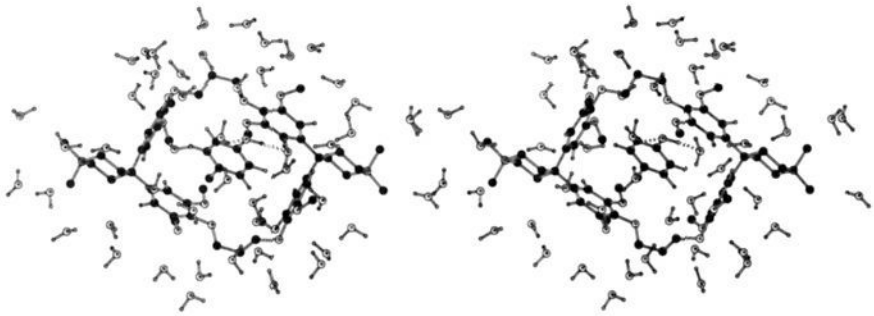

Figure 2. Stereoplot of the complex of host **1** with *p*-cresol oriented with the hydroxyl group hydrated. Water molecules within 3.5 Å of any solute atom are shown.

of **1**.[10] Included in the calculations for the complexes and isolated guests were 768 and 500 TIP4P water molecules,[11] respectively. All calculations were run at 298 K and 1 atm with ca. 10 Å energy cutoffs, periodic boundary conditions, and Metropolis sampling, as before.[4] A series of six or seven simulations was required to mutate gradually *p*-xylene to the other guests.[12] Each simulation had 1M to 4M configurations of equilibration, followed by 2M to 4M configurations of averaging. Solute variations were attempted every 20–25 configurations with changes in a random subset of internal coordinates.[13]

p-Xylene was first perturbed to hydroquinone. The calculated preference for binding *p*-xylene was 2.8 ± 0.3 kcal/mol, in good accord with the previous experimental result of 2.2 ± 0.2 kcal/mol (Table I).[2] On the basis of a notably exothermic ΔH_b and negative $T\Delta S_b$, it was proposed that an intracomplex hydrogen bond occurred between ether oxygens of host **2** and a hydroxyl group of hydroquinone.[3] This was confirmed in the calculations for **1**; the hydrogen bond primarily involves one of the ether oxygens in the macrocycle and requires that the phenolic hydrogen rotate 40–50° out of plane. This OH group is too buried to be hydrated, while the other hydroxyl has two hydrogen bonds with water molecules (Figure 1). Good accord was also obtained between theory and experiment for *p*-dicyanobenzene (Table I).

Subsequent perturbations to benzene predicted a 2.0 ± 0.2 kcal/mol preference for binding *p*-xylene. **1** was then prepared, and its binding constant with benzene was measured by ^{1}H NMR titrations in D_2O, as before.[2] The resultant ΔG_b of −2.69 ± 0.20 kcal/mol at 293 K implies weaker binding for benzene than *p*-xylene[2] by 1.5 ± 0.2 kcal/mol. The results for *p*-cresol proved particularly interesting. On the basis of the observed ΔH_b and $T\Delta S_b$ for **2** with *p*-cresol, it was also expected than an intracomplex hydrogen bond existed.[3] With evolution into this geometry, the computed $\Delta\Delta G_b$ was −2.8 ± 0.3 kcal/mol, favoring *p*-xylene. The NMR experiment was then performed; ΔG_b is −3.81 ± 0.10 kcal/mol, which gives $\Delta\Delta G_b$ = −0.4 ± 0.1 kcal/mol. The discrepancy prompted running the simulation with evolution into the geometry with the hydroxyl group hydrated (Figure 2), which yielded a $\Delta\Delta G_b$ of 0.1 ± 0.3 kcal/mol. Thus, the calculations make a clear choice for this orientation. Confirmation comes from the pattern of upfield induced ^{1}H NMR chemical shifts at saturation binding ($\Delta\delta_{sat}$) in *p*-cresol complexed to **1**, 1.29 ppm for the methyl group protons and 1.09 and 2.96 ppm for the protons ortho to the hydroxyl and methyl groups.

These observations cause us to reinterpret the origin of the anomalously exothermic ΔH_b and negative $T\Delta S_b$ for *p*-cresol and hydroquinone binding to **2**. Images as in Figure 2 suggest that the hydrated hydroxyl group of these guests helps nucleate an extended hydrogen-bonded network on the surface of the complex that yields enhanced hydration of the host's proximal ether groups and a lower ΔH_b. The participating water molecules are highly ordered to fit into the network and the host's crevices. A nonhydroxylic guest such as *p*-xylene also protrudes on one side of the host; the methyl group inhibits full formation of the network and leads to a less favorable ΔH_b, but more favorable $T\Delta S_b$.

Acknowledgment. This work was supported by the National Science Foundation and Office of Naval Research.

Supplementary Material Available: The OPLS parameters for the solutes and plots of the free energy changes for the mutations (7 pages). Ordering information is given on any current masthead page.

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Use of Cholestanylindene-Derived Nonbridged Group 4 Bent Metallocene/Methylalumoxane Catalysts for Stereoselective Propene Polymerization

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Brintzinger's C_2-symmetric group 4 *ansa*-metallocenes and related compounds[1] have brought remarkable progress to the use of homogeneous Sinn/Kaminsky type bent metallocene/alumoxane-derived Ziegler catalysts for stereoselective α-olefin polymerization.[2-4] An a priori assessment of nonbridged planarly

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(2) Sinn, H.; Kaminsky, W.; Vollmer, H.-J.; Woldt, R. *Angew. Chem.* **1980**, *92*, 396; *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 390. Review: Sinn, H.; Kaminsky, W. *Adv. Organomet. Chem.* **1980**, *18*, 99.
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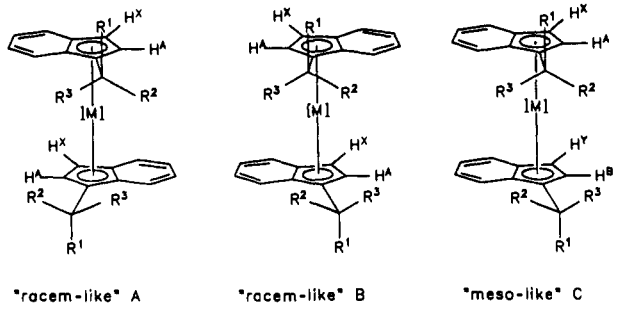
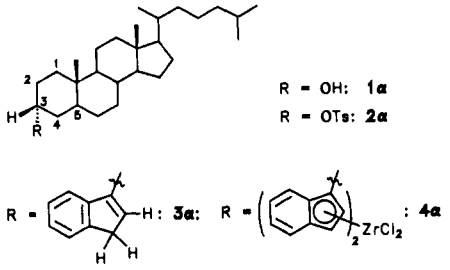
Scheme I



Scheme II



chiral substituted bis(indenyl)zirconium halide systems does not reveal fundamental stereochemical differences to the related *ansa*-metallocene systems aside from features associated with the metal–indenyl torsional potential. Therefore, we have investigated if a suitably substituted chiral nonbridged bis(indenyl)zirconocene halide can also serve as a component of a metallocene/alumoxane catalyst system for the production of isotactic polypropylene by means of enantiomorphic site control.[5] The presence of a pair of homochiral side chains at the 1-positions of the indenyl ligands may lead to the formation of a total of three diastereoisomers, namely two "racem-like" forms (A and B in Scheme I) and a "meso-like" congener (C). All three are chiral and should be formed in an enantiomeric excess determined by the optical purity of the chiral auxiliary R*–X used.[6]

We have realized this simple stereochemical concept by introducing 3-cholestanyl substituents at the 1-indenyl positions. 5α-Cholestan-3β-ol (**1β**) was transformed into the 3β-tosylate **2β**. S_N2 substitution by indenyllithium furnished 3-(5′α-cholestan-3′α-yl)indene (**3α**). The corresponding reaction sequence starting from 5α-cholestan-3α-ol (**1α**) gave the epimeric cholestanylindene **3β**. The hydrocarbon **3α** was deprotonated by treatment with *n*-butyllithium in hexane/THF and then reacted with 0.5 molar equiv of $ZrCl_4(THF)_2$ to give the bis[3′α-cholestanyl)indenyl]-zirconium dichlorides **4α**. The formation of the two racem-like isomers **4α**-A and **4α**-B is favored over their meso-like **4α**-C congener (**4α**-A:B:C ratio ≈ 40:55:5). Workup of the reaction mixture by extraction with pentane gave one racem-like diastereomer of **4α** ($[\alpha]_D = +85°$), admixed with ca. 5% of **4α**-C. The second racem-like diastereoisomer was recovered from dichloromethane in equal purity ($[\alpha]_D = -57°$). Each of the two racem-like isomers exhibits only one indene ^1H NMR methine hydrogen AX pattern at 6.06, 5.86 (^3J = 3.0 Hz) and 5.97, 5.91 (^3J = 3.0 Hz), respectively, whereas the meso-like **4α**-C shows four respective signals at δ 6.51, 6.33, 5.50, and 5.49.

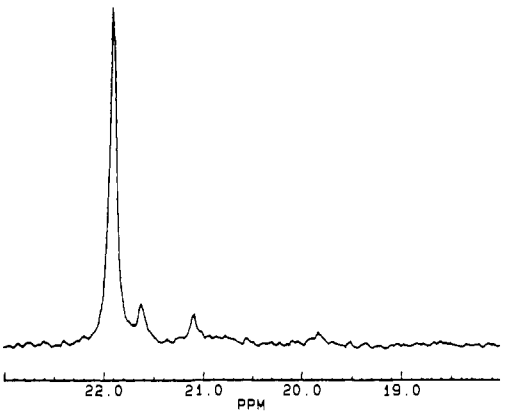


Figure 1. ^{13}C NMR methyl pentad signals of polypropylene (in 1,2,4-trichlorobenzene at 95 °C) obtained at −30 °C in toluene solution with the metallocene/alumoxane catalyst derived from the "racem-like" metallocene **4α**-B.

The three **4β** diastereomers were prepared analogously (**4β**-A:B:C ≈ 15:20:65). Meso-like **4β**-C [^1H NMR indene hydrogens at δ 6.35 (1 H), 6.27 (1 H), 5.34 (2 H); $[\alpha]_D = +11.6°$] was isolated from the reaction mixture by extraction with methylene chloride at ambient temperature. The mixture of the very poorly soluble racem-like isomers was recovered only after prolonged extraction with CH_2Cl_2 at reflux temperature.

Complex **4β**-C, the **4β**-A-B mixture, and the separate isomers **4α**-A and **4α**-B were used for generating the homogeneous Ziegler propene polymerization catalysts. In a typical experiment, the meso-like complex **4β**-C (17 μmol in 250 mL of toluene containing ca. 50 mL of propene at −30 °C[7]) was activated by methylalumoxane ([Al]/[Zr] ≈ 1080). Polypropylene ($\bar{M}_\eta \approx 240000$) was isolated (activity ≈ 160 [g PP/g Zr·h] and stereochemically characterized by ^{13}C NMR methyl pentad analysis[4,8,9] (~40% mmmm; ca. 70% enantiomorphic site control, the rest is due to chain end control).

The catalyst derived from the **4β**-A-B mixture produced a mixture of polymers (activity 230, averaged $\bar{M}_\eta \approx 170000$) which was fractionated[10] by extraction with cold pentane (15%) and boiling pentane (11%, both fractions were nearly atactic). The remaining fraction was analyzed as an isotactic polypropylene [ca. 55% controlled by the enantiomorphic site, $\langle m \rangle_{n,\alpha} \approx 16$ (= averaged length of isotactic units terminated by a singular "mistake"), and 45% by the chiral chain end, $\langle m \rangle_{n,\sigma} \approx 4$ (= averaged length of the isotactic blocks formally attributed in this double stereodifferentiating situation[9] to be formed by chain end control)].

(4) Ewen, J. A. *J. Am. Chem. Soc.* **1984**, *106*, 6355; loc. cit. See also: Ewen, J. A. Ligand Effects on Metallocene Catalyzed Polymerizations. In *Catalytic Polymerization of Olefins*; Keii, T, Soga, K., Eds.; Elsevier: New York, 1986; p 271.

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(7) Reactions carried out at 0 °C gave similar results.

(8) Farina, M. *Top. Stereochem.* **1987**, *17*, 1 and references cited therein. Inoue, Y.; Itabashi, Y.; Chujo, R.; Doi, Y. *Polymer* **1984**, *25*, 1640 and references cited therein.

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The 4α-A and 4α-B/methylalumoxane catalysts ([Al]/[Zr] ≈ 1000) both produced isotactic polypropylene almost completely by means of enantiomorphic site control [activities at −30 °C ≈ 450, $\bar{M}_\eta \approx 260000$ (4α-A) and 470000 (4α-B)]. Most of the polymer (≥93%) was only soluble in boiling hexane. The ^{13}C NMR methyl pentad distribution (see Figure 1) indicated effective control of the CC coupling step by the chiral metal center of the active catalyst[7] (4α-B/$(MeAlO)_x$ 80% mmmm, $\langle m \rangle_{n,\alpha} \approx 24$).

The isotacticity achieved with the homogeneous Ziegler catalysts derived from the conformationally free nonbridged bent metallocene complexes **4** is still smaller and the activities are lower compared to some of the commonly employed *ansa*-metallocene/$(MeAlO)_x$ systems.[3,4,10,11] However, our study shows that there may be only gradual but not principal differences between the two types of catalyst systems. As extensive structural variation can be carried out much more easily with the nonbridged chiral metallocene precursors, we are optimistic that many of the current shortcomings of these new systems will be overcome in the future. From our preliminary studies it appears that enantiomerically pure catalyst systems are easily accessible from these nonbridged systems. We are currently looking for applications of such optically active homogeneous Ziegler systems in the enantioselective catalytic formation of monomeric organic target molecules.

Acknowledgment. Financial support from the Fonds der Chemischen Industrie, the Volkswagen-Stiftung, and the Alfried Krupp von Bohlen und Halbach-Stiftung is gratefully acknowledged.

Supplementary Material Available: Experimental details of the preparation and characterization of compounds **1–4** (10 pages). Ordering information is given on any current masthead page.

(11) See, for example: Collins, S.; Gauthier, W. J.; Holden, D. A.; Kuntz, B. A.; Taylor, N. J.; Ward, D. G. *Organometallics* **1991**, *10*, 2061 and references cited therein.

Oligonucleosides: Synthesis of a Novel Methylhydroxylamine-Linked Nucleoside Dimer and Its Incorporation into Antisense Sequences

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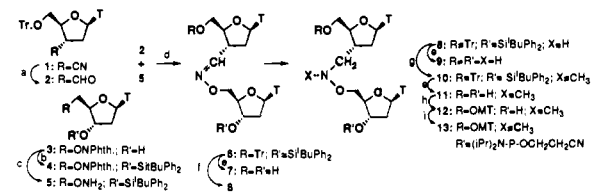
Modulation of gene expression by antisense technologies requires the development of modified oligonucleotides possessing enhanced cellular uptake, resistance toward degradation by nucleases, and appropriate hybridization to target RNAs.[1] These oligonucleotide pharmacokinetic design features are amenable to structure–activity relationship (SAR) studies and lead to antisense oligonucleotides modified in the heterocycle, sugar, phosphodiester linkage, and phosphorus atom.[1] Our research in this area has focused on the development of neutral or positively charged, achiral linkages between the 3′-carbon and the 4′-carbon of the sugars of an oligonucleoside.[2] Linkages of this type would circumvent the chirality problem found with phosphorus-modified oligonucleotides such as methyl phosphonates, phosphorothioates, and phosphoramidates[1h] and may provide resistance to enzymatic cleavage.[1f] Reasonable linkages that one may envisage of this type (four atoms, neutral or positively charged and achiral) would require the replacement of the phosphorus atom in the sugar–phosphate backbone of an oligonucleotide. One-to-one atom replacement of the phosphorus atom has been recently reported.[3] This communication describes the replacement of the anionic 3′-OP-$(O)_2^-OCH_2$-5′ linkage in an oligodeoxynucleotide by a neutral 3′-$CH_2NH(Me)OCH_2$-5′ linkage.[4]

Retrosynthetic analysis of desired dimer **11** indicated that 3′-deoxy-3′-*C*-formyl-5′-*O*-tritylthymidine (**2**) and 5′-*O*-amino-3′-*O*-(*tert*-butyldiphenylsilyl)thymidine (**5**) would serve as key building blocks (Scheme I). Thus, DIBAL-H reduction of 3′-*C*-cyano-3′-deoxy-5′-*O*-tritylthymidine[5] (**1**) led to the aldehyde **2**.[6] The α-stereochemistry of the 3′-CHO group in **2** was established by ^1H NOE experiments. A Mitsunobu reaction[7] of thymidine with *N*-hydroxyphthalimide resulted in the exclusive formation of 5′-*O*-phthalimidothymidine (**3**). Silylation of **3** followed by treatment with methylhydrazine provided **5**.[6] Hydroxylamine **5** was condensed with aldehyde **2** under acid catalysis to afford oxime dimer **6** (88%, mixture of *E*/*Z* isomers).[8] Dinucleoside **6** was reduced with $NaBH_3CN$/AcOH to provide protected dimer **8**[8] in 78% yield. Reductive alkylation of dimer **8** with HCHO/$NaBH_3CN$/AcOH furnished methylated dimer

Scheme I[a]



[a] (a) DIBAL/THF (55%). (b) *t*-$BuPh_2SiCl$/imidazole/DMF (92%). (c) $MeNHNH_2/CH_2Cl_2$ (89%). (d) 1.5% AcOH/CH_2Cl_2 (88%). (e) nBu_4NF/THF, 30 min → 0.14 M HCl/MeOH (89% of **7**, 90% of **9**, 87% of **11**). (f) $NaBH_3CN$/AcOH (78%). (g) HCHO/$NaBH_3CN$/AcOH (87%). (h) DMTCl/pyridine (85%). (i) 2-cyanoethyl *N*,*N*-diisopropylchlorophosphoramidite/*N*,*N*-diisopropylethylamine/THF (78%); DMT = 4,4′-dimethoxytrityl; T = thymine.

Table I. Hybridization Data on Oligonucleosides[a]

oligonucleoside	sequence (5′ → 3′)	T_m, °C[b]
i[c]	d(GpCpGpT*TpT*TpT*TpT*TpT*TpGpCpG)	50.8
ii[c]	d(CpTpCpGpTpApCpCpT*TpTpCpCpGpGpTpCpC)	64.9
iii[c]	d(CpTpCpGpTpApCpT*TpT*TpCpCpGpGpTpCpC)	57.3
iv[c]	d(CpGpApCpTpApTpGpCpApApTpT*TpC)	43.6

[a] Oligonucleosides i–iv were hybridized with complement RNA; p = 3′-$OP(O)_2OCH_2$-5′; * = 3′-$CH_2N(Me)OCH_2$-5′. [b] Absorbance vs temperature profiles were measured at 4 mM of each strand in 100 mM Na^+, 10 mM phosphate, 0.1 mM EDTA, pH 7.0 (see ref 11 for details). [c] T_m's of unmodified sequences: i, 50.2 °C; ii, 63.4 °C; iii, 56.3 °C; iv, 44.1 °C.

† Visiting Scientists from CNRS (France).

(1) Selected review articles: (a) Goodchild, J. *Bioconjugate Chem.* **1990**, *1*, 165. (b) Uhlmann, E.; Peyman, A. *Chem. Rev.* **1990**, *90*, 543. (c) Hélène, C.; Toulmé, J. J. *Biochim. Biophys. Acta* **1990**, *1049*, 99. (d) Cohen, J. S. *Antiviral Res.* **1991**, *16*, 121. (e) Matteucci, M. D.; Bischofberger, N. *Annu. Rep. Med. Chem.* **1991**, *26*, 287. (f) Cook, P. D. *Anticancer Drug Des.* **1991**, *6*, 585. (g) Chrisey, L. A. *Antisense Res. Develop.* **1991**, *1*, 65. (h) *Gene Regulation: Biology of Antisense RNA and DNA*; Erickson, R. P., Izant, J. G., Eds.; Raven Press: New York, 1992.

(2) We refer to modified oligonucleotides that lack the phosphorus atom in the backbone linkage as oligonucleosides. Designation of the backbone linkage as the moiety that connects the 3′-carbon of one furanosyl ring with the 4′-carbon of another furanosyl ring is generally applicable in describing various backbone linkages.

(3) Tittensor, J. R. *J. Chem. Soc. C* **1971**, 2656. Cormier, J. F.; Ogilvie, K. K. *Nucleic Acids Res.* **1988**, *16*, 4583. Seliger, H.; Feger, G. *Nucleosides Nucleotides* **1987**, *6*, 483. Matteucci, M. D. *Tetrahedron Lett.* **1990**, *31*, 2385. Matteucci, M. D.; Lin, K.-Y.; Butcher, S.; Moulds, C. *J. Am. Chem. Soc.* **1991**, *113*, 7767. Veeneman, G. H.; VanDer Marel, G. A.; Van Der Elst, H.; Van Boom, J. H. *Tetrahedron* **1991**, *47*, 1547. Quaedflieg, P.; VanDer Marel, G. A.; Kuyl-Yeheskiely, E.; Van Boom, J. H. *Recl. Trav. Chim. Pays-Bas* **1991**, *110*, 435.

(4) The pK_a of $H_3CON(CH_3)_2$ is 3.65 (Bissot, T. C.; Parry, R. W.; Campbell, D. H. *J. Am. Chem. Soc.* **1957**, *79*, 796), which would indicate that at physiological pH the dinucleoside methylhydroxylamine linkage would be neutral.

(5) Parkes, K. E. B.; Taylor, K. *Tetrahedron Lett.* **1988**, *29*, 2995. We thank Dr. Parkes for providing a preparation of **1**.

(6) All new compounds exhibited satisfactory spectral and analytical and/or exact FAB-MS data.

(7) Mitsunobu, O. *Synthesis* **1981**, 1.

(8) Dimers **6** and **8** were deprotected to give **7** and **9**, respectively, for complete characterization.

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