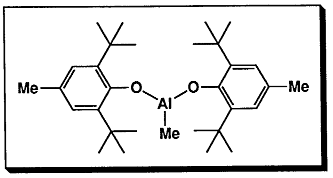
NOTES *Bull. Chem. Soc. Jpn.*, ***63***, *3354—3355 (1990)* [Vol. 63, No. 11

Selective Separation of Structurally or Electronically Similar Ethers with MAD

Keiji MARUOKA, Sigeru NAGAHARA, and Hisashi YAMAMOTO*
Department of Applied Chemistry, Faculty of Engineering, Nagoya University,
Chikusa, Nagoya 464-01
(Received June 11, 1990)

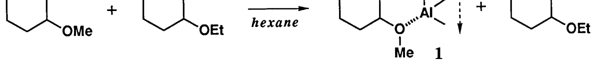
Synopsis. Selective separation of the less hindered or electronically more labile of two different ethers has been accomplished with exceptionally bulky, Lewis acidic MAD by the yield of precipitates as selective Lewis acid-base complexes.

We recently described the binding behavior of the exceptionally bulky, oxygenophilic methylaluminum bis(2,6-di-*t*-butyl-4-methylphenoxide) (MAD) as a Lewis acidic receptor for recognition of structurally or electronically similar ether substrates based on the selective Lewis acid-base complex formation.[1,2] Since the separation of structurally or electronically very similar ethers cannot be easily accomplished by the ordinary separation technique such as distillation, recrystallization, and silica-gel chromatography,[3] we are interested in the possibility of effecting the purification of such ether substrates by applying our recognition chemistry. Here we wish to report the successful purification of structurally or electronically very similar ethers by the selective separation of the less hindered or electronically more labile of two different ethers with exceptionally bulky MAD by the yield of precipitates as selective Lewis acid-base complexes.

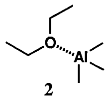


(MAD)

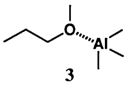
The 125 MHz ^{13}C NMR measurement of a mixture of 1 equiv each of MAD, cyclohexyl methyl ether and cyclohexyl ethyl ether in CD_2Cl_2 (0.4 M solution, $1\,M=1\,mol\,dm^{-3}$) at −90 °C showed the virtually complete recognition between the methyl and ethyl ethers with MAD giving Lewis acid-base complex **1** exclusively.[1] At higher temperature, however, facile decomplexation of **1** by ligand exchange with the ethyl ether was observed by ^{13}C NMR spectroscopy. In contrast, when an equimolar mixture of cyclohexyl methyl ether and cyclohexyl ethyl ether was treated with MAD (1 equiv) in hexane at room temperature for 1 h, a white precipitate gradually formed.[4] This precipitate was dissolved by addition of more hexane and recrystallized at room temperature for 5 h to furnish MAD-methyl ether complex **1** (68% yield) exclusively, which has been characterized by elemental analysis, ^{1}H and ^{13}C NMR spectroscopy. This complex **1** shows downfield shifts in the ^{1}H NMR spectrum for the ethereal α-methyl and α-methine protons, when compared to the "free" ether, consistent with coordination of the ether to aluminum. The pure cyclohexyl methyl ether can be generated upon acid hydrolysis of **1**. Under similar conditions, MAD-diethyl ether, MAD-methyl propyl ether, and MAD-THF complexes, **2**—**4**, can be selectively generated as white crystals from the combination of two different ethereal substrates: diethyl ether and ethyl vinyl ether, methyl propyl ether and *t*-butyl methyl ether, tetrahydrofuran and 2-methyltetrahydrofuran, or tetrahydrofuran and tetrahydropyran.



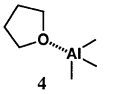
ether-MAD complex as a white precipitate



2



3



4

In conclusion, the present method demonstrates an effective way to purify not only these simple ethers but also a variety of structurally or electronically very similar ether substrates in the segment synthesis of polyether natural products.[5]

Experimental

The IR spectra were measured on a Hitachi 260-10 spectrometer. The ^{1}H NMR spectra were recorded on a Varian Gemini-200 spectrometer, using TMS (tetramethylsilane) as an internal standard. Splitting patterns are indicated as s, singlet; t, triplet; q, quartet; m, multiplet. Melting points are not corrected. The microanalysis was performed at the Elemental Analyses Center of Kyoto University. All experiments were carried out under an atmosphere of dry argon.

In experiments requiring dry solvents, dichloromethane, hexane, and toluene were freshly distilled before use. Diethyl ether, tetrahydrofuran (THF), and tetrahydropyran (THP) were freshly distilled from sodium metal using diphenylketyl as indicator. Trimethylaluminum was obtained from Toso-Akzo Chemical Co., Ltd., Japan. Other simple chemicals were purchased and used as such.

Preparation and Purification of Methylaluminum Bis(2,6-di-*t*-butyl-4-methylphenoxide) (MAD):[6] To a solution of 2,6-di-*t*-butyl-4-methylphenol (13.22 g, 60 mmol) in degassed hexane (40 mL) was added a 2 M hexane solution of Me_3Al (15 mL, 30 mmol) at room temperature. The white precipitate appeared immediately. After 1 h, this mixture was heated until the precipitate redissolved in hexane. The resulting solution was allowed to stand for 3 h and yielded colorless crystal which was filtered in an argon box. Since the crystal includes some impurities such as 2,6-di-*t*-butyl-4-methylphenol and inorganic aluminum salts, this was further recrystallized from hexane (45 mL) at −20 °C to give essentially pure MAD (7.83 g, 54% yield): ^{1}H NMR ($CDCl_3$) δ=7.04 (4H, s, C_6H_2), 2.28 (6H, s, CH_3), 1.53 (36H, s, $C(CH_3)_3$), −0.35 (3H, s, Al-CH_3); ^{13}C NMR ($CDCl_3$) δ=152.02, 138.19, 127.71, 125.94, 34.94, 31.56, 21.40, −9.09 (Al-$\underline{C}H_3$).

Selective Synthesis of Cyclohexyl Methyl Ether-MAD Complex (1) from a Mixture of Cyclohexy Methyl Ether and Cyclohexyl Ethyl Ether with MAD: A mixture of cyclohexyl methyl ether and cyclohexyl ethyl ether (0.4 mmol each) was added to MAD (0.4 mmol) in hexane (0.5 mL) at room temperature. A white precipitate gradually formed over a period of 1 h. This mixture was heated and diluted with more hexane (1.5 mL) until the precipitate redissolved. The resulting solution was allowed to stand at room temperature for 3 h to furnish, after filtration, cyclohexyl methyl ether-MAD complex (**1**) (158 mg, 68% yield) as white crystals: mp 36—38 °C; ^{1}H NMR ($CDCl_3$) δ=6.95 (4H, s, C_6H_2), 4.2—4.4 (1H, m, CH-O), 3.54 (3H, s, OCH_3), 2.23 (6H, s, CH_3), 1.11—2.05 (10H, m, CH_2), 1.36 (36H, s, $C(CH_3)_3$), −0.28 (3H, s, Al-CH_3); ^{13}C NMR ($CDCl_3$ at −50 °C) δ=154.56, 137.95, 125.76, 125.41, 84.66, 53.07, 35.05, 32.48, 31.13, 29.03, 24.78, 21.20, −3.44 (Al-$\underline{C}H_3$). Anal. Calcd for $C_{38}H_{63}O_3Al$: C, 76.72; H, 10.67%. Found: C, 75.80; H, 10.89%.

Selective Synthesis of Diethyl Ether-MAD Complex (2) from a Mixture of Diethyl Ether and Ethyl Vinyl Ether with MAD: To MAD (0.4 mmol) in hexane (0.5 mL) was added a mixture of diethyl ether and ethyl vinyl ether (0.4 mmol each) at room temperature. A white precipitate gradually formed over a period of 1 h. This mixture was heated and diluted with more hexane (0.5 mL) until the precipitate redissolved. This was allowed to stand at room temperature for 3 h to furnish, after filtration, diethyl ether-MAD complex (**2**) (178 mg, 80% yield) as white crystals: mp 60 °C; ^{1}H NMR ($CDCl_3$) δ=6.98 (4H, s, C_6H_2), 4.18 (4H, q, J=6.9 Hz, CH_2-O), 2.25 (6H, s, CH_3), 1.39 (36H, s, $C(CH_3)_3$), 1.27 (6H, t, J=6.9 Hz, O-C-CH_3), −0.27 (3H, s, Al-CH_3); ^{13}C NMR ($CDCl_3$ at −50 °C) δ=154.42, 137.89, 125.79, 125.42, 64.67, 35.00, 31.04, 21.24, 11.38, −3.47 (Al-$\underline{C}H_3$). Anal. Calcd for $C_{35}H_{59}O_3Al$: C, 75.77; H, 10.72%. Found: C, 74.98; H, 10.92%.

Selective Synthesis of Methyl Propyl Ether-MAD Complex (3) from a Mixture of Methyl Propyl Ether and *t*-Butyl Methyl Ether with MAD: To MAD (0.4 mmol) in hexane (0.5 mL) was added a mixture of methyl propyl ether and *t*-butyl methyl ether (0.4 mmol each) at room temperature. A white precipitate gradually formed over a period of 1 h. This mixture was heated until the precipitate redissolved. On standing at room temperature for 3 h, methyl propyl ether-MAD complex (**3**) was formed in 60% yield (133 mg) as white crystals after filtration: mp 51—52 °C; ^{1}H NMR ($CDCl_3$) δ=6.96 (4H, s, C_6H_2), 4.03 (2H, t, J=6.9 Hz, CH_2-O), 3.64 (3H, s, OCH_3), 2.24 (6H, s, CH_3), 1.75 (2H, m, $CH_3C\underline{H}_2$), 1.36 (36H, s, $C(CH_3)_3$), 0.85 (3H, t, J=7.5 Hz, CH_3), −0.27 (3H, s, Al-CH_3); ^{13}C NMR ($CDCl_3$ at −50 °C) δ=154.44, 137.80, 125.83, 125.45, 76.87, 59.97, 35.00, 30.95, 21.21, 19.02, 9.24, −3.82 (Al-$\underline{C}H_3$). Anal. Calcd for $C_{35}H_{59}O_3Al$: C, 75.77; H, 10.72%. Found: C, 74.08; H, 10.85%.

Selective Synthesis of THF-MAD Complex (4) from a Mixture of THF and 2-Methyltetrahydrofuran with MAD: To MAD (0.4 mmol) in hexane (0.5 mL) was added a mixture of THF and 2-methyltetrahydrofuran (0.4 mmol each) at room temperature. A white precipitate gradually formed over a period of 1 h. This mixture was heated and diluted with more hexane (4.5 mL) until the precipitate redissolved. This was allowed to stand at room temperature for 3 h to furnish, after filtration, THF-MAD complex (**4**) (138 mg, 63% yield) as white crystals: mp 56—57 °C; ^{1}H NMR ($CDCl_3$) δ=6.97 (4H, s, C_6H_2), 4.25 (4H, m, CH_2-O), 2.24 (6H, s, CH_3), 1.98 (4H, m, CH_2), 1.38 (36H, s, $C(CH_3)_3$), −0.31 (3H, s, Al-CH_3); ^{13}C NMR ($CDCl_3$ at −50 °C) δ=154.47, 137.78, 125.87, 125.28, 73.23, 35.07, 30.98, 25.10, 21.30, −3.97 (Al-$\underline{C}H_3$). Anal. Calcd for $C_{35}H_{57}O_3Al$: C, 76.04; H, 10.39%. Found: C, 75.82; H, 10.59%.

Selective Synthesis of THF-MAD Complex (4) from a Mixture of THF and THP with MAD: To MAD (0.4 mmol) in hexane (0.5 mL) was added a mixture of THF and THP (0.4 mmol each) at room temperature. A white precipitate gradually formed over a period of 1 h. This mixture was heated with more hexane (4.5 mL) until the precipitate redissolved. This was allowed to stand at room temerature for 3 h to funish, after filtration, THF-MAD complex (**4**) (114 mg, 53% yield) as white crystals. The analytical and physical data are listed above.

References

1) K. Maruoka, S. Nagahara, and H. Yamamoto, *J. Am. Chem. Soc.*, **112**, 6115 (1990).

2) For recognition of two different ketones with MAD, see: K. Maruoka, Y. Araki, and H. Yamamoto, *J. Am. Chem. Soc.*, **110**, 2650 (1988).

3) D. W. Mayo, R. M. Pike, and S. S. Butcher, "Microscale Organic Laboratory," John Wiley & Sons, New York (1986).

4) Attempted recrystallization with more polar solvents such as toluene or CH_2Cl_2 was unsuccessful.

5) W. Wierenga, "The total Synthesis of Natural Products," ed by J. ApSimon, John Wiley & Sons, New York, N. Y. (1981), Vol. 4, p. 263.

6) K. B. Strarowieyski, S. Pasynkiewicz, and M. Skowronska-Ptasinska, *J. Organomet. Chem.*, **90**, C43 (1975).