

Cooperativity in Aqueous Organometallic Catalysis: Contribution of Cyclodextrin-Substituted Polymers

Jonathan Potier,[†] Stéphane Menuel,[†] David Fournier,[‡] Sophie Fourmentin,[§] Patrice Woisel,[‡] Eric Monflier,[†] and Frédéric Hapiot^{*,†}

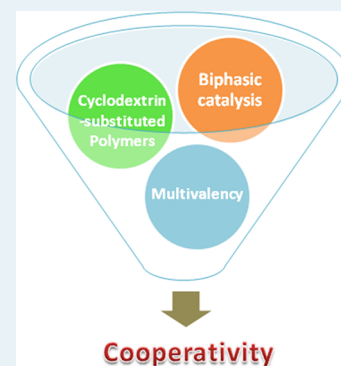
[†]Université Lille Nord de France, CNRS UMR 8181, Unité de Catalyse et de Chimie du Solide–UCCS, UArtois, Faculté des Sciences Jean Perrin, rue Jean Souvraz, SP18, 62307 Lens Cedex, France

[‡]Université Lille Nord de France, ENSCL, CNRS UMR 8207, Unité des Matériaux et Transformations–UMET, USTL, 59655 Villeneuve d'Ascq Cedex, France

[§]Université Lille Nord de France, UCEIV–ULCO, 145 Avenue Maurice Schumann, MREI 1, 59140 Dunkerque, France

S Supporting Information

ABSTRACT: Cooperativity has been implicated to explain the catalytic performances of cyclodextrin-substituted polymers in aqueous rhodium-catalyzed hydroformylation of 1-hexadecene, thus opening the door to the transformation of very hydrophobic substrates in aqueous biphasic catalysis by supramolecular means.



KEYWORDS: cyclodextrins, polymer, biphasic catalysis, molecular recognition, cooperative effects

Multivalency and cooperativity are currently hot topics in chemistry and biology.^{1–3} While multivalency is mainly related to the increase in binding strength resulting from additive interactions, cooperativity assesses the influence of the binding of one ligand on the receptor's affinity toward further binding interactions.^{4–7} The implication of multivalency and cooperativity in many chemical and biological processes prompted researchers to imagine novel systems where at least one of these two concepts is expressed.^{8–15} In this context, polymers recently proved to be promising materials because of their multivalent binding properties. For example, cooperativity has been clearly demonstrated (i) by incorporating supramolecular binding sites into flexible polymers,¹⁶ (ii) for W- and M-type multivalent polymers in adsorption and colloidal stabilization,¹⁷ and (iii) on the activity of a hydrolytic kinetic resolution of epichlorohydrin using a Co^{III}-salen polymer brush architecture.¹⁸ We recently reported that cyclodextrin (CD)-dimers are effective mass transfer promoters to convert long alkyl-chain substrates in aqueous biphasic catalysis.¹⁹ On the basis of these findings, we anticipated that a CD-based polymer structure could be even more effective to supramolecularly recognize such substrates through multivalency. CD-based polymers have already been the subject of intense investigations during the past ten years.^{20–26} However, no study has been devoted to their application in aqueous biphasic catalysis. Herein we report on the synthesis of novel CD-substituted

polymers and their catalytic application in aqueous Rh-catalyzed hydroformylation. This reaction is currently the most successful industrial application using a biphasic catalytic system and enables the conversion of lower olefins into butyraldehydes to access surfactants, detergents, or lubricants.²⁷

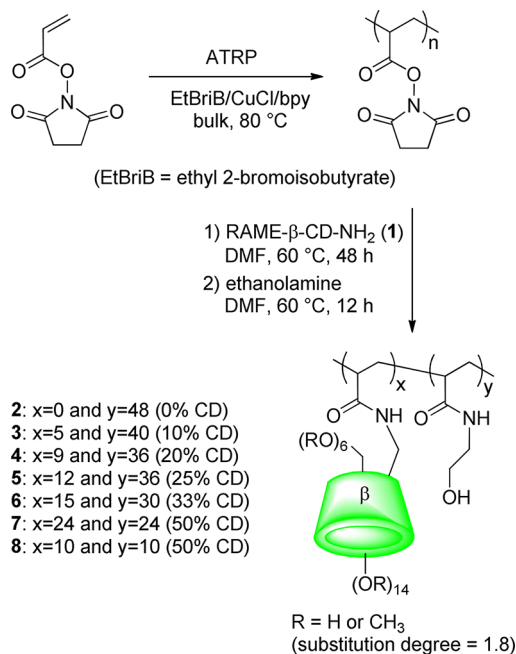
The synthesis of the CD-based polymers was implemented in several steps as described in Scheme 1. Once the *N*-acryloyloxysuccinimide (NAS) monomer was synthesized,²⁸ Atom Transfer Radical Polymerization (ATRP)²⁹ produced size-controlled poly(*N*-acryloyloxysuccinimide) (polyNAS) with narrow molecular weight distributions around 1.2 (Supporting Information). Subsequent reactions with first the monoamino randomly methylated β -CD (RAME- β -CD-NH₂, **1**), then ethanolamine in DMF at 60 °C gave the desired water-soluble polymers **2–8** in good recovery yields (80–85%). Introduction of hydroxyethyl groups on the polymer chain ensured its solubility in water. The CD units were randomly incorporated into the polymer chain.

Throughout this synthetic strategy, the length of the polymer chain and the number of CDs per chain could be accurately controlled. However, no more than one out of two monomers units could be substituted by **1**. Attempts to reach higher CD-

Received: April 19, 2012

Revised: June 5, 2012

Published: June 6, 2012

Scheme 1. Synthesis of β -CD-Functionalized Polymers 2–8

substitution degree than 50% failed probably because of the steric hindrance resulting from the bulky CD structure. Polymers 2–8 have been characterized by NMR and size exclusion chromatography (SEC). As an example, Figure 1

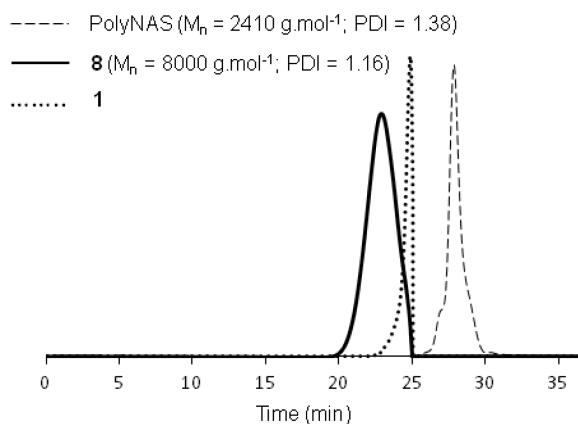


Figure 1. SEC chromatograms of **1**, **8**, and the polyNAS chain from which it was derived. Recorded in DMF (+ LiBr, 1 g/L) at 60 °C.

shows the SEC chromatograms for **1**, **8**, and the polyNAS chain from which it was derived. All the synthesized polymers were highly water-soluble (up to 800 g/L at 20 °C). They were all surface-active as clearly demonstrated by surface tension measurements (Figure 2). Actually, when compared to pure water, a significant decrease in γ was observed (from 72 to 50–60 mN·m⁻¹, respectively). This decrease is particularly noteworthy considering that the CD-substitution rate on the polymer chain was low. None of the synthesized polymers showed any critical micellar concentration within the studied concentration range (from 4×10^{-3} to 30×10^{-3} mol/L).

The catalytic performance of 2–8 was evaluated in aqueous Rh-catalyzed hydroformylation of 1-decene (**9**) and 1-hexadecene (**10**) under 50 bar CO/H₂ at 80 °C (Table 1). For all experiments, the CDs molar amount was kept constant.

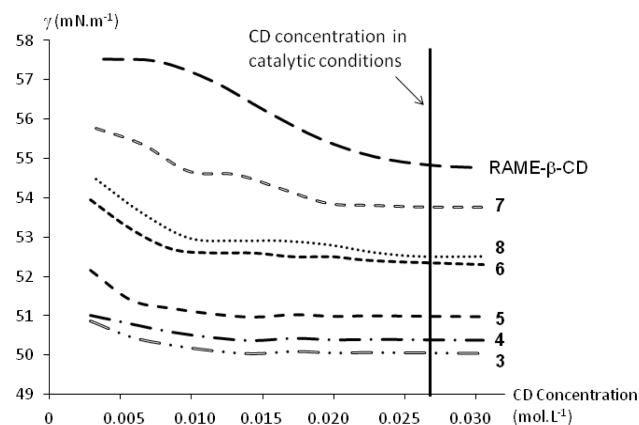


Figure 2. Surface tension as a function of the CD concentration for RAME- β -CD and polymers 3–8 in water at 20 °C.

Table 1. Catalytic Performance of RAME- β -CD and β -CD-Functionalized Polymers 2–8 in Rh-Catalyzed Hydroformylation of **9** and **10**^a

run	S	additive	t (h)	conv. (%) ^b	sel. (%) ^b	l/b ^b
1	9		6	10	59	2.8
2	9	RAME- β -CD	1	80	96	1.9
3	9	RAME- β -CD	6	100	95	1.8
4	9	RAME- β -CD+2 ^c	1	79	96	1.9
5	9	RAME- β -CD+2 ^d	1	43	97	1.6
6	9	3	1	14	98	1.8
7	9	4	1	39	93	1.8
8	9	5	1	52	91	1.9
9	9	6	1	70	88	2.0
10	9	7	1	74	87	2.0
11	9	8	1	74	88	2.2
12	10		6	6	30	2.5
13	10	RAME- β -CD	1	36	65	1.6
14	10	RAME- β -CD	6	74	64	1.2
15	10	RAME- β -CD+2 ^c	6	47	38	1.7
16	10	RAME- β -CD+2 ^d	1	1	44	1.4
17	10	3	1	42	46	2.1
18	10	4	1	55	46	1.8
19	10	5	1	67	50	2.1
20	10	6	1	81	61	1.8
21	10	7	1	80	62	2.1
22	10	8	1	81	64	2.1
23	10	8	3	100	64	1.9

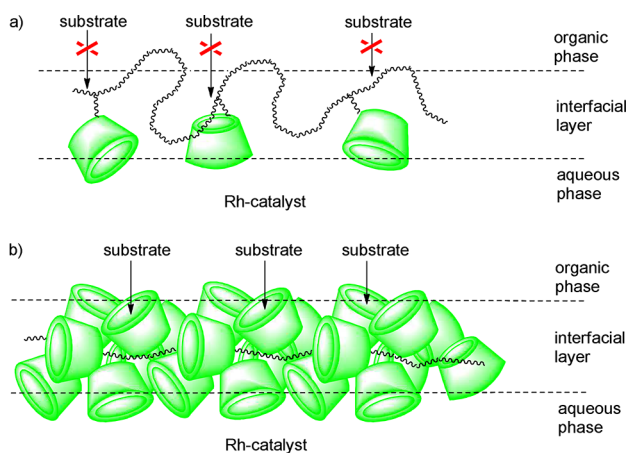
^aCatalytic conditions: substrate (1.63 mmol), Rh(CO)₂(acac) (3 mg, 0.012 mmol), TPPTS (33 mg, 0.058 mmol), additive (calculated for 0.116 mmol equiv. CDs), 6 mL of H₂O, 80 °C, 50 bar CO/H₂.

^bDetermined by GC for **9** and by NMR for **10**. ^cMass of **2** adjusted to match polymer main chain and hydroxyethyl groups of **7**. ^dMass of **2** adjusted to match polymer main chain and hydroxyethyl groups of **3**.

More precisely, the β -CD-functionalized polymer amounts have been adjusted for each run to match the RAME- β -CD quantity used for the blank run (equal number of CDs available in the aqueous medium). Control experiments confirmed that RAME- β -CD can be used as mass transfer promoter in this reaction

(Table 1, runs 2, 3, 13, and 14). Actually, its adsorption ability at the aqueous/organic interface allowed for the molecular recognition of the substrate and its subsequent reaction with the water-soluble catalyst. With CD-substituted polymers, the catalytic performances were greatly dependent upon both the substrate alkyl-chain length and the CD substitution rate on the polymer chain. The activity and chemo-selectivity were especially impacted while the regioselectivity (*l/b* ratio) remained virtually constant (ranging from 1.8 to 2.3). Two main effects accounted for the catalytic results, one related to the substrate alkyl chain length and the other to the nature of the polymers. Let us first examine the behavior of **9** through the prism of the surface activity of polymers **2**–**8**. First, the impact of increasing amounts of **2** regarding the surface tension γ at the water–air interface has been evaluated. A regular decrease in γ was observed when increasing the concentration of **2** (Supporting Information). Yet, whatever its concentration, **2** proved inappropriate when mixed with RAME- β -CD (0.027 mM) to improve the catalytic activity in hydroformylation of **9** (Table 1, runs 4 and 5). This suggests that **2** disfavored RAME- β -CD adsorption at the aqueous/organic interface. Polymer **3** also proved ineffective to convert **9** while its impact on the surface tension was high (Figure 2). This clearly indicated that the tensiometric properties of the polymer were not responsible for the catalytic performances. The results have better been interpreted in terms of interface shielding. As the main chains of **2** and **3** were mostly adsorbed at the interface, reaching the interface was then more difficult for CDs. An illustration of this shielding effect is given in Scheme 2a. The hydrophobic

Scheme 2. (a) Shielding Effect of Low-Multivalent CD-Based Polymers and (b) Enhanced Molecular Recognition of High-Multivalent CD-Based Polymers^a



^aHydroxyethyl groups have been removed for clarity.

polymer chain was oriented toward the organic phase thus preventing the CD/substrate molecular recognition. Oppositely, the surface activities of high CD-substituted polymers such as **7** and **8** were very close to that of RAME- β -CD, indicative of a similar ability to adsorb at the aqueous/organic interface. In fact, increasing the CD-substitution rate yielded polymer chains surrounded by CDs (Scheme 2b).

The shielding effect of the polymer main chain being reduced, **9** could be more readily recognized by the CD cavity and converted into aldehydes. The catalytic performances of RAME- β -CD could even almost be achieved using **7** or **8** as

mass transfer promoters (80% vs 74% conv., respectively). As **9** is well-known to perfectly fit the cavity of only one CD,³⁰ each CD covalently attached to a polymer chain acted as RAME- β -CD did, suggesting that no multivalent processes took place whatever the number of CDs per polymer chain. The conversion variation depicted in Figure 3a was illustrative of

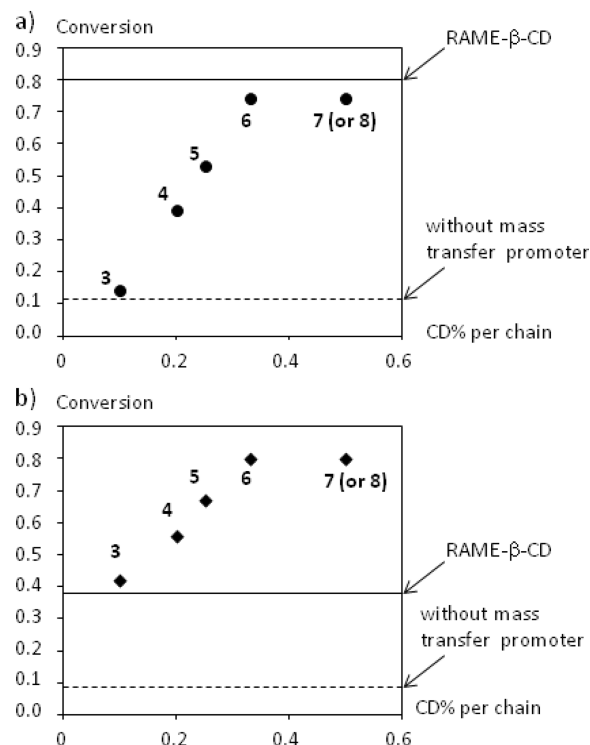


Figure 3. Conversion of **9** (a) and **10** (b) as a function of the CD substitution degree on the polymer chains. Conversions obtained without any mass transfer promoter and with RAME- β -CD have been added for clarity.

the CD-substitution effect. The CD-substitution rate also slightly impacted the chemoselectivity (Table 1, runs 6–11) and found expression in the lower affinity of **9** toward the CD cavities of high-CD-substituted polymers. Actually, in that case, the substrate alkyl chain was probably less included within the CD cavity and the terminal C=C double bond could competitively undergo Rh-catalyzed isomerization.

Compound **10** behaved very differently as it could not be properly recognized by a single CD cavity. Thus, **10** combined the disadvantage of a higher insolubility than **9** in water and the need for a larger hydrophobic pocket for the recognition process to take place at the interface. The use of CD-substituted polymers could overcome these two drawbacks. As such, Figure 3b was very illustrative of the impact of CD-substituted polymers **3**–**8** toward **10**. A mixture of RAME- β -CD and large amounts of **2** (which does not bear any CD moiety) proved especially ineffective (Table 1, runs 15 and 16) and confirmed the above results regarding the shielding effect. The low CD-substituted polymer **3**, for its part, led to a conversion hardly better than that obtained using RAME- β -CD (Table 1, runs 13 and 17). On the contrary, high-multivalent CD-based polymers were much more effective than RAME- β -CD in terms of catalytic activity to convert **10** into aldehydes. For instance, 81% of **10** was converted within 1 h using **6** (Table 1, run 20) whereas 6 h were necessary to convert 74% of

10 using RAME- β -CD (Table 1, run 14). It thus appeared that high CD-substituted polymers were required for a long alkyl-chain substrate to be efficiently transferred from the organic phase to the water-soluble Rh-catalyst. This result clearly originated from multivalent molecular recognition processes. As the alkyl chain of **10** was too long to be properly recognized by only one CD cavity, two close-in-space CDs contributed to improve the recognition process by multivalency. Consequently, increasing the number of CDs per polymer chain logically led to a higher conversion rate. The substrate being more available at the aqueous/organic interface, its conversion into aldehydes was then greatly enhanced. Note that there was no need to unnecessarily substitute the polymer chain by too many CDs as a plateau was already reached for a CD-substitution rate of 33% (Figure 3b). The chemoselectivity variation observed for **10** corroborated the above findings. Contrary to what was observed for **9**, increasing the number of CDs per polymer chain resulted in an increase in aldehyde proportions (Table 1, runs 17–23). Here again, the explanation lies in the better molecular recognition existing between **10** and high CD-substituted polymers. While the vicinity of several CDs had a detrimental effect on the molecular recognition of **9** in terms of chemoselectivity (see above), two close-in-space CDs grafted on a polymer chain acted as a hydrophobic protecting pocket into which the substrate could slip, thus orienting the reaction preferentially to the C=C hydroformylation rather than to internal isomerization. This observation was confirmed by volatility measurements that showed the volatility reduction with the CD-based polymers to be significantly higher for **10** than for **9** (Supporting Information). This unambiguously demonstrated the higher affinity of **10** for the high CD-substituted polymers.

Finally, it is important to note that cooperativity was operative in this system. Indeed, the three fundamental criteria recently set forth by Ercolani and co-workers have been validated.³ First, RAME- β -CD allowed for an evaluation of the single isolated interaction (the reference). Second, a non-cooperative model (**3**) where each CD behaved independently of the others showed similar catalytic performances than the reference. Third, the positive deviation (Figure 3b) observed with the CD-substituted polymers **4–8** was an unambiguous mark of cooperativity.

In summary, we showed that size-controlled CD-functionalized polymers are powerful tools to overcome mass transfer limitations in biphasic systems by supramolecular means. Additionally, the results of this structure–activity investigation have provided compelling evidence that positive cooperativity was operative in this catalytic system, thus encouraging the elaboration of even more effective polytopic receptors for aqueous organometallic catalysis.

■ ASSOCIATED CONTENT

Supporting Information

Syntheses and characterizations of **1** and polymers **2–8**, copies of NMR spectra, SEC analysis, surface tension measurements of polymer **2**, volatility measurements, details of catalytic experiments and cooperativity. This material is available free of charge via the Internet at <http://pubs.acs.org>.

■ AUTHOR INFORMATION

Corresponding Author

*Phone: +33 3 21 79 17 55. Fax: +33 3 21 79 17 55. E-mail: frederic.hapiot@univ-artois.fr.

Author Contributions

The manuscript was written through contributions of all authors.

Funding

J.P. is grateful to the Région Nord-Pas-Calais and the Centre National de la Recherche Scientifique (CNRS) for financial support (2010–2013).

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Roquette Frères (Lestrem, France) is gratefully acknowledged for generous gifts of cyclodextrins.

■ REFERENCES

- (1) Whitty, A. *Nat. Chem. Biol.* **2008**, *4*, 435–439.
- (2) Hunter, C. A.; Anderson, H. L. *Angew. Chem., Int. Ed.* **2009**, *48*, 7488–7499.
- (3) Ercolani, G.; Schiaffino, L. *Angew. Chem., Int. Ed.* **2011**, *50*, 1762–1768.
- (4) Baldini, L.; Casnati, A.; Sansone, F.; Ungaro, R. *Chem. Soc. Rev.* **2007**, *36*, 254–266.
- (5) Grützmacher, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 1814–1818.
- (6) Schneider, H. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 3924–3977.
- (7) Brière, J.-F.; Oudeyer, S.; Dalla, V.; Levacher, V. *Chem. Soc. Rev.* **2012**, *41*, 1696–1707.
- (8) Mulder, A.; Huskens, J.; Reinhoudt, D. N. *Org. Biomol. Chem.* **2004**, *2*, 3409–3424.
- (9) Badjić, J. D.; Nelson, A.; Cantrill, S. J.; Turnbull, W. B.; Stoddart, J. F. *Acc. Chem. Res.* **2005**, *38*, 723–732.
- (10) Notestein, J. M.; Katz, A. *Chem.—Eur. J.* **2006**, *12*, 3954–3965.
- (11) Manuel, S.; Fontanay, S.; Clarot, I.; Duval, R. E.; Diez, L.; Marsura, A. *Bioconjugate Chem.* **2008**, *19*, 2357–2362.
- (12) Sansone, F.; Baldini, L.; Casnati, A.; Ungaro, R. *New J. Chem.* **2010**, *34*, 2715–2728.
- (13) Björk, J.; Stafström, S.; Hanke, F. J. *Am. Chem. Soc.* **2011**, *133*, 14884–14887.
- (14) Hunter, C. A.; Misuraca, M. C.; Turega, S. M. *J. Am. Chem. Soc.* **2011**, *133*, 20416–20425.
- (15) Carrillo, R.; Feher-Voelger, A.; Martín, T. *Angew. Chem., Int. Ed.* **2011**, *50*, 10616–10620.
- (16) Schneider, H. J.; Tianjun, L.; Lomadze, N.; Palm, B. *Adv. Mater.* **2004**, *16*, 613–615.
- (17) Cao, D.; Wu, J. *Langmuir* **2005**, *21*, 9786–9791.
- (18) Gill, C. S.; Venkatasubbaiah, K.; Phan, N. T. S.; Weck, M.; Jones, C. W. *Chem.—Eur. J.* **2008**, *14*, 7306–7313.
- (19) Six, N.; Manuel, S.; Bricout, H.; Hapiot, F.; Monflier, E. *Adv. Synth. Catal.* **2010**, *352*, 1467–1475.
- (20) Davis, M. E.; Brewster, M. E. *Nat. Rev. Drug Discovery* **2004**, *3*, 1023–1035.
- (21) Koopmans, C.; Ritter, H. *Macromolecules* **2008**, *41*, 7418–7422.
- (22) Davies, M. E. *Adv. Drug Delivery Rev.* **2009**, *61*, 1189–1192.
- (23) Trellenkamp, T.; Ritter, H. *Macromolecules* **2010**, *43*, 5538–5543.
- (24) Zhou, J.; Ritter, H. *Polym. Chem.* **2010**, *1*, 1552–1559.
- (25) Jazkewitsch, O.; Ritter, H. *Macromolecules* **2011**, *44*, 375–382.
- (26) Jazkewitsch, O.; Mondrzyk, A.; Staffel, R.; Ritter, H. *Macromolecules* **2011**, *44*, 1365–1371.
- (27) Wiebus, E.; Schmid, K.; Cornils, B. In *Water in Organic Synthesis, Science of Synthesis*; Kobayashi, S., Ed.; Georg Thieme Verlag KG: Stuttgart, Germany, 2012; pp 807–829.
- (28) Hu, Z.; Liu, Y.; Hong, C.; Pan, C. *J. Appl. Polym. Sci.* **2005**, *98*, 189–194.
- (29) Matyjaszewski, K.; Xia, J. *Chem. Rev.* **2001**, *101*, 2921–2990.
- (30) Siefert, N.; Wipff, G. *Chem.—Eur. J.* **2007**, *13*, 1978–1990.