a rippled structure. It has a good resemblance to the P_{β} phase observed for lecithin–water phases.[21]

In conclusion, by contact AFM we directly observed for the first time a hierarchical formation of structures (bent molecule–distorted layer–columnar domain) as a vertical profile of the microtube membranes.

Experimental Section

Supramolecular vesicle-encapsulated microtubes were prepared with a weak alkaline aqueous solution of glycylglycine bolaamphiphile **1** (10 mM, $\mathrm{pH} \approx 8$).[10] The formation of microtubes with uniform diameter (1.5–2.2 μm) was confirmed by phase-contrast and dark-field light microscopy (Figure 1b). Droplets (20–30 μL) of the solution containing the microtubes were placed with a pipette on to a clean glass substrate (Matsunami micro slide glass, precleaned, S-1111) and allowed to air-dry slowly (14 h) in an electric desiccator (Toyo Living auto dry, type FHO, humidity 15 ± 5 %). All AFM measurements were performed with a commercial atomic force microscope (Digital Instruments Inc., Santa Barbara, CA, Nanoscope IIIa) at room temperature in air. We used the contact-mode AFM with a microfabricated silicon nitride cantilever (spring constant 0.12 N m^{-1}). Images were recorded in the height or friction mode.

Received: May 5, 1998 [Z11821IE]
German version: *Angew. Chem.* **1998**, *110*, 3509–3511

Keywords: amphiphiles · atomic force microscopy · hydrogen bonds · nanostructures · supramolecular chemistry

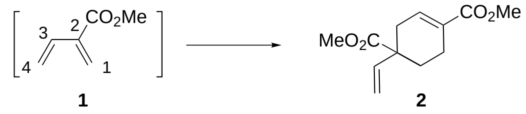
---

[1] H. G. Hansma, S. A. C. Gould, P. K. Hansma, *Langmuir* **1991**, *7*, 1051–1054.
[2] J. Y. Josefowicz, N. C. Maliszewskyi, S. H. J. Idziak, P. A. Heiney, J. J. P. McCauley, A. B. Smith III, *Science* **1993**, *260*, 323–326.
[3] S. Chiang in *Scanning Tunneling Microscopy I* (Eds.: R. Wiesendanger, H. J. Guntherodt), Springer, Berlin, **1991**, p. 181.
[4] S. M. Linsay in *Scanning Tunneling Microscope and Spectroscopy* (Ed.: D. A. Donned), VCH, New York, **1992**, p. 335.
[5] E. T. Kool, P. K. Hansma, M. Kashlev, S. Kasas, N. H. Thomson, B. L. Smith, H. G. Hansma, X. Zhu, M. Guthold, C. Bustamante, *Biochemistry* **1997**, *36*, 461–468.
[6] C. Bustamante, G. Zuccheri, S. H. Leuba, G. Yang, B. Samori, *Methods* **1997**, *12*, 73–83.
[7] I. Tuzov, K. Cramer, B. Pfannemuller, W. Kreutz, S. N. Magonov, *Adv. Mater.* **1995**, *7*, 656–659.
[8] K. Craemer, S. Demharter, R. Muelhaupt, H. Frey, S. N. Magonov, I. Tuzov, M.-H. Whangbo, *New. J. Chem.* **1996**, *20*, 5–11.
[9] K. Ariga, N. Yamada, M. Naito, E. Koyama, Y. Okahata, *Chem. Lett.* **1998**, 493–494.
[10] M. Kogiso, S. Ohnishi, K. Yase, M. Masuda, T. Shimizu, *Langmuir* **1998**, *14*, 4978–4986.
[11] J.-H. Fuhrhop, W. Helfrich, *Chem. Rev.* **1993**, *93*, 1565–1582.
[12] F. M. Menger, S. J. Lee, *J. Am. Chem. Soc.* **1994**, *116*, 5987–5988.
[13] C. F. v. Nostrum, R. J. M. Nolte, *Chem. Commun.* **1996**, 2385–2392.
[14] T. Shimizu, M. Masuda, *J. Am. Chem. Soc.* **1997**, *119*, 2812–2818.
[15] T. Shimizu, M. Kogiso, M. Masuda, *Nature* **1996**, *383*, 487–488.
[16] T. Shimizu, M. Kogiso, M. Masuda, *J. Am. Chem. Soc.* **1997**, *119*, 6209–6210.
[17] T. Shimizu, M. Masuda, M. Kogiso, M. Asakawa, *Kobunshi Ronbunsyu* **1997**, *54*, 815–828.
[18] M. Kogiso, M. Masuda, T. Shimizu, *Supramol. Chem.* **1998**, in press.
[19] J. H. Dumbleton, T. R. Lomer, *Acta. Crystallogr.* **1965**, *19*, 301–307.
[20] J.-H. Fuhrhop, J. Koening in *Membranes and Molecular Assemblies: The Synkinetic Approach,* The Royal Society of Chemistry, Cambridge, **1994**, p. 186.
[21] A. Tardieu, V. Luzzati, *J. Mol. Biol.* **1973**, *75*, 711–733.

A New Look at the Diels–Alder Transition State[**]

Claude Spino,[*] Marc Pesant, and Yves Dory[*]

In relation to the unexpectedly high reactivity of 2-carbomethoxy-1,3-butadiene (**1**) in Diels–Alder reactions (Scheme 1), we recently suggested the presence of a strong double-bond character between C2 and C3 in the transition state (TS).[1] To gain better insight into the mechanism of the Diels–Alder reaction, we reconstructed the whole butadiene–ethylene reaction pathway by means of the intrinsic reaction coordinate (IRC) approach.[2] Then, selected structures were extracted to obtain their orbitals, geometries, and energies. We were surprised to witness that the various orbital interactions do not occur simultaneously during the Diels–Alder reaction. The four-electron interaction of symmetric orbitals (Figure 1, green and red curves) begins well in advance at a distance of over 3.0 Å between the diene and dienophile.[3] By comparison the two-electron interaction between the antisymmetric orbitals (blue curve) commences at a distance near 2.4 Å! The reason behind this chronology is not yet clear. Remarkably though, many of the geometrical features observed in most (if not all) calculated concerted TS (Scheme 2) of the ethylene–butadiene reaction (and indeed of other systems) reflect perfectly this asynchronicity of molecular orbital interactions.[4] Shorter C2−C3 and longer C5−C6 bonds reflect an advanced HOMO$_{\text{dienophile}}$–LUMO$_{\text{diene}}$ interaction, while short C1−C2/C3−C4 and long forming σ bonds are indicative of an emerging HOMO$_{\text{diene}}$–LUMO$_{\text{dienophile}}$ interaction.[3] In effect, the long σ bonds reflect an early TS, while the well-developed C2−C3 π bond is reminiscent of a late TS, as we suggested earlier.[1]



Scheme 1. Dimerization of **1**. The reaction is fast at or below room temperature.

Fukui's frontier molecular orbital (FMO) theory[5] has proved to be a valuable tool in predicting the rate and selectivity of organic reactions, in particular pericyclic reactions and cycloadditions.[6] This principle was used to predict

---

[*] Prof. C. Spino, Prof. Y. Dory, M. Pesant
Université de Sherbrooke
Département de Chimie
Sherbrooke, Qc, J1 K 2R1 (Canada)
Fax: (+1) 819-821-8017
E-mail: cspino@courrier.usherb.ca
ydory@aix1.si.usherb.ca

[**] We thank Prof. Jean Lessard for useful discussions. We acknowledge the Natural Sciences and Engineering Council of Canada for financial support. We thank Brett Bode for his great software MacMolPlt, which was used to display the orbital drawings of Figure 1.

Supporting information for this article is available on the WWW under http://www.wiley-vch.de/home/angewandte/ or from the author.

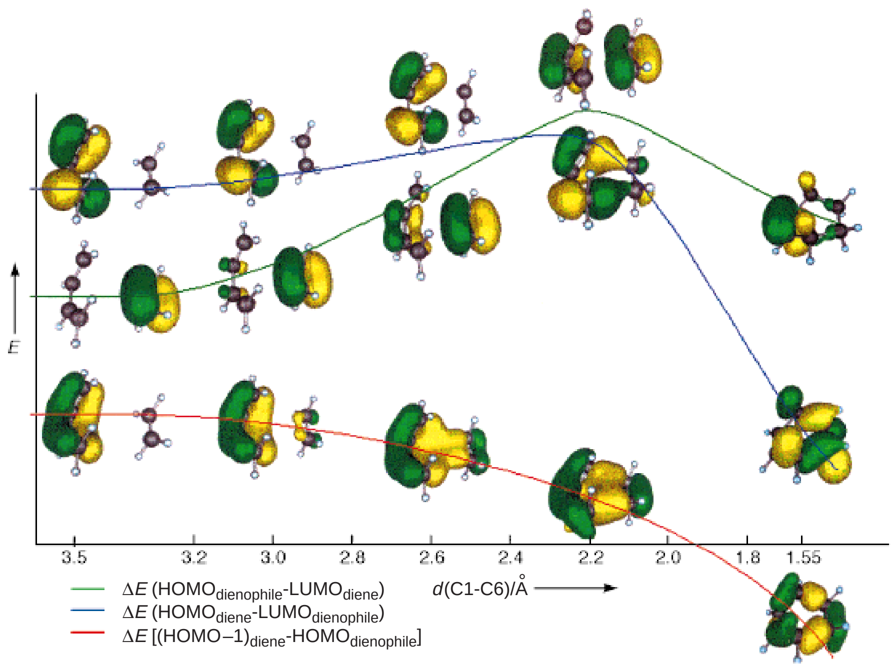
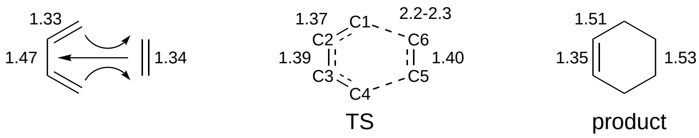


Figure 1. Energy profiles (approximately to scale) and chronology of orbital mixing for the three occupied π orbitals during the Diels – Alder reaction between butadiene and ethylene. For clarity, the total energy is not included.

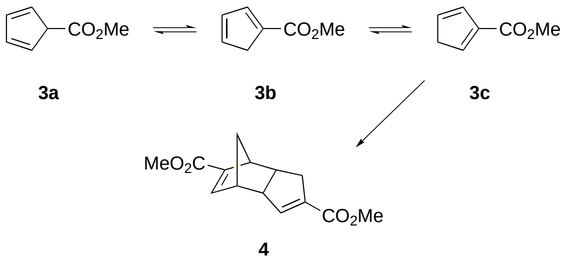


Scheme 2. Proposed formalism for the orbital interaction in Diels – Alder reactions (left) and typical bond lengths calculated for the transition state (TS) of the Diels – Alder reaction between ethylene and butadiene. On the right the bond lengths in the product are shown.

reactivity and selectivity issues in Diels – Alder reactions based on the strength of a single MO interaction, the "dominant" interaction. However, many reactions appear to disobey the FMO rules of regiochemistry[3] or reactivity,[7] including reactions of butadienes with conjugating substituents at C2 or C3.[1]

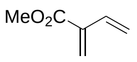
After examining Figure 1, we became convinced that the practice of taking only the dominant FMO interaction into account when assessing diene – dienophile reactivities is groundless in many cases. Our findings suggest two things: Firstly, the clearly well-developed C2–C3 π bond in the TS should allow conjugating substituents at C2 or C3 or aromatic systems (as in the *o*-quinodimethanes) to decrease the energy of the TS, supporting our earlier argument.[1] Secondly, predictions based on the energetic state of the initial HOMO$_{dienophile}$ – LUMO$_{diene}$ interaction should be unreliable because this interaction is very different from that in the starting reagents. The drawing on the left of Scheme 2 expresses our perceptions of the orbital interactions in the Diels – Alder mechanism. We believe that this symbolism reflects the proper transfer of electrons in concerted [4+2] cycloadditions, especially those involving symmetrical partners.

The following three sets of experiments highlight some consequences of our findings in dealing with diene – dienophile reactivity. Earlier we had pointed out that the electron-deficient diene **1** is as or more reactive than electron-rich dienes (Scheme 1).[1] Many other dienes having conjugating substituents at C2 or C3—including cyano, sulfone, and ketone groups—are also highly reactive toward electron-deficient dienophiles.[8] Inukai and Kojima have reported that 2-cyanobutadiene is more reactive than isoprene, 2,3-dimethyl-1,3-butadiene, and 1,3-pentadiene in thermal Diels – Alder reactions with methyl acrylate.[9] This oddity is related to the well-known dimerization of methyl cyclopentadienylcarboxylate (**3**) to Thiele's ester (**4**, Scheme 3).[10] Diene **3a** should be more reactive, but only diene **3c** with the ester functionality in the 2-position gives an adduct with dienophile **3b**.

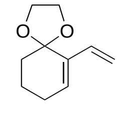


Scheme 3. Dimerization of **3**. The reaction is fast at or below room temperature.

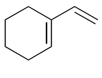
Likewise, diene **7** was similar in reactivity to **5** or **6** with respect to various electron-poor dienophiles, while its analogue **8**, having the oxo group attached to C1, could not compete at all with any of the former dienes, including **7**. From



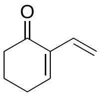
1



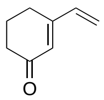
5



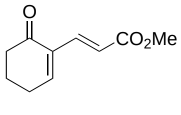
6



7



8



9

a FMO stand point, **7** and **8** should have displayed a similar reactivity.[6a] Moreover, dienes **8** and **9** competed for one equivalent of *N*-methylmaleimide to give a 45:55 mixture of adducts favoring reaction with **9**. Dienes **7** and **9** are reactive because the conjugating ketone at the 2- or 3-position will decrease the overall energy of the TS through its capacity to stabilize the developing cycloadduct π bond.

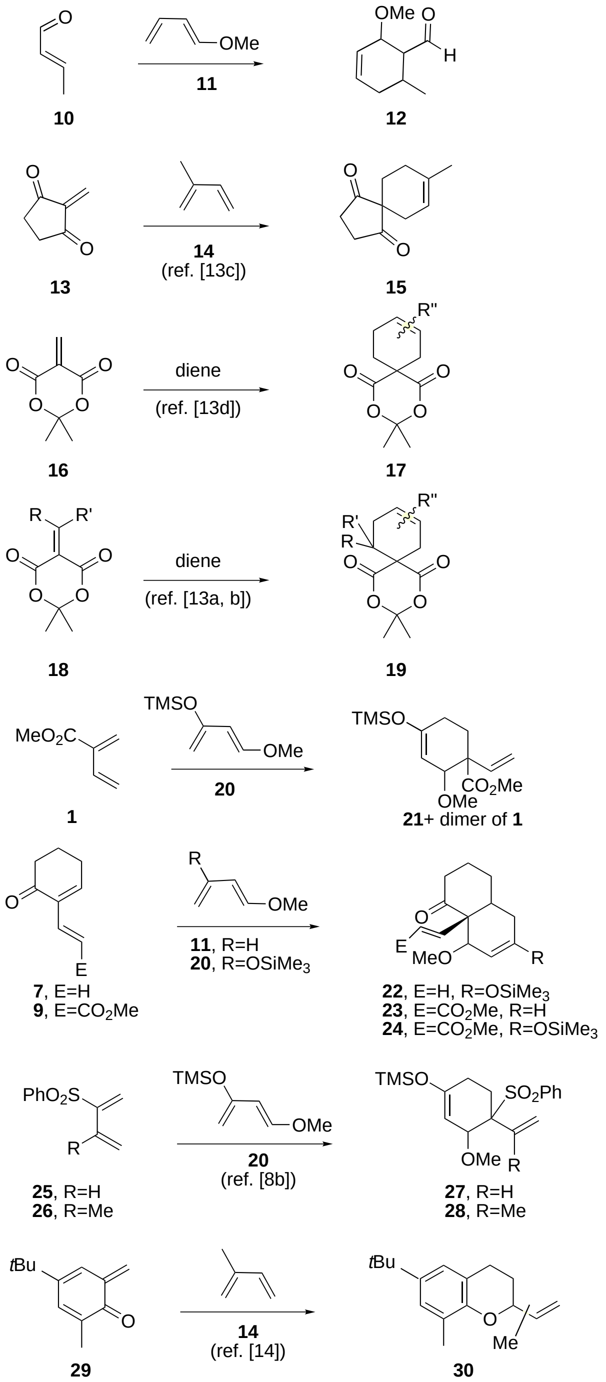
In the same vein, many electron-poor dienes reacted exclusively with electron-poor dienophiles even in the presence of electron-rich dienophiles. This has been previously demonstrated with diene **1**,[1, 11] but the trend held for many electron-poor dienes, for example **7**–**9**. In fact, for each of these three dienes, the reaction rate increased significantly with increasing electron deficiency of the dienophile (tetracyanoethylene > maleic anhydride > methyl vinyl ketone > ethyl vinyl ether).

The inability of the FMO theory to explain these cases may come from the fact that the dominant interaction is the $\mathrm{HOMO}_{\mathrm{dienophile}}-\mathrm{LUMO}_{\mathrm{diene}}$ interaction, leading to the cycloadduct π bond. As we said, predictive arguments based on the energetic state of the starting materials in this case is at least partly invalid. Therefore, the energy difference between the ground-state HOMOs of the electron-poor and the electron-rich dienophiles (ca. 2 eV)[6a] has a reduced significance in the TS. Still, why would electron-poor dienophiles be preferred? We suggest it is because electron-poor dienophiles provide an energetically lower lying LUMO (often by more than 3.0 eV).[6a] This results in a stronger $\mathrm{HOMO}_{\mathrm{diene}}-\mathrm{LUMO}_{\mathrm{dienophile}}$ interaction, which should be more influential for the energy of the TS than the $\mathrm{HOMO}_{\mathrm{dienophile}}-\mathrm{LUMO}_{\mathrm{diene}}$ interaction (despite its larger energy gap). This may also explain why Diels–Alder reactions with inverse electron demand are generally slower and more sluggish than normal Diels–Alder reactions.[12]

Lastly, and perhaps more convincingly, we have observed that electron-poor dienes react readily with electron-rich dienes in cross-Diels–Alder reactions to give exclusively the normal Diels–Alder cycloadducts. From unrelated examples in the literature, as well as our own work, we could find almost no exceptions to this rule (Scheme 4).[8b, 13] Reactions with **18** (R = Ar) or **9** constitute rather convincing examples, when one considers that the Diels–Alder cycloaddition is sensitive to sterically demanding groups on the dienophile. Also impressive are the examples with compounds **13**, **16**, and **18** in which the α,β-unsaturated ketone is held in a cisoid conformation and should have an advantage as a diene.[13a-c]

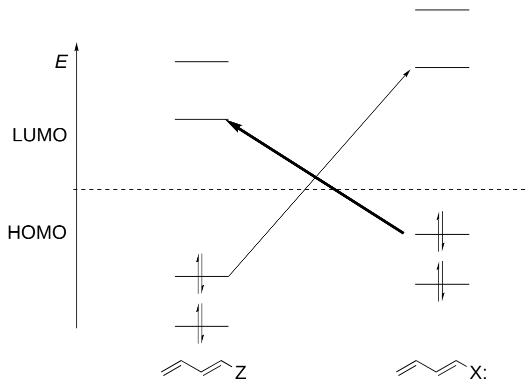
These cross-cycloaddition experiments offer unambiguous evidence since the dominant orbital interaction involves the same MOs in either electronic sense. However, in the normal reactions the dominant orbital interaction is $\mathrm{HOMO}_{\mathrm{diene}}-\mathrm{LUMO}_{\mathrm{dienophile}}$, while in the sense of inverse electron demand the same orbitals are involved in the $\mathrm{HOMO}_{\mathrm{dienophile}}-\mathrm{LUMO}_{\mathrm{diene}}$ interaction (Scheme 5). We conclude that the dienes will inherently prefer the cross-reaction path with the smaller $\mathrm{HOMO}_{\mathrm{diene}}-\mathrm{LUMO}_{\mathrm{dienophile}}$ energy gap, that is, the normal Diels–Alder pathway. Thus, the dienes minimize the energy of the TS by maximizing the strength of the interaction playing the predominant role in the relative rate of the reaction.

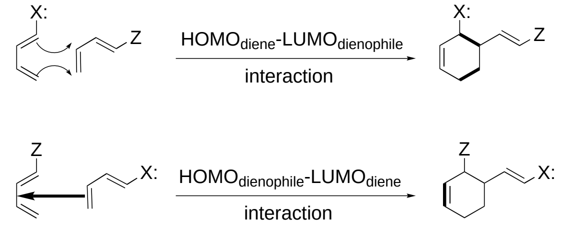
Finally, *o*-quinone methide (**29**) reacted with isoprene to give a product of a Diels–Alder reaction with inverse electron demand (Scheme 4).[14] The developing aromatic character of the quinone methide ring caused by the strong double-bond character between C2 and C3 in the TS overpowers any stabilizing effect from MO interactions. The high reactivity of *o*-quinone dimethides with electron-poor, electron-rich, or even unactivated dienophiles must be due to that same phenomenon. This notion has never been formally proposed before because it conflicts with the accepted idea of an aromatic and "early" TS for the Diels–Alder reaction.



Scheme 4. Examples of cross-Diels–Alder reactions; in each case the cycloadduct shown is the exclusive product. TMS = Me_3Si.

Our discovery changes and complements the current FMO treatment of the Diels–Alder reaction as pertaining to the reactivity of diene–dienophile partners. Our model should





Scheme 5. The dominant interaction in cross-cycloaddition experiments leads to different orbitals in the final cycloadduct depending on the reaction path.

prove useful in predicting more accurately the reactivity of dienes and dienophiles. It will likely have repercussions on predictions of the regio- and stereoselectivity of the process as well.

Received: May 14, 1998
Revised version: August 24, 1998 [Z 11857 IE]
German version: *Angew. Chem.* **1998**, *110*, 3454–3457

Keywords: computer chemistry · cycloadditions · reaction mechanisms · transition states

---

[1] a) C. Spino, J. Crawford, M. Gugelchuk, Y. Cui, *J. Chem. Soc. Perkin Trans. 2* **1998**, 1499–1506; b) C. Spino, J. Crawford, *Can. J. Chem.* **1993**, *71*, 1094–1097.

[2] K. Fukui, *Acc. Chem. Res.* **1981**, *14*, 363–368.

[3] For a detailed description of the various orbital interactions in the Diels–Alder reaction of butadiene and ethylene, see R. D. Bach, J. J. W. McDouall, H. B. Schlegel, *J. Org. Chem.* **1989**, *54*, 2931–2935.

[4] a) K. N. Houk, Y. Li, J. D. Evanseck, *Angew. Chem.* **1992**, *104*, 711–739; *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 682–708; b) R. E. Townshend, G. Ramunni, L. E. Overmann, W. J. Hehre, L. Salem, *J. Am. Chem. Soc.* **1976**, *98*, 2190–2198; c) E. Goldstein, B. Beno, K. N. Houk, *J. Am. Chem. Soc.* **1996**, *118*, 6036–6043; d) K. N. Houk, *Pure Appl. Chem.* **1989**, *61*, 643–650; e) Y. Li, K. N. Houk, *J. Am. Chem. Soc.* **1993**, *115*, 7478–7485.

[5] a) K. Fukui, *Molecular Orbitals in Chemistry, Physics, and Biology*, Academic Press, New York, **1964**, p. 525; b) K. Fukui, *Acc. Chem. Res.* **1971**, *4*, 57–64.

[6] a) I. Fleming, *Frontier Orbitals and Organic Chemical Reactions*, Wiley, Chichester, **1976**, p. 249; b) T. N. Anh, *Orbitales frontières, manuel pratique*, InterEditions & CNRS Éditions, Paris, **1995**, p. 265.

[7] V. D. Kiselev, A. I. Konovalov, *Russ. Chem. Rev.* **1988**, *58*, 230–249, and references therein.

[8] a) P. G. Baraldi, A. Barco, S. Benetti, S. Manfredini, G. P. Pollini, D. Simoni, V. Zanirato, *Tetrahedron* **1988**, *44*, 6451–6454; b) T.-S. Chou, S.-C. Hung, *J. Org. Chem.* **1988**, *53*, 3020–3027; c) J. F. Honek, M. L. Mancini, B. Belleau, *Synthetic Comm.* **1984**, *14*, 483–491.

[9] T. Inukai, T. Kojima, *J. Org. Chem.* **1971**, *36*, 924–928.

[10] G. L. Dunn, J. K. Donohue, *Tetrahedron Lett.* **1968**, 3485–3487.

[11] J. M. McIntosh, R. A. Sieler, *J. Org. Chem.* **1978**, *43*, 4431–4433.

[12] D. L. Boger, S. M. Weinreb, *Hetero Diels–Alder Methodology in Organic Synthesis*, Academic Press, New York, **1987**, p. 366.

[13] a) G. A. K. Kraus, M. E., *J. Org. Chem.* **1986**, *51*, 3347–3350; b) G. A. Mock, A. B. Holmes, R. A. Raphael, *Tetrahedron Lett.* **1977**, 4539–4540; c) P. E. Eaton, W. H. Bunnelle, *Tetrahedron Lett.* **1984**, *25*, 23–26; d) J. F. Buzinkai, D. M. Hrubowchak, F. X. Smith, *Tetrahedron Lett.* **1985**, *26*, 3195–3198.

[14] D. A. Bolon, *J. Org. Chem.* **1970**, *35*, 3666–3670.

Kinetic and Thermodynamic Control in Self-Assembly: Sequential Formation of Linear and Circular Helicates

Bernold Hasenknopf, Jean-Marie Lehn,*
Nedjia Boumediene, Emmanuelle Leize, and
Alain Van Dorsselaer

The self-assembly of polynuclear metal coordination compounds has been very actively investigated in recent years, in particular that of complexes presenting a helical arrangement of ligand strands.[1–3] Whereas most of these helicates present linear axes, circular helical architectures have also been reported.[4–6] We recently described the self-assembly of circular helicates based on the octahedral coordination of three tris-bipyridine ligands such as **L** (see Figure 1) with iron(II) ions.[4, 5] On the other hand, with nickel(II) ions ligand **L** had earlier been found to lead to the formation of a complex presenting a triple-helicate structure.[7] Thus, the same ligand yields two different architectures with two metal ions that display the same coordination geometry. In view of these intriguing results we decided to follow more closely the self-assembly process, in order to gain insight into the structural, mechanistic, and physicochemical factors that may be at play.

In particular, whereas in the self-assembly of both synthetic and biological systems the thermodynamic product is usually formed (and should finally result in reversible equilibrium conditions), kinetic products may also be obtained if the shape of the energy hypersurface is such that the system becomes trapped in local minima. Indeed, self-assembly[1] is evidently a time-dependent process, and it may thus display kinetic control.

---

[*] Prof. J.-M. Lehn
Laboratoire de Chimie Supramoléculaire
ISIS, Université Louis Pasteur
4 rue Blaise Pascal, F-67000 Strasbourg (France)
Fax: (+33) 3-88411020
E-mail: lehn@chimie.u-strasbg.fr

Dr. B. Hasenknopf
Université Pierre et Marie Curie
Chimie Inorganique et Matériaux Moléculaires, Paris (France)

N. Boumediene, Dr. E. Leize, Prof. A. Van Dorsselaer
Laboratoire de Spectrométrie de Masse Bio-Organique,
Université Louis Pasteur, Strasbourg (France)