results in decomposition to multiple products including BHT-H.

Addition of excess NH_3 to a toluene-d_8 solution of **1** (3.4×10^{-2} M) at room temperature results in the formation of an apparent 1:2 complex, "$AlMe_2(BHT)(NH_3)_2$", as indicated by ^1H NMR spectroscopy. The chemical shift of the coordinated NH_3 proton is upfield of that observed for **1** [0.52 ppm vs 1.10 ppm (**1**)]. Given that uncoordinated NH_3 has a ^1H shift, in toluene-d_8 solution, of 6.98 ppm, this upfield shift is counter to that expected if a degenerate exchange between free and coordinated NH_3 were present in solution (eq 6). As the NMR sample is cooled to −40

$$AlMe_2(BHT)(NH_3) + {}^*NH_3 \rightleftharpoons AlMe_2(BHT)({}^*NH_3) + NH_3 \quad (6)$$

°C, the resonance due to "coordinated" NH_3 broadens ($W_{1/2}$(max) = 216 Hz), increases in intensity, and moves further upfield. Between 10 and −5 °C the ^1H NMR spectrum indicates that an assembly of coordination complexes occurs, finally resulting in a single resonance ($W_{1/2}$(max) = 13 Hz) becoming sharper with a constant chemical shift (0.13 ppm) and an integration consistent with an extended coordination sphere complex $AlMe_2(BHT)(NH_3)_x$ ($13 \leq x \leq 15$).[16] This complex formation is irreversible, since no dissociation occurs upon warming to room temperature, although the resonance for the "coordinated" NH_3 becomes sharper ($W_{1/2}$ = 12 Hz). In fact the composition is retained for at least 24 h before significant decomposition of the sample occurs, primarily through formation of BHT-H. Removal of the solvent and excess NH_3 under vacuum results in the reisolation of **1**.

We have previously shown that the ^1H NMR chemical shift of an aluminum–methyl group is a highly sensitive probe to changes in the coordination environment around aluminum.[17] In the present case, however, no change is observed for the Al–CH_3 of **1** in the presence of excess NH_3, at or below room temperature. This suggests that there is no change in the aluminum coordination number. Further conformation of this is demonstrated by the ^{27}Al NMR spectrum, which remains essentially constant, consistent with a four-coordinate aluminum. The ^{14}N NMR spectrum of **1** consists of a single resonance (91 ppm, $W_{1/2}$ = 4200 Hz). In the presence of excess NH_3, at room temperature, this is replaced by a broad resonance (136 ppm, $W_{1/2}$ = 1500 Hz), in addition to the peak for uncoordinated NH_3 (−385 ppm $W_{1/2}$ = 1000 Hz).

Given the above data, we propose the formation of a hydrocarbon-soluble extended coordination sphere complex, $AlMe_2(BHT)(NH_3)_x$, in which aggregation does not take place within the aluminum first coordination sphere.[18] We note that polyammonia solvates have been observed, especially in liquid NH_3,[19] but this is to our knowledge a rare example of such a complex which is formed in hydrocarbon solution and is stable at room temperature, although hydrogen-bonding outer sphere has previously been observed for a number of transition-metal coordination complexes.[20]

Acknowledgment. Financial support of this work is provided by the donors of the Petroleum Research Fund, administered by the American Chemical Society.

Supplementary Material Available: Tables of atomic positional and isotropic equivalent thermal parameters, anisotropic thermal parameters, and bond distances and angles for **1** (3 pages); listing of observed and calculated structure factors for **1** (9 pages). Ordering information is given on any current masthead page.

Catalytic Tail-to-Tail Dimerization of Methyl Acrylate Using Rh(III) Catalysts

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Adipic acid, an intermediate in nylon-66 production, is currently produced by oxidation of cyclohexane.[2] The catalytic tail-to-tail dimerization of acrylates (eq 1) represents an attractive alternate route to adipic acid from C_3 feedstocks and has received considerable attention.[3-5] The systems examined thus far exhibit

$$CH_2{=}CHCO_2R \xrightarrow{cat.} \underset{\textbf{1a} \text{ (trans)}; \textbf{1b} \text{ (cis)}}{RO_2CCH{=}CHCH_2CH_2CO_2R} + \underset{\textbf{2a} \text{ (trans)}; \textbf{2b} \text{ (cis)}}{RO_2CCH_2CH{=}CHCH_2CO_2R} \quad (1)$$

one or more drawbacks including short catalyst lifetime (low total turnover numbers), low turnover frequencies, formation of branched (head-to-tail) dimers and oligomers, and a requirement for high temperatures. We report here a catalyst system that dimerizes methyl acrylate at ambient temperatures, even in the absence of solvent, with very high tail-to-tail selectivity, high total turnover numbers, and good turnover frequency.

Initial attempts to achieve acrylate dimerization were based on the observation that $Cp^*(P(OMe)_3)Rh(C_2H_4)(H)^+$ (**3**) ($Cp^* = C_5Me_5$) catalyzes ethylene dimerization.[6] Treatment of **3** with methyl acrylate (MA, 34 equiv) in CD_2Cl_2 (25 °C) results in initial formation of the cyclic complex $Cp^*(P(OMe)_3Rh(CH_2CH_2CO_2Me)^+$ (**4**)[7] followed by slow tail-to-tail dimerization of MA (50% conversion after 100 h). Complex **4** was synthesized

(16) A signal for uncomplexed NH_3 remains present in the ^1H NMR spectrum at the lowest temperatures studied (−40 °C).

(17) Barron, A. R. *J. Chem. Soc., Dalton Trans.* **1988**, 3047.

(18) The possibility exists that either the ammonia hydrogens in **1** are sufficiently acidic to protonate ammonia or a dissociation of **1** occurs, both of these resulting in a solvated ionic complex. In both cases, significant changes in the chemical environment of the aluminum and/or the BHT ligand would be observed. However, the unchanging nature of the aluminum–methyl, BHT, and ^{27}Al NMR resonances would tend to discount either possibility.

$$AlMe_2(BHT)(NH_3) + NH_3 \rightarrow \{[NH_4][AlMe_2(BHT)NH_2](NH_3)_x\}$$

$$AlMe_2(BHT)(NH_3) \xrightarrow{NH_3} \{[AlMe_2(NH_3)](BHT)(NH_3)_x\}$$

(19) The insoluble polyammonia complexes $EtAlCl_2{\cdot}(NH_3)_x$ and $Et_2AlCl(NH_3)_x$ (x = 2–5) have been isolated but shown to be ionic, for example $[Et_2Al(NH_3)_2]^+Cl^-$. (a) Cohen, M.; Gilbert, J. K.; Smith, J. D. *J. Chem. Soc.* **1965**, 1092. (b) Gilbert, J. K.; Smith, J. D. *J. Chem. Soc. A* **1968**, 233. The polyammonia complexes $AlI_3{\cdot}(NH_3)_x$ (x = 6, 20) have been reported, but with no spectroscopic characterization. (c) Franklin, E. C. *J. Am. Chem. Soc.* **1915**, *37*, 847.

(20) See, for example: (a) Gudel, H. U.; Ludi, A.; Fischer, P.; Halg, W. *J. Chem. Phys.* **1970**, *53*, 1917. (b) Bailey, N. A.; McKenzie, E. D.; Worthington, J. M. *J. Chem. Soc., Dalton Trans.* **1973**, 1227. (c) Bertrand, J. A.; Howard, W. J.; Kalyamaraman, A. R. *J. Chem. Soc., Chem. Commun.* **1971**, 437. (d) Bertrand, J. A.; Helm, F. T. *J. Am. Chem. Soc.* **1973**, *95*, 8184. (e) Duggan, D. M.; Hendrickson, D. H. *Inorg. Chem.* **1974**, *13*, 1911.

(1) On leave from CNRS, URA322, Brest, France. Present address: Laboratoire de Chimie de Coordination du CNRS, 31077 Toulouse Cedex, France.

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(3) Rh-based catalysts: (a) Alderson, T. U.S. Patent 3013066, 1961. (b) Alderson, T.; Jenner, E. L.; Lindsey, R. V. *J. Am. Chem. Soc.* **1965**, *87*, 5638. (c) Nugent, W. A.; McKinney, R. J. *J. Mol. Catal.* **1985**, *29*, 65. (d) Singleton, D. M. U.S. Patent 4638084, 1987.

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(7) See supplementary material for synthesis and characterization.

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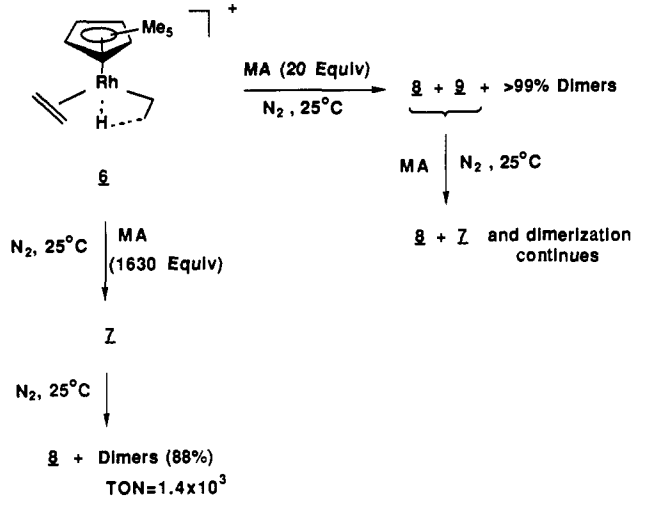
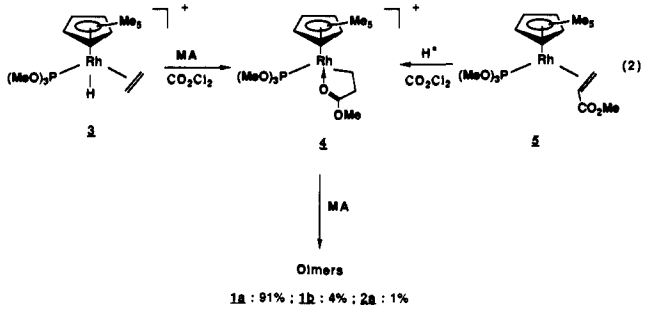
Scheme I



independently by protonation of $Cp^*(P(OMe)_3)Rh(CH_2{=}CHCO_2Me)$ (**5**)[7] (eq 2).



A much more reactive catalyst is generated when $Cp^*(C_2H_4)RhCH_2CH_2$-μ-H^+ (**6**)[8] is employed, in which $P(OMe)_3$ has been replaced by a labile ethylene ligand (see Scheme I). Thus when **6** is treated with 1630 equiv of MA (CH_2Cl_2, 25 °C), 79% conversion to dimers is achieved after 5 h. After 88% conversion (total turnover number (TON) = 1.4×10^3, 92% **1a**, 8% **1b**, traces of **2a**), the catalyst is no longer active. Monitoring the reaction by ^1H NMR spectroscopy reveals that **6** is rapidly and cleanly converted to a new species **7** with a Cp* ^1H resonance at 1.6 ppm (catalyst "resting state"). As dimerization proceeds, **7** slowly converts to a new species **8** with $\delta(Cp^*)$ = 1.7 ppm ("deactivated" catalyst). When **7** is totally depleted, dimerization ceases. Under these conditions, the maximum total turnover number that can be achieved with **6** alone is ca. 1500. When less than 100 equiv of MA was used, a new species, **9** ($\delta(Cp^*)$ = 1.53 ppm), appears at the end of the reaction (see Scheme I). Addition of MA to these solutions results in regeneration of **7** from **9**, and further catalytic dimerization ensues.

Both **8** and **9** have been isolated and identified.[7,9,10] Reaction of **6** with pure dimer gives a ca. 1:1 mixture of **8** and **9** which can be separated by fractional crystallization. Alternatively, **8** can be isolated from solutions of MA plus dimers after catalysis has ceased.

Scheme II

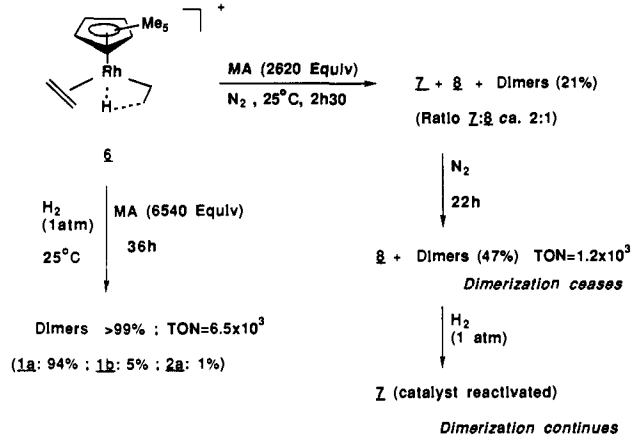
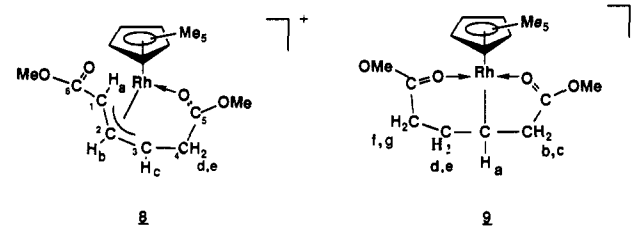


Table I. Catalytic Dimerization of Methyl Acrylate (MA) Using **6** under 1 atm of H_2

run[a]	equiv of MA/[Rh]	T, °C	time, h	% conv	TON[b]	ratio of MA dimers 1a:1b:2a
1	6540	25	2	12		85:15:0
			5	34		85:15:0
			13	77		87:13:0
			20	97		92:8:traces
			36	>99[c]	6.5×10^3	94:5:1
2	6540	60	1	65		89:11:0
			2	89		91:9:traces
			3	94	6.2×10^3	94:6:traces
	6540 additional		3	47		94:6:traces
	equiv of MA		4	55		94:6:traces
	added at		5	63		94:6:traces
	this point		6	70		94:6:traces
			22	>99[c]	1.3×10^4	93:6:1

[a] MA used contained 200 ppm MEHQ as stabilizer. Solutions were not degassed. [b] TON = total turnover number based on monomer MA. [c] Ca. 2% of $CH_3CH_2CO_2Me$ formed in addition to dimers.



Realizing that the inactive catalyst **8** corresponds to loss of H_2 from a rhodium complex of the dimer, we have successfully regenerated **7** (the catalyst resting state) by exposure of **8** to H_2 (1 atm) in the presence of MA. An informative sequence of experiments is shown in Scheme II.

A long-lived catalyst system can be simply generated by adding neat MA to **6** under 1 atm of H_2. A summary of two typical runs is given in Table I. Total turnover numbers of up to 1.3×10^4 have been achieved with >99% conversion of MA; clearly much higher total turnovers can be achieved. Selectivity is extremely high for tail-to-tail coupling (>99%, ca. 1–2% of methyl propionate is produced). The reaction can be run at 60 °C with a 10-fold increase in initial turnover rates (6.6 equiv of MA/min at 25 °C, 65 equiv of MA/min at 60 °C) without loss in selectivity or generation of side products.

This catalyst system is the most attractive system discovered to date for tail-to-tail dimerization of acrylates. We are continuing to develop this system and other analogues for dimerizations of acrylates and other substituted olefins.

(8) (a) Brookhart, M.; Lincoln, D. M.; Bennett, M. A.; Pelling, S. *J. Am. Chem. Soc.* **1990**, *112*, 2691. (b) Complex **6** has also been generated by protonation of $Cp^*Rh(C_2H_4)_2$ with $HB(C_6H_3(CF_3)_2)_4(Et_2O)_2$. This counterion increases solubility of salts of **6**, **7**, **8**, and **9**. Isolations of **8** and **9** were carried out by using this counterion.

(9) (a) **8**: ^1H NMR (400 MHz, CD_2Cl_2, 23 °C) δ 5.49 (ddd, J_{Ha-Hb} = 11 Hz, J_{Hc-Hb} = 8 Hz, J_{Rh-Hb} = 2 Hz, H_b), 4.70 (ddd, J_{Hb-Hc} = 8 Hz, J_{Hc-Ha} = 7.5 Hz, J_{Hc-He} = 2 Hz, H_c) 3.85 (s, CO_2CH_3) 3.82 (s, CO_2CH_3), 3.42 (dd, J_{Hd-Hc} = 7.5 Hz, J_{Hd-He} = 21 Hz, H_d) 3.11 (d, J_{Ha-Hb} = 11 Hz, H_a), 2.61 (dd, J_{He-Hd} = 21 Hz, J_{He-Hc} = 2 Hz, H_e), 1.70 (s, $C_5(CH_3)_5$). ^{13}C NMR data for **8** is summarized in the supplementary material. (b) Structure confirmed by X-ray analysis. Sabo-Etienne, S.; Brookhart, M.; White, P., unpublished results.

(10) Attempts to isolate **7** have been unsuccessful, and interference of resonances of methyl acrylate and dimers **1a**,**b** and **2a** has precluded NMR identification. The absence of a high-field signal indicates that **7** is not a rhodium hydride species. On the basis of the structure of **4**, a reasonable proposal for the structure of **7** is $Cp^*(CH_2{=}CHCO_2Me)Rh\overline{CH_2CH_2(O)}$-$OCH_3^+$.

Acknowledgement is made to the National Science Foundation (CHE-8705534) for support and to Johnson Matthey for a loan of $RhCl_3$. S.S.-E. acknowledges partial support from a CNRS-NSF grant.

Supplementary Material Available: A listing of the synthetic procedures used to prepare **4**, **5**, **8**, and **9**, ^1H and ^{13}C NMR spectral data for **4**, **5**, **8**, and **9**, and microanalytical data for **5** and **9** (5 pages). Ordering information is given on any current masthead page.

(+)-CC-1065 DNA Alkylation: Observation of an Unexpected Relationship between Cyclopropane Electrophile Reactivity and the Intensity of DNA Alkylation

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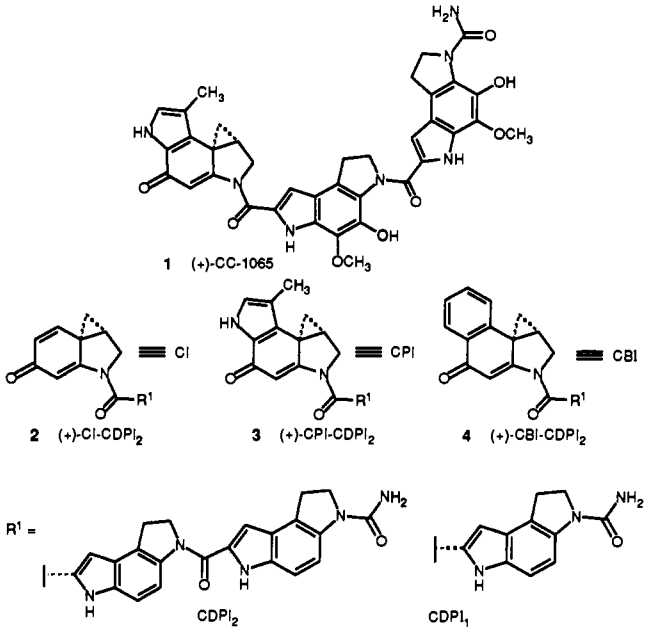
(+)-CC-1065 (**1**), a potent antitumor antibiotic and the subject of extensive investigations,[2-4] has been shown to exert its effects through the selective alkylation of DNA within the minor groove.[2-5] For (+)-CC-1065, the alkylation has been demonstrated to proceed by 3′-adenine N-3 alkylation of the electrophilic cyclopropane present in the left-hand (CPI) subunit within A-T-rich minor groove regions of DNA.[5,6] In an extensive evaluation of a series of agents possessing the natural enantiomer of the authentic alkylation subunit of (+)-CC-1065, the relative in vitro cytotoxic potency of the agents has been correlated with the relative intensity of the adenine N-3 alkylation with cell-free double-stranded DNA.[2,4,5] It has been further suggested that the cytotoxic potency of the agents may be a direct expression of their rate of DNA covalent alkylation[2] and directly related to the agent relative rate of acid-catalyzed solvolysis[4] by virtue of a sequence-dependent autocatalytic activation of the alkylation event by a strategically located phosphate (carbonyl protonation/complexation).[5] Thus, in the course of our investigations which have resulted in the preparation and evaluation of (+)-CPI-$CDPI_n$,[7-10] (+)-CI-$CPDI_n$,[6,11-13] and (+)-CBI-$CDPI_n$,[14-16] the observation that an inverse versus direct relationship between the solvolytic reactivity and cytotoxic potency of the agent may constitute a relevant relationship in the design of functional analogues has proven unexpected.[15,16] Herein, we detail the results of a comparative study of the DNA alkylation properties of (+)-CPI-$CDPI_2$ (**3**), (+)-CI-$CDPI_2$ (**2**), and (+)-CBI-$CDPI_2$ (**4**) representative of comparisons made with a full series of agents[17] which additionally demonstrate that the intensity of DNA alkylation follows *the same inverse relationship*: (+)-*CBI-CDPI*$_2$ > (+)-*CPI-CDPI*$_2$ > (+)-*CI-CDPI*$_2$.

Table I

	(+)-CBI-$CDPI_2$ (**4**)	(+)-CPI-$CDPI_2$ (**3**)	(+)-CI-$CDPI_2$ (**2**)
rel int (37 °C, 24 h) of DNA alkylation[a] (%)	1.1 (100%)	1.0 (100%)	0.6 (100%)
rel int (4 °C, 24 h) of DNA alkylation[a] (%)	1.0 (90%)	0.2 (20%)	0.02 (3%)
k (rel), 4 °C[b]	1.0	0.05	nd[e]
rel stability[c]	1.0	0.27	0.0001
rel in vitro cytotoxic act. (L1210)[d]	1.0	0.24	0.0005

[a] Relative intensity of alkylation (thermally induced strand cleavage) at the high-affinity alkylation site [5′-d(AATTA)-3′] within w794 DNA determined by using a scanning densitometer. Percent reaction (%) is expressed as the percentage of the total alkylation at this site observed when the alkylation is taken to >90% completion (37 °C, 24 h); the relative intensities of alkylation detectable at 10^{-8} M at this point are compared to (+)-**4** (4 °C, 24 h) = 1.0. [b] Relative first-order rate constants for DNA alkylation at the high-affinity site taken from plots of the intensity of DNA cleavage versus time (4 °C, 10^{-7} M agent; 12, 24, 48, 96, and 192 h). [c] Taken from refs 13, 15 and 16. Solvolysis studies conducted spectrophotometrically (UV) at pH = 3 (50% buffer–CH_3OH, buffer = 4:1:20 (v/v/v) 0.1 M citric acid, 0.2 M Na_2HPO_4, and H_2O). [d] Relative IC_{50} for in vitro cytotoxic activity against L1210 mouse lymphocytic leukemia, (+)-**2**, 10000 pM; (+)-**3**, 20 pM; (+)-**4**, 4.8 pM. [e] Not determined.



Singly 5′ ^{32}P end labeled double-stranded DNA constituting SV40 DNA nucleotides no. 5238-138 (144 base pairs) cloned into the *Sma*I site of M13mp10 was prepared by treatment of single-stranded templates (clone w794)[18] with 5′ ^{32}P end labeled universal primer [5′-d(GTAAAACGACGGCCAGT)-3′], extension of the primer-template duplex with the Klenow fragment of DNA polymerase I, and subsequent *Eco*RI cleavage of the double-stranded DNA immediately following the inserted DNA.

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(17) Similarly, the following trends in the intensity of DNA alkylation (4 °C, 24 h) and cytotoxic activity (L1210) have been observed: (+)-CBI-$CDPI_1$ (1, 5 pM) > (+)-CPI-$CDPI_1$ (0.2, 40 pM) > (+)-CI-$CDPI_1$ (24000 pM); (+)-CBI-$(indole)_2$ (1, 5 pM) > (+)-CPI-$(indole)_2$ (0.1, 20 pM).

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