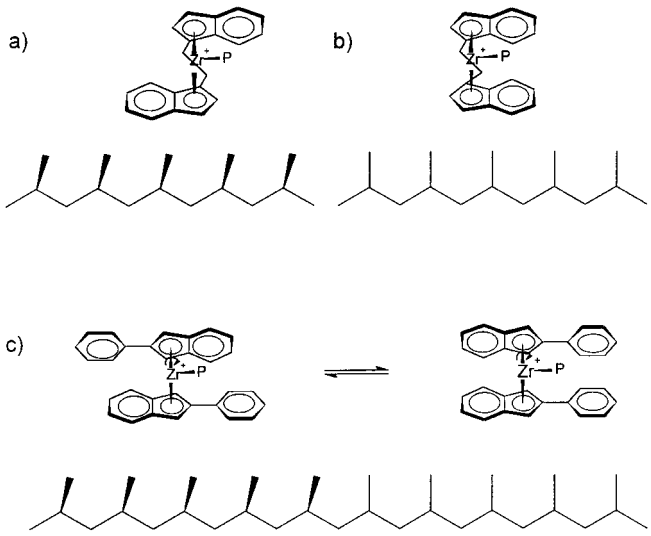
"Oscillating" Metallocene Catalysts: How Do They Oscillate?**

Vincenzo Busico,* Roberta Cipullo, Winfried P. Kretschmer, Giovanni Talarico, Michele Vacatello, and Valeria Van Axel Castelli

The "metallocene breakthrough"[1, 2] has made the dream of tailoring an olefin polymerization catalyst for a desired polymer architecture move closer to reality. In less than one decade since the initial discoveries in the mid-1980s, classes of metallocene catalysts were developed with almost any conceivable kind of stereocontrol (isotactic, syndiotactic, atactic, hemiisotactic), and—most importantly—the relationship was clarified between selectivity on the one hand and symmetry and structure of the catalytic species on the other.[1, 2] Therefore, when in 1995 a rational route to isotactic/atactic stereoblock polypropylene (a material of high potential interest for applications as a thermoplastic elastomer[3]) was announced,[4] the scientific community was—in a way—prepared and there was little room for skepticism.

The idea behind the catalyst design was elegant and conceptually simple (Scheme 1). As is well-known, stereorigid ansa-metallocene catalysts in which two indenyl ligands are locked by a bridge in a *rac*-C_2-symmetric (Scheme 1a) or a *meso*-C_s symmetric (Scheme 1b) configuration afford isotactic and atactic polypropylene, respectively.[1, 2] The former is a semicrystalline thermoplastic material, with a melting temperature of up to 165 °C; the latter, instead, is uncrystallizable and moderately elastomeric.[3] Thus, it was considered worthwhile to try to prepare *unbridged* bis(indenyl) catalysts with substituents of tunable size on the rings, in such a way that hindered ligand rotation is allowed, and a *rac*/*meso* conformational rearrangement occurs at a rate intermediate between those of monomer insertion and chain growth (transfer).

Support for this strategy was gained from results with [(2-Ar-indenyl)$_2$ZrCl$_2$] complexes, where Ar is an aryl group which can range from a simple phenyl (**1**; Scheme 1c)[4] to much more complicated and bulky moieties, such as 3,5-di-*tert*-butyl-4-methoxyphenyl (**2**).[5] Single-crystal X-ray diffraction had proved that complex **1** crystallizes in mixed "*rac*-like" and "*meso*-like" conformations.[4] Once combined with suitable cocatalysts,[1, 2] it gives rise to a moderately active propene polymerization catalyst.[4] Remarkably, the polypropylene produced is largely stereoirregular, but also contains a highly isotactic part;[4, 5] the fact that it does perform as a thermoplastic elastomer[4–6] was taken as an indication that at least part of the isotactic and stereoirregular sequences are chemically bound, and that therefore crystalline domains act as physical crosslinks between amorphous ones.[6] In turn, this was perceived as a validation of the "oscillating" mechanism of Scheme 1c , and the whole class of [(2-Ar-indenyl)$_2$ZrCl$_2$] catalysts were depicted as clean "molecular switches".[4–8]



Scheme 1. Mechanistic basis for isotactic/atactic stereoblock propene polymerization with [(2-Ar-indenyl)$_2$ZrCl$_2$]-based "oscillating" metallocene catalysts (c), according to Coates and Waymouth.[4] P = Polymer chain; only C–C bonds traced in the saw-horse chain representations. Stereorigid ansa-metallocene catalysts in which two indenyl ligands are locked by a bridge in a *rac*-C_2-symmetric (a) or a *meso*-C_s symmetric (b) configuration afford isotactic and atactic polypropylene, respectively.

On the other hand, a number of facts should have suggested that the reality is somewhat more complicated. In particular:

1) Solution NMR investigations on model complexes, down to very low temperatures, did not provide evidence for a slow *rac*/*meso* interconversion, and only *rac*-like species were detected with certainty.[9]
2) Computer modeling by means of molecular mechanics, alone[10] or combined with quantum mechanics[11, 12] confirmed that, for complex **1** and the derived active cation, the *rac*-like and *meso*-like conformations correspond to energy minima, the former being somewhat deeper. However, the activation energy for their interconversion was estimated to be fairly low (2–5 kcal mol^{-1}),[11, 12] and—at most—comparable with that for monomer insertion (5–15 kcal mol^{-1}).[1] Considering that the latter is a bimolecular process (hence with a large negative activation entropy), it is difficult to imagine how it can be (much) faster than the intramolecular *rac*-like/*meso*-like rearrangement. Slightly higher interconversion barriers were calculated for complexes with bulkier Ar substituents, such as **2**,[12] but in that case the *meso*-like conformation turned

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out to be further disfavored (relative to the *rac*-like one) by steric repulsions between the Ar groups.

3) Last but not least, the polymers have broad molecular mass distributions, which is rather unusual with homogeneous catalysts; moreover, they can be solvent-separated in fractions largely differing in stereoregularity, from completely amorphous (though not purely atactic) to highly crystalline (though not completely isotactic).[2, 5, 6] Altogether, this strongly suggests the presence of more than one catalytic species, possibly in equilibrium but with average lifetimes longer than the average growth time of individual macromolecules.

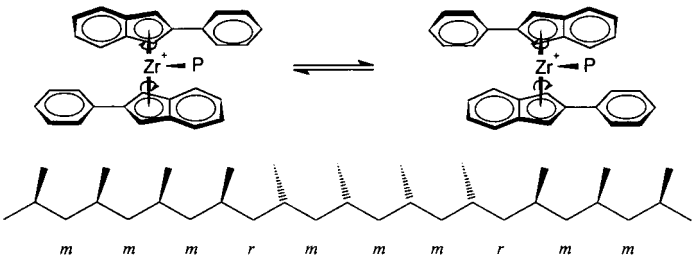
Recently, we decided to investigate this complicated subject by means of in-depth microstructural polymer analysis.[13] With the aid of advanced high-field (150 MHz) ^{13}C NMR tools,[13] we achieved the first clear-cut microstructural evidence[14] that polypropylene samples produced with catalyst systems based on complex **1** can contain a true stereoblock fraction, with fairly long crystallizable isotactic sequences chemically bound to stereoirregular ones.

To our surprise, however, we also found that the relative amount of crystallizable blocks is strongly dependent on the cocatalyst and on the solvent. Although appreciable when **1** was activated in toluene with *N*,*N*-dimethylanilinium tetrakis(perfluorophenyl)borate/[Al(isobutyl)$_3$], polymer crystallinity, at least in our hands, dropped practically to zero when methylalumoxane (MAO) in toluene was used, or—irrespectively of the cocatalyst—when the polymerization was carried out in a more polar solvent such as 1,2-dichlorobenzene (Table 1, entries 1–5).

This indicates that the active species of **1** is intrinsically much more mobile than has been assumed up to now[1, 2, 4–8] and that, at least under certain experimental conditions, ligand rotation takes place at a rate comparable with that of monomer insertion.

Another surprise came from the finding that, in all cases, the stereoirregular part of the polymer is *not* truly atactic, but rather contains an excess of *meso* (*m*) diads, separated by predominantly isolated *racemo* (*r*) diads (*…mrmmrmrmmrmr…*).[14]

Revealingly, the fraction P_m of *m* diads was found to increase with increasing monomer concentration (Table 1, entries 1–4); this led us to rule out the hypothesis of a weak 1,3-like asymmetric induction[13, 15] exerted by the growing chain end when the catalytic species is in the achiral *meso*-like conformation. Instead, we concluded[14] that the said microstructure reflects the fact that the *rac*-like conformation is more stable than the *meso*-like one,[12] and that—rather (or more) than involving the latter—catalyst "oscillation" mostly occurs *within* the *rac*-like conformation, that is between its two enantiomorphous forms with opposite enantioselectivities ("*rac*/*rac** oscillation", Scheme 2).



Scheme 2. "Oscillation" of a [(2-Ar-indenyl)$_2$ZrCl$_2$]-based catalyst (shown for Ar = phenyl) between the two enantiomorphous forms of the *rac*-like conformation, and resulting polypropylene microstructure.

Clear evidence in support of the above interpretation now comes from the microstructural characterization of polymers prepared with the slightly "stiffer" catalyst **2**. Figure 1 shows the methyl region of the 150 MHz ^{13}C NMR spectrum of a typical polypropylene sample obtained with catalyst system **2**/MAO (Table 1, entry 7). The spectrum reveals that the polymer contains isotactic sequences spanned by *isolated r* diads (see, in particular, the intense peak no. 13 of the *mmmrmm* heptad[13, 16]), and with just traces of *rr* stereodefects. Quantitative statistical analysis of polymer configuration[13] on the basis of the model of Scheme 2 gives a very good match between experimental and calculated stereosequence distributions (see Table S1 in the Supporting Information), with a best-fit value of the *average* stochastic probability of "oscillation" $P_{osc} \approx (1 - P_m) \approx 0.09$ and an estimated enantioselectivity of the catalytic species of 0.985.

Plausibly, as already observed with catalyst **1**, samples prepared at lower monomer concentration have lower ^{13}C NMR P_m (i.e., higher P_{osc}) values (Table 1, entries 6 and 7); indeed, decreasing monomer concentration is expected to slow down monomer insertion, but not catalyst oscillation. As an example, the number average length of the isotactic strands with opposite relative configurations (see Scheme 2), $\langle L_{iso} \rangle \approx (1/P_{osc})$, turned out to be approximately 5 and approximately 10 monomeric units for samples 6 and 7 of Table 1, respectively.[17]

On the other hand, in comparison with **1**, the performance of **2** is less sensitive to the nature of the solvent and/or of the cocatalyst (Table 1, entries 6–9). We will comment on this point later on.

Table 1. Results of propene polymerization in the presence of the "oscillating" metallocene catalysts **1** and **2** (see text).[a]

Entry	Catalyst/ Cocatalyst[b]	Solvent	$[C_3H_6]$ [M]	[*mmmmmm*][c] [%]	P_m[d]	T_m[g] [°C]	Δh_m[g] [J g^{-1}]
1	**1**/MAO	toluene	1.5	5	0.56[e]	–	Am[b]
2	**1**/MAO	toluene	6.7	8	0.58[e]	–	Am[b]
3	**1**/borate/TIBAl	toluene	1.5	13	0.53[e]	133	7
4	**1**/borate/TIBAl	toluene	6.7	23	0.59[e]	140	10
5	**1**/borate/TIBAl	ODCB[b]	1.5	4	0.52[e]	–	Am[b]
6	**2**/MAO	toluene	1.5	30	0.79[f]	90	4
7	**2**/MAO	toluene	6.7	52	0.90[f]	140	34
8	**2**/borate/TIBAl	toluene	1.5	31	0.76[f]	145	9
9	**2**/borate/TIBAl	ODCB[b]	1.5	30	0.75[f]	145	6

[a] Experimental conditions: $T = 20\,^{\circ}C$; $[Zr] = 3 \times 10^{-5}$ M; $[Al]/[Zr] = 1.0 \times 10^3$ (for activation with MAO); $[B]/[Zr] = 2.5$, $[Al]/[Zr] = 3.0 \times 10^2$ (for activation with *N*,*N*-dimethylanilinium tetrakis(perfluorophenyl)borate/[Al(isobutyl)$_3$]); polymerization time, 1.0 h. [b] Abbreviations: borate = *N*,*N*-dimethylanilinium tetrakis(perfluorophenyl)borate; TIBAl = [Al(isobutyl)$_3$]; ODCB = 1,2-dichlorobenzene; Am = Amorphous. [c] ^{13}C NMR fraction of isotactic heptad in the whole sample. [d] Probability of *m* diad formation, estimated by statistical analysis of the 150 MHz ^{13}C NMR stereosequence distribution.[13, 14] [e] In the stereoirregular sequences. [f] In the whole sample. [g] Measured by differential scanning calorimetry (DSC) on second heating scan.

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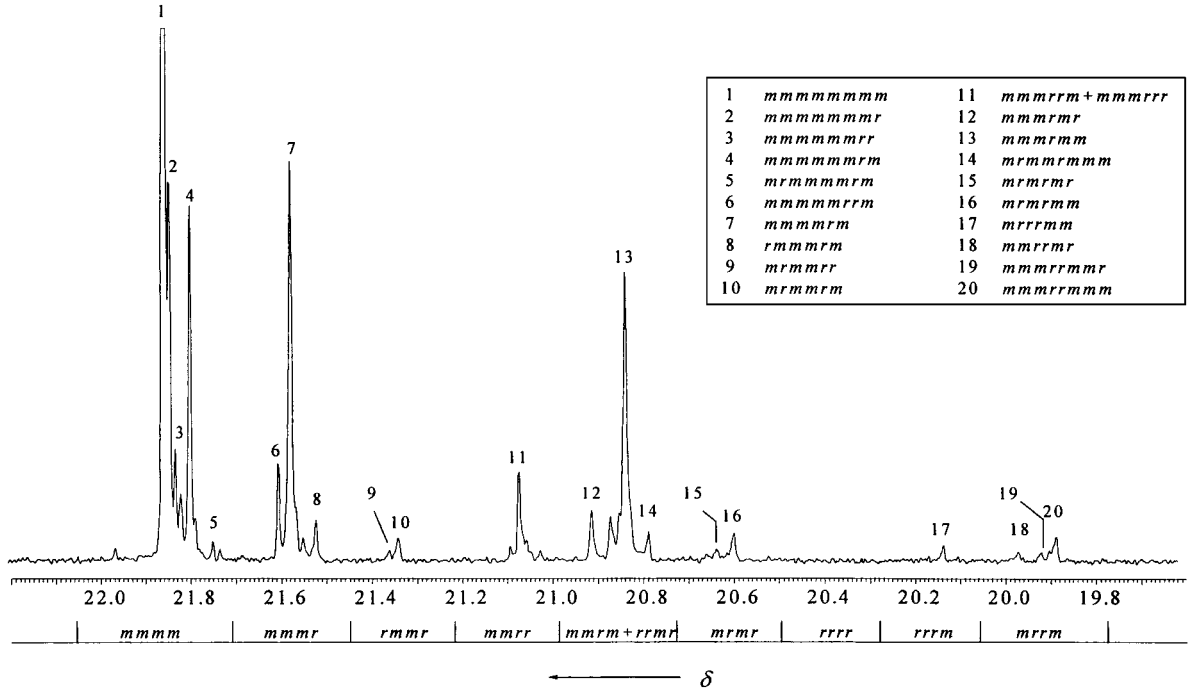

Figure 1. Methyl region of the 150 MHz ^{13}C NMR spectrum (in 1,2-[D_2]tetrachloroethane at 90 °C) of a polypropylene sample prepared with catalyst **2** (Table 1, entry 7). The chemical shift scale is referenced to the signal for tetramethylsilane; the assignment is based on references [13, 16]. The presence in the sample of isotactic sequences separated by *single r* diads is apparent (see, in particular, the intense peaks numbered as 4, 7, and 13).

From the results presented so far, one can easily see that (coeteris paribus) the ratio between the average frequencies of monomer insertion and catalyst oscillation is critically dependent on the Ar substituent: comparatively high for the bulky catalyst **2**, with $(1 - P_{osc})/P_{osc}$ values of up to approximately 10; fairly low instead for catalyst **1**. For the latter, particularly in a (weakly) polar medium, ligand rotation can be regarded as almost free on the time scale of monomer insertion, with a resulting "quasi-atactic" chain propagation (which obviously implies that some contribution of the *meso*-like form to the catalytic activity[4–8] cannot be ruled out). All this fits with the previously discussed results of computer modeling.[10–12, 18]

Now we need to explain why, particularly with catalyst **1**, the active species can be frozen *occasionally* in one of the two mirror images of the *rac*-like conformation for a comparatively long time, and thus produce long (well-crystallizable) isotactic blocks. In our opinion, the remarkable cocatalyst and solvent effects documented in Table 1 point to a cation/anion "interlocking" as one of the possible reasons. In this respect, tetrakis(perfluorophenyl)borate, which can establish directional interactions with metallocene cations, seems to be more effective than the large and highly delocalized anion of MAO.[19, 20]

The high sensitivity of the stereoselectivity to "environmental factors" is a peculiar and intriguing aspect of this fascinating catalysis. For most stereorigid ansa-metallocene catalysts, and in particular for *rac*-C_2-symmetric ones with homotopic sites, the enantioselectivity is the direct result of the intrinsic ligand structure, and (in spite of the fact that the reaction is normally carried out in a nonpolar medium) the existence of a counterion can practically be ignored as far as the microstructure of the polymer produced is concerned.[1, 2, 13] Only recently have some counterion and solvent effects been documented on the relative rates of monomer insertion and site epimerization (chain back-skip),[1, 2, 13] and hence on the syndiotactic selectivity, for C_s-symmetric ansa-zirconocenes with enantiotopic sites.[21] At the other extreme, unbridged achiral bis(cyclopentadienyl) catalysts afford substantially stereoirregular polymers practically under all conditions (apart from a weak chain-end control at very low temperatures in a few cases).[1, 2, 13]

Conversely, with their highly mobile but "hooked" ancillary ligands, [(2-Ar-indenyl)$_2$$ZrCl_2$]-based catalysts can change their stereoselectivity dramatically depending on how they interact with the "outer world", to the point that they can lose the "single-site" character typical of homogeneous systems.[1, 2] As shown in Table 1, a different choice of solvent and/or counterion can affect the dynamics of ligand rotation at least as much as the nature and size of the "built-in" Ar substituents, particularly when the latter are not too bulky and the complex therefore is not too constrained. We will report in more depth on these aspects in the near future.

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[17] The observed DSC melting endotherms, with a flat maximum at fairly high temperatures and a very long "tail" toward lower temperatures, are clearly indicative that L_{iso} is broadly distributed. This is consistent with the fact (already commented in the text) that the samples have a broad molecular mass distribution ($M_w/M_n \gg 2$) and can be solvent-separated in fractions widely differing in stereoregularity.

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Total Synthesis of the Presumed Amphidinolide A**

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The amphidinolides are a family of biologically active macrolides isolated from the marine dinoflagellate *Amphidinium sp.*, which lives in a symbiotic relationship with the Okinawan flatworm *Amphiscolops sp.*[1] Many of the amphidinolides show potent cytotoxic activity against murine lymphoma L1210 cells, human epidermoid carcinoma KB cells, and human colon tumor HCT 116 cells.[1] Amphidinolide A (**1**) was the first member of the family to be isolated and characterized.[2] Its structure incorporates a 20-membered macrolactone that contains six double bonds, three of which are exocyclic. The relative stereochemistry of the nine stereocenters in **1** was suggested by Kobayashi and co-workers on the basis of extensive NMR spectroscopy experiments.[3]

Studies towards the synthesis of amphidinolide A (**1**) have been described by O'Connor and Williard,[4] by Maleczka and co-workers,[5] and by ourselves. In an earlier communication, we described an approach to the macrolactone core of **1** in which a key step involved an intramolecular sp^2-sp^3 Stille reaction of a precursor that contains an alkenyl stannane and an allylic chloride.[6] In subsequent studies, we also described a concise synthesis of the C7–C13 fragment **2**, starting from commercially available methyl-α-D-glucopyranoside.[7] Herein we describe a total synthesis of **1**, the proposed structure of amphidinolide A, and also of the diastereomer **34**, which is epimeric to **1** at C20 and C21.

Our synthetic strategy to amphidinolide A (**1**) required the preparation of two major fragments **3** and **4**, which we planned to elaborate into **1** through the following sequence of operations: 1) an intermolecular sp^2-sp^2 Stille reaction[8] between the less sterically hindered C4 alkenyl stannane unit in **3** and the C3 alkenyl iodide of **4**; 2) deprotection of all the silyl ethers originally in **3**; and 3) an intramolecular sp^2-sp^3 Stille reaction[9] between the C14 alkenyl stannane and the C15 allylic acetate (Scheme 1). The intermolecular Stille reaction of **3** with **4** was deemed to be highly challenging, as it requires not only the discrimination between the two alkenyl stannane units in **3**, but also between the alkenyl iodide and the allylic acetate units in **4**, both of which are potentially reactive under palladium-catalyzed coupling conditions. However, the observation that sterically encumbered alkenyl stannanes are often poor substrates in the Stille reaction,[10] together with our expectation that an alkenyl iodide would be more reactive than an allylic acetate, led us to believe that the reaction could be selective. We planned to prepare the bis-alkenyl stannane **3** from the known aldehyde **5**,[7] and to prepare the iodide acetate **4** by using a modified Julia olefination reaction[11] between aldehyde **6** and benzothiazolyl sulfone **7** as a key step.

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