm for **1a**-*trans*; 40%, 0.78 (DCM-EA (5:1)), 417, 531, and 564 nm for **1a**-*cis*; 10%, 0.44 (DCM-EA (5:1)), 416, 530, and 560 nm for **1b**-*trans*; 21%, 0.71 (DCM-EA (7:3)), 414, 543, and 577 nm for **1d**; 50%, 0.91 (DCM-EA (10:1)), 417, 531, and 564 nm for **1e**; 40%, 0.23–0.05 (DCM-EA (5:2)), 421 and 532 nm for **3a** as a mixture of atropisomers; 56%, 0.55–0.23 (DCM-EA (10:1)), 421 and 532 nm for **3c** as a mixture of atropisomers; 32%, 0.21 (DCM-EA (5:2)), 422 and 533 nm for **3d**. All the Rh(III) complexes gave the ^{1}H NMR spectra (270 MHz) consistent with the structures. For free base porphyrins, see: (a) Ogoshi, H.; Saita, K.; Sakurai, K.; Watanabe, T.; Toi, H.; Aoyama, Y.; Okamoto, Y. *Tetrahedron Lett.* **1986**, *27*, 6365–6368. (b) Aoyama, Y.; Kamohara, T.; Yamagishi, A.; Toi, H.; Ogoshi, H. *Ibid.* **1987**, *28*, 2143–2146. (c) Ogoshi, H.; Sugimito, H.; Nishiguchi, T.; Matsuda, Y.; Yoshida, Z. *Chem. Lett.* **1978**, 29–32. (d) Momenteau, M.; Mispelter, J.; Loock, B.; Bisagni, E. *J. Chem. Soc., Perkin Trans. 1* **1983**, 189–196.

(7) The reaction mixture was chromatographed on silica gel with $CHCl_3$ as eluant to give the product (**2a**-*trans* or **2a**-*cis*), which was recrystallized from CH_2Cl_2–hexane. Further elution with $CHCl_3$–$CH_3CO_2CH_2CH_3$ (5:1) afforded unreacted starting maerial (**1a**-*trans* or **1a**-*cis*, ca. 30%). **2a**-*trans*: yield 53% (>90% based on **1a**-*trans* consumed); R_f (CH_2Cl_2) 0.61; δ ($CDCl_3$) 12.23 (meso-H, 2 H), 8.30–6.39 (naphthyl H, 12 H), 7.58 and 5.58 (OH, each 1 H, disappeared on deuteriation), 3.90, 2.77, and 2.50 (CH_2CH_3, 16 H in a ratio of 2:1:1), 1.80 and 0.90 (CH_2CH_3, 24 H in a ratio of 1:1), −1.85 (Rh–CH_2COCH_3, 3 H), −4.67 (Rh–CH_2COCH_3, 2 H, J_{Rh-H} = 4 Hz); λ_{max} (CH_2Cl_2) 410, 526, 557 nm; ν_{CO} 1660 cm^{-1}. **2a**-*cis*: yield 49% (>90% based on **1a**-*cis* consumed); R_f (CH_2Cl_2) 0.30; δ 10.23 (meso H, 2 H), 8.28–7.09 (naphthyl H, 12 H), 6.18 (OH, 2 H, disappeared on deuteriation), 3.89, 2.72, and 2.49 (CH_2CH_3, 16 H in a ratio of 2:1:1), 1.80 and 0.91 (CH_2CH_3, 24 H in a ratio of 1:1), −1.82 (Rh–CH_2COCH_3, 3 H), −4.67 (Rh–CH_2COCH_3, 2 H, J_{Rh-H} = 4 Hz); λ_{max} 410, 525, 557 nm; ν_{CO} 1660 cm^{-1}.

(8) (a) Aoyama, Y.; Yoshida, T.; Ogoshi, H. *Tetrahedron Lett.* **1985**, *26*, 6107–6108. (b) Aoyama, Y.; Tanaka, Y.; Yoshida, T.; Toi, H.; Ogoshi, H. *J. Organomet. Chem.*, in press.

(9) The single NMR signal suggests a rapid rotation of the acetone moiety which results in averaging of the resonances for the hydrogen bonded and free OH protons.

(10) The reaction of **3a** and acetone at 50 °C for 6 h afforded the metalation product in 21% yield together with **3a** unreacted.

(11) **2b**-*trans*: yield 40% (>90% based on **1b**-*trans* consumed); R_f (CH_2Cl_2–$CH_3CO_2CH_2CH_3$ (1:1) 0.33; δ ($CDCl_3$) 10.12 (meso H, 2 H), 8.67–7.40 (quinolyl H, 12 H), 3.90, 2.61, and 2.29 (CH_2CH_3, 16 H in a ratio of 2:1:1), 1.80 and 0.85 (CH_2CH_3, 24 H in a ratio of 1:1), −1.91 (Rh–CH_2COCH_3, 3 H), −4.76 (Rh–CH_2COCH_3, 2 H, J_{Rh-H} = 4 Hz); λ_{max} 414, 527, 558 nm.

spectra of **1a** and **1b** showed no abnormality which may arise from their intermolecular aggregation.

The present study demonstrates a novel, intramolecular cooperation of otherwise weak Brønsted base and Lewis acid in the bifunctional activation of a simple ketone under mild conditions. The efficient cooperation arises from a rigid steric restraint imposed on the basic and metal centers, which forces them in proximity but prevents their direct interaction. The present finding is significant for the development of catalytic organic reactions under neutral and mild conditions since so many organic reactions are subject to catalysis by acid and base, and the concerted acid-base catalysis is one of the general mechanisms by which the enzymes catalyze biological reactions.

Acknowledgment. This work was supported by a Grant-in-Aid for Special Project Researches from the Ministry of Education, Science, and Culture of Japan.

Novel Photoinduced Carbon-Carbon Bond Formation via Metal-Alkyl and -Enolate Porphyrins—Visible Light-Mediated Polymerization of Alkyl Methacrylate Catalyzed by Aluminum Porphyrin

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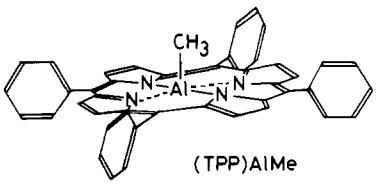
Photocatalysis with metalloporphyrin has been studied mainly in connection with biological photosynthesis. Electron transfer from excited metalloporphyrin to an acceptor resulting in charge separation, eventually leading to hydrogen evolution from water, has been the subject of much interest.[1] In the present communication, we report an unprecedented type of the photocatalysis with metalloporphyrin, in which the formation of carbon-carbon bonds proceeds by the effect of visible light. The reaction is the polymerization of alkyl methacrylate catalyzed by (tetraphenylporphinato)aluminum methyl ((TPP)AlMe)[2] upon irradiation with visible light to give a polymer of narrow molecular weight distribution.



(TPP)AlMe

For example, to a 50-cm^3 flask containing 0.4 mmol of (TPP)AlMe (16-cm^3 CH_2Cl_2 solution) was added 100-fold of methyl methacrylate (4.3 cm^3) through a three-way stopcock by a syringe in dry nitrogen atmosphere. The flask was illuminated by a 300-W xenon arc lamp from a distance of 25 cm through a glass filter to cut out light of wavelength shorter than 420 nm and thermostated at 30 °C. Within an hour the reaction mixture turned from bluish purple to brownish purple. After 12 h, an excess of methanol was added, and the volatile materials were removed under reduced pressure to leave the product, which was identified as poly(methyl methacrylate) by ^{13}C NMR.[3] The polymer could be separated from the residual catalyst by dissolving the product in acetone followed by filtration.

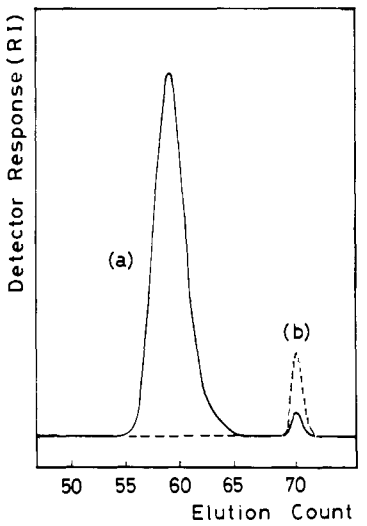


Figure 1. GPC profile (in THF) of the reaction mixture of methyl methacrylate with (TPP)AlMe (100/1). Reaction in benzene, 30 °C, 13 h: (a) upon irradiation, conversion = 43%, $\bar{M}n$ = 3960, $\bar{M}w/\bar{M}n$ = 1.19 and (b) in the dark.

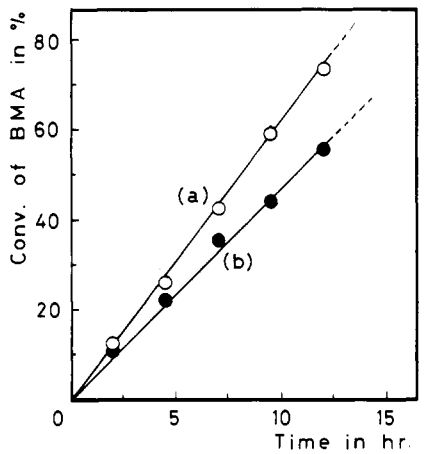


Figure 2. Block copolymerization of butyl methacrylate (BMA) from the living polymer of methyl methacrylate ($\bar{M}n$ = 9100) prepared with (TPP)AlMe (100/100/1), in CH_2Cl_2 15 °C: (a) upon irradiation and (b) in the dark.

It is of particular interest to note that the reaction did not substantially proceed in the dark, as exemplified in the gel permeation chromatogram (GPC) of the reaction mixture (Figure 1). A unimodal, sharp peak of the polymer is observed for the light-induced reaction, while the reaction mixture in the dark only shows the peak corresponding to the porphyrin. Figure 1 also demonstrates the very narrow molecular weight distribution of the polymer formed. The ratio of the weight average to number average molecular weights ($\bar{M}w/\bar{M}n$), as estimated from the GPC by using polystyrene as standard, ranged from 1.06 to 1.20. $\bar{M}n$ as determined by vapor pressure osmometry (VPO) was in good agreement with the value calculated on the basis of the ratio of the monomer to (TPP)AlMe and conversion; for example, for the product from methyl methacrylate/(TPP)AlMe = 200:1 at 100% conversion, $\bar{M}n$(VPO) = 19 960, $\bar{M}n$(calcd) = 20 040. This behavior indicates the "living" character of the present polymerization reaction.[4]

In accordance with this, block copolymer with narrow molecular weight distribution could be prepared with a quantitative efficiency by the addition of butyl methacrylate to the living prepolymer

(1) For example, (a) Handman, J.; Harriman, A.; Porter, G. *Nature (London)* **1984**, *307*, 534. (b) Okura, I.; Takeuchi, M.; Kim-Thuan, N. *Chem. Lett.* **1980**, 765.

(2) (TPP)AlMe was prepared by the equimolar reaction between 5,10,15,20-tetraphenylporphine and trimethylaluminum in benzene or in methylene chloride, see: Inoue, S.; Takeda, N. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 984.

(3) C=O (δ 178-177 ppm), CH_2 (δ 55-53 ppm), OCH_3 (δ 51 ppm), $-CH_2-CMe(CO_2Me)-$ (δ 45-44 ppm), CH_3 (δ 21-16 ppm) in $CDCl_3$.

(4) For the living polymerization of alkyl methacrylate: (a) Webster, O. W.; Hertler, W. R.; Sogah, D. Y.; Farnham, W. B.; RajanBabu, T. V. *J. Am. Chem. Soc.* **1983**, *105*, 5706. (b) Allen, R. D.; McGrath, J. E. *Am. Chem. Soc., Polymer Preprints* **1984**, *25*(2), 9. (c) Hatada, K.; Ute, K.; Tanaka, K.; Kitayama, T.; Okamoto, Y. *Polym. J.* **1985**, *17*, 977.

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