LOW MOLECULAR WEIGHT BIS-UREA ORGANOGELATORS

Reported by Kimberly R. Deaton February 21, 2002

INTRODUCTION

Gels are pervasive materials that behave much like solids and are composed of a fibrous three-dimensional network whose interstitial spaces are filled with liquid.[1] Historically, most gels are composed of covalently crosslinked polymers that have typical molecular weights above 3000. More recently it has been found that the aggregation of certain low molecular weight compounds in an organic medium can result in the formation of organogels. These compounds often form gels in a variety of organic solvents at a concentration of less than 2% weight/volume.[2] They are referred to as low molecular weight organic gelators (LMOG) because contrary to polymer gels they usually have molecular weights less than 1000. In solution, low molecular weight organogelators self-assemble strictly by non-covalent interactions. The nature of the intermolecular interactions between the organogelator molecules, whether van der Waals interactions, π-π stacking, dipole-dipole interactions, electrostatic interactions, or hydrogen bonding, allows these molecules to assemble in one-dimensional arrays producing elongated fibrous structures.[2a] Entanglement of the fibers subsequently produces a three-dimensional network capable of trapping the solvent and yielding the gel (Figure 1).

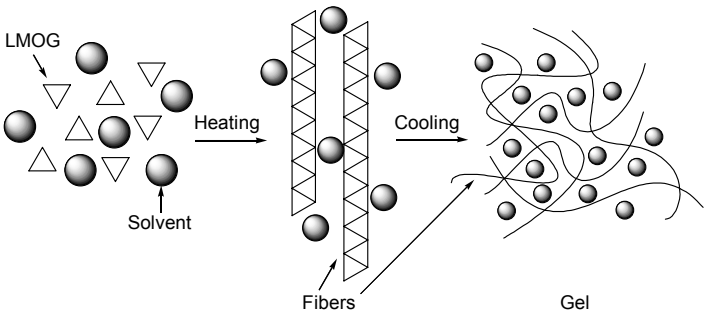


Figure 1. Steps in gelation of low molecular weight organogelators (LMOG)

Many classes of LMOG have been discovered, including fatty acids, steroidal compounds, anthracene derivatives, porphyrins, carbohydrates, peptide derivatives, calixarenes, and various two-component systems.[2c] Several characteristics have been noted among the various organogelators, including limited solubility at room temperature, complete dissolution upon heating, and highly directional self-assembly into linear fibers. Little is understood about why these molecules prefer an ordered self-assembly in dilute solutions versus a disordered state. To elucidate the driving force for gelation, many researchers have focused on reducing the structural complexity of LMOG.[3] Compounds composed of two urea groups with acyclic, cyclic, and geminal linkages have been designed. These bis-urea compounds show highly directional aggregation for gel formation which comprise a new class of organogelators to be surveyed in this abstract.[4]

DESIGN OF BIS-UREA ORGANIC GELATORS

Intermolecular hydrogen bonds between urea groups are effective self-assembly triggers in organic molecules.[5] Previous modeling and crystallographic studies have demonstrated that urea compounds are capable of highly directional self-assembly by means of complementary hydrogen bonds (Figure 2).[6] The directional assembly of urea groups has been applied to a number of modeling and synthesis efforts involving acyclic, cyclic, and geminal bis-urea compounds.

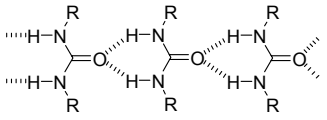
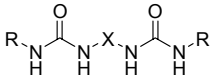


Figure 2. Complementary hydrogen bonds between urea

Acyclic Bis-Ureas

Initial investigations of bis-urea compounds as organogelators began with acyclic derivatives bearing two identically substituted urea groups connected by a linker (Table 1).[4] The end groups (R) and linkers (X) in the bis-ureas provide a delicate balance between solubility and crystallization, which is essential to gelation in organic solvents. The general procedure for gel formation consists of heating the bis-urea in a closed test tube to promote dissolution, and cooling to trap solvent in the assembled entangled network. The resulting materials are considered organogels if upon inversion of the test tube they retain their original shape and are resistant to flow.[2a]

Table 1. Acyclic *bis*-urea compounds



Compound	R	X
1	*n*-dodecyl	$-C_6H_4-CH_2-C_6H_4-$
2	*n*-dodecyl	4,4'-biphenyl
3	*n*-dodecyl	$-(CH_2)_6-$
4	*n*-dodecyl	$-(CH_2)_9-$
5	*n*-dodecyl	$-(CH_2)_{12}-$
6	benzyl	$-(CH_2)_3-$
7	benzyl	$-(CH_2)_6-$
8	benzyl	$-(CH_2)_9-$
9	benzyl	$-(CH_2)_{12}-$
10	(*R*)-1-phenylethyl	$-(CH_2)_9-$

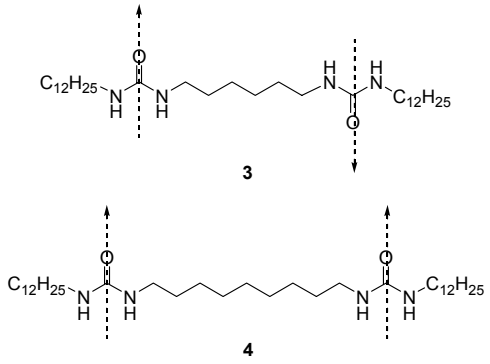
Compounds **1**-**10** were tested for gelation in several organic solvents to identify a correlation between gelation ability and structural features. Because heating between 90-150 ºC was necessary for dissolution of the bis-ureas, solvents with high boiling points were chosen. In this study the organogelators with *N*,*N*'-*n*-dodecyl groups were able to gel a great variety of organic solvents, likely from conformational freedom in the end chains (**3**-**5**). The symmetric di-benzyl substituted bis-ureas (**6**-**9**) were excellent gelators in 1-octanol, 2-octanol, and tetralin, often at less than 1% weight/volume. Compounds with internal polymethylene chains of nine or twelve carbons resulted in the gelation of many organic solvents (**4**, **5**, **8**, **9**). Rigid linkers such as 4,4'-biphenyl in compound **2** were not as susceptible to the gelation of organic solvents (**1**-**2**). The authors concluded that gelation ability of these acyclic bis-urea compounds is related to the conformational freedom in the linker unit.[4b,c]

The gels formed by **3**-**10** were studied using X-ray diffraction, light microscopy, and electron microscopy. All three techniques verified the presence of a fibrous network. The networks were

composed of rectangular sheets consisting of five to ten flat fibers. The fibers ranged in length from 300 to 400 microns and often displayed twists. The shapes of the fibers suggested ordered growth at the molecular level during assembly.[4b,c]

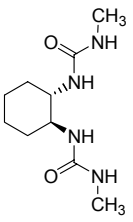
To obtain further evidence that supports the highly ordered molecular assemblies in the fibers, the Dutch authors performed molecular modeling studies of bis-ureas **3** and **4**. The lowest energy conformation for **4** had a slight twist that pointed the urea groups in the same direction (Figure 3). Interestingly, changing the linker chain by one carbon, as in compound **3**, resulted in an anti-parallel positioning of the urea groups in the lowest energy conformer (Figure 3). The parallel and anti-parallel positioning of the urea groups in both of these models suggests that one-dimensional self-assembly was likely the type of molecular order present in the fibers.[4c]

Figure 3. Linear directionality of urea groups in compounds **3** & **4**



Cyclic Bis-Ureas

The acyclic bis-urea compounds confirmed the effectiveness of urea groups in the formation of organogels. However, owing to the conformational freedom in these structures, correlations between the linker groups and the gelation ability were difficult to comprehend. Geometric constraints of the urea groups seemed a plausible method to enforce one-dimensional aggregation along an axis while monitoring the differences of the various end groups. Kellogg and coworkers performed some preliminary molecular modeling studies on rigid, cyclic compounds to determine if they were capable of one-dimensional self-assembly through intermolecular hydrogen bonds.[7]



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Preliminary molecular modeling studies of (*S*,*S*)-*trans*-1,2-bis(methylureido)cyclohexane **(11)** were performed to predict its crystallographic packing arrangement. Three energy minima were found for **11**; the most stable conformation had one intramolecular hydrogen bond, while in the remaining minima the urea groups were oriented in parallel and antiparallel positions (Figure 4).[7] It was inferred from docking experiments with a second molecule that all three conformations are capable of linear packing. Two crystal packing arrays were modeled for **11** according to the crystallographic symmetry operations that allowed formation of eight hydrogen bonds between each bis-urea and the adjacent molecules. Since the cyclohexane bis-urea **11** is chiral, it is restricted to the translational and screw axis symmetry operations. The resulting arrays showed extensively hydrogen bonded networks which were modeled with intermolecular distances

between 4.4 to 4.5 Å, consistent with X-ray scattering data. The modeled linear fibers were estimated to be 25- 29 kcal mol^{-1} more stable than the lowest energy conformer of **11**.

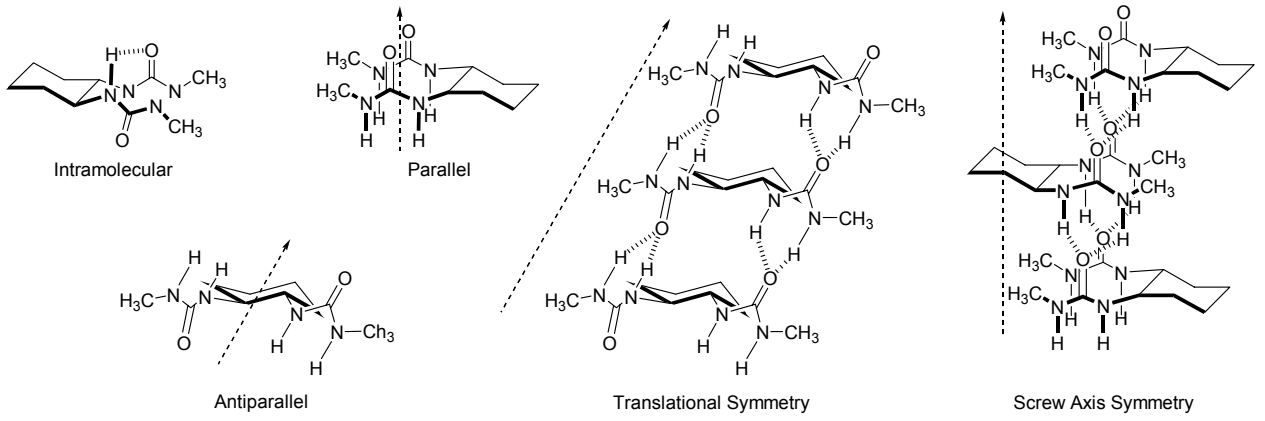
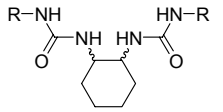
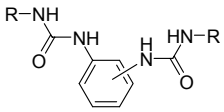
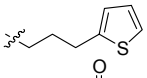
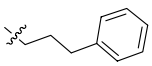
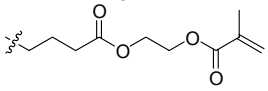
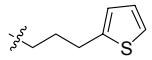


Figure 4. Three energy minima for **11** ad the linear arrays formed by translation and screw axis operations

These modeling results implied that cyclic bis–urea compounds would be potential LMOG candidates. Bis-ureas **13-23** were synthesized by addition of 1,2–diaminocyclohexane or 1,2-diaminobenzene to the corresponding isocyanate (Table 2).[7] Gelation studies were conducted in a variety of polar and apolar solvents. Of the solvents tested, toluene, *p*-xylene, and 1,2-dichloroethane appeared to be the best for the gelation of these cyclic compounds. When the urea groups are trans di-equatorial on the cyclohexane rings and the side chains can adopt conformations similar to the modeled energy minima (**13-16**), gelation was observed. Compound **17** did not gel any organic solvent tested, which was likely a direct result of the inability of this cis isomer to adopt the same conformation of the axial ureido group. In the di-substituted benzenes, the ortho substituted isomers **18-21** afforded organogels presumably owing to the ability of the urea groups to twist out of the plane of the aromatic ring forming linearly stacked aggregates. The meta and para substituted isomers **22** and **23** did not yield organogels. In most cases these compounds were either insoluble or precipitated during the gelation procedure. These studies indicated that the orientation and position of the urea groups is critical for gelation.

Table 2. Cyclic bis-urea compounds

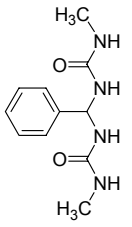



Compound	R	Compound	R
13a (*S*,*S*)	*n*-dodecyl	**18** *ortho*	*n*-dodecyl
13b (*R*,*R*)	*n*-dodecyl		
14 (*R*,*R*)	$-CH(C_2H_5)(CH_2)_3CH_3$	**19** *ortho*	
15 (*R*,*R*)		**20** *ortho*	
16 (*R*,*R*)		**21** *ortho*	
17 (*R*,*S*)	*n*-dodecyl	**22** *meta* **23** *para*	*n*-dodecyl *n*-dodecyl

Analysis of the gels using Small Angle X-ray Scattering (SAXS) confirmed the lamellar shape of the fibers in the gels of bis-ureas **13**-**16**, **18**, **20**, and **21**. Further investigations with compound **13** indicated that the molecular packing of the gels did not depend on the solvent used. The SAXS data confirmed that the packing at the molecular level is very regular, as predicted by the modeling. Feringa and coworkers believe that understanding of crystal packing and the modeling of such crystal lattices may assist in the design of other LMOG.[7]

Geminal Bis-Ureas

The relative orientation of the two urea groups could be further restricted by using a one-carbon linker. Feringa and coworkers modeled the geminal bis-urea **24** to determine if crystal packing of the energy-minimized structure would lead to highly directional aggregation.[8] Two of the minima found placed the urea groups in parallel and antiparallel geometries. Self-assembly of these two conformations using the allowed crystallographic symmetry operations produced four linear arrays. Representations of the direction and the molecular arrangements in the arrays are shown in Figure 5.



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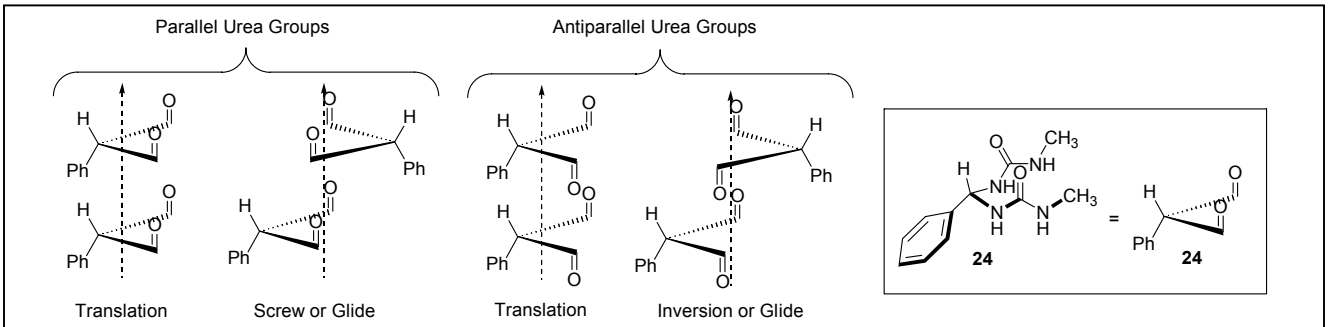
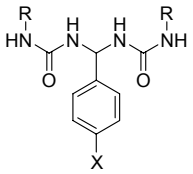


Figure 5. Linear arrays for **24** according to urea group alignments and symmetry operations

The symmetry elements of the parallel minima included translation, a screw axis, and a glide plane. The application of these symmetry operations produced two possible arrays. The antiparallel minima had an inversion center, a translation, and a glide plane that resulted in two more linear arrays. In all cases the linear aggregates of compound **24** produced linear chains of molecules lower in energy than the lowest energy conformation of **24**.[8]

Feringa and coworkers synthesized geminal bis-ureas **24**-**30** by acid-catalyzed condensation of the corresponding benzaldehydes and monoalkylureas (Table 3).[8] During the preparation of these compounds, gelation frequently occurred preventing complete conversion to the products. This suggested that the geminal bis-urea compounds would be excellent organogellators. Toluene, *p*-xylene, and tetralin produced the most stable gels that were homogeneous within these solvents and stable for

Table 3.



24: X = H	R = *n*-butyl
25: X = H	R = benzyl
26: X = Cl	R = *n*-butyl
27: X = OMe	R = *n*-butyl
28: X = NMe_2	R = *n*-butyl
29: X = NO_2	R = *n*-butyl
30: X = H	R = methyl

several weeks. Decomposition of the geminal bis-ureas was facile in the presence of acid and water, which shortened the lifetimes of the gels. The gels were analyzed using electron microscopy to confirm the three-dimensional network of fibers.[8]

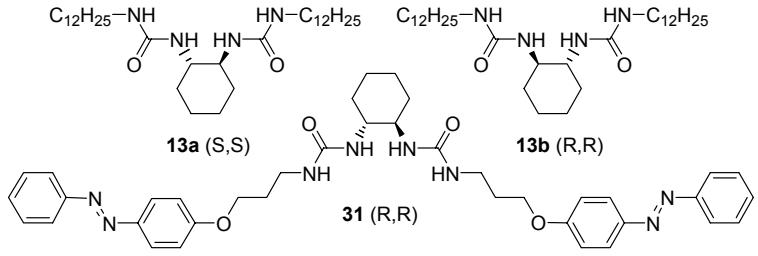
APPLICATIONS

Bis-urea self-assembled organogels are novel materials owing to their thermoreversibility and highly ordered but low-density packing. Structural modifications to the organogelators provide a means to confer other interesting properties onto the gels. Several groups have reported structurally modified gels that exhibited chiral recognition, intermolecular charge transport, and the production of microporous aerogels.[9]

Chiral Recongnition

Chiral recognition between gels and an aggregating guest has recently been demonstrated by Kellogg and coworkers.[10] The enantiomer cyclohexanes **13a** and **13b** used in this study are shown with the similar guest molecule (*R*,*R*)-**31** in Chart 1. Compound **31** was distinguished from the organogelators by the attachment of chromophores. Solution experiments using ^{1}H NMR spectroscopy and Circular Dichroism indicated the preferred aggregation of (*R*,*R*)-**31** with gels of (*S*,*S*)-**13a**.[10] Electron micrographs of gels for the chiral cyclohexanes **13a** and **13b** indicate helical twists in the fiber network that may influence the preferential aggregation.

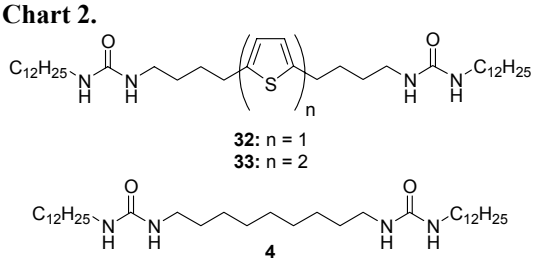
Chart 1. Chiral LMOG's and guest



Charge Transport

Organic molecules capable of producing materials with semiconducting properties are of great interest in the production of thin film transitors, light-emitting diodes, and electrical devices.[11] Thiophenes are one class of organic compounds capable of internal charge transport when closely packed. The highly ordered self-association of bis-urea compounds with high directionality poses enormous potential for the close π-stacking of thiophene units. Feringa and coworkers synthesized two acyclic bis-urea compounds linked by one or two thiophene rings (Chart 2).[11] Thiophene linked bis-ureas 32 and 33 exhibited self-

Chart 2.



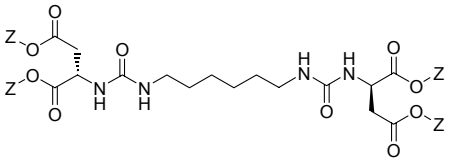
assembly in tetralin and 1,2-dichloroethane forming organogels. Conductivity measurements of the solid-state powders of 32, 33, and 4, which lacked the thiophene connector, using pulse-radiolysis time-resolved microwave conductivity techniques, revealed a distinct increase in conductivity as each thiophene moiety was introduced (Table 4). Although the conductivity is still below that of a typical semi-conductor, this data suggests the potential application of organogels as charge transport media.[11]

Table 4. Solid state conductivities of **4**, **32**, & **33**

Compound	Conductivity (Sm^2/J)
4	$9x10^{-10}$
32	$8x10^{-9}$
33	$4x10^{-8}$

Aerogels

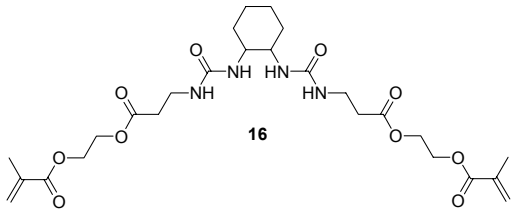
Microporous materials are of particular interest for use as separation agents, insulating materials, and catalyst supports. An aerogel is a microporous material that forms when solvent is removed from a gel, leaving the skeleton of the three-dimensional fiber network.[12] Several groups have reported the preparation of aerogels using bis-urea compounds. Hamilton and coworkers synthesized bis-urea gelators represented by **34**, which are capable of gel formation in super-critical CO_2.[11, 13] Aerogels were produced when super-critical CO_2 was removed by decreasing pressure. The solubility of **34** in super-critical CO_2 was facilitated by the presence of the highly fluorous end groups, Z.[13b] The resulting gels were thermoreversible and pressure-reversible.[13a,b] The entire process provides a potentially green method for the development of microporous aerogels.



34

Z = $-(CH_2)(CF_2)_7CF_3$

Polymerization of the organogels of bis-urea **16** resulted in the formation of a low-density porous aerogel.[14] The gels were formed in cyclohexane, butyl acetate, benzene, tetralin, 1,2-dichloroethane, and benzene in the presence of the photoinitiator. Following gelation, UV-initiated polymerization of the methacryl chain termini and subsequent drying of the gels yielded a highly stable and porous material. The resulting aerogel exhibited significantly increased stability owing to the covalent linking of the gel network. Small angle X-ray scattering measurements indicated that the diameter of the smallest fibers were 50 nm. Developments in gelation techniques to control the fibrous network and the dimensions of the resultant pores will aid the formation of specific aerogels that can achieve separation of compounds by size and even chirality.[14]



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CONCLUSIONS

The bis-urea compounds described herein constitute to a new class of organogelators. These compounds have been shown to pack in regular linear patterns dictated by the geometry of the two urea groups, yielding elongated fibers that produce a network capable of trapping solvent. Introduction of chirality and other functionalities capable of conferring interesting properties, such as thiophenes, into these bis-urea gelators offers great potential for the creation of many novel materials with intriguing properties.

REFERENCES

(1) Osada, Y.; Gong, J-P. *Adv. Mater.* **1998**, *10*, 827-837.

(2) a) Terech, P.; Weiss R. G. *Chem. Rev.* **1997**, *97*, 3133-3159. b) van Esch, J.; Schoonbeek, F.; de Loos, M.; Kooijman, H.; Spek, A. L.; Kellogg, R. M.; Feringa, B. L. *Chem. Eur. J.* **1999**, *5*, 937-950. c) Brinksma, J.; Feringa, B. L.; Kellogg, R. M.; Vreeker, R.; van Esch, J. *Langmuir* **2000**, *16*, 9249-9255.

(3) Abdallah, D. J.; Weiss, R. G. *J. Braz. Chem. Soc.* **2000**, *11*, 209-218.

(4) a) Hanabusa, K.; Shimura, K.; Hirose, K.; Kimura, M.; Shirai, H. *Chem. Lett.* **1996**, 885-886. b) van Esch, J.; Kellogg, R. M.; Feringa, B. L. *Tet. Lett.* **1997**, *38*, 281-284. c) van Esch, J.; De Feyter, S.; Kellogg, R. M.' De Schryver, R.; Feringa, B. L. *Chem. Eur. J.* **1997**, *3*, 1238-1243.

(5) a) Jadzyn, J.; Stockhausen, M.; Zywucki, B. *J. Phys. Chem.* **1987**, *91*, 754-757. b) Chang, Y-L.; West, M-A.; Fowler, F. W.; Lauher, J. W. *J. Am. Chem. Soc.* **1993**, *115*, 5991-6000.

(6) a) Etter, M. C.; Urbanczyk-Lipkowska, Z.; zia-Ebrahimi, M.; Pannunto, T. W. *J. Am. Chem. Soc.* **1990**, *112*, 8415-8426. b) Desiraju, G. R. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2311-2327.

(7) van Esch, J.; Schoonbeek, R.; de Loos, M.; Kooijman, H.; Spek, A.L.; Kellogg, R. M.; Feringa, B. L. *Chem. Eur. J.* **1999**, *5*, 937-950.

(8) Schoonbeek, F. S.; van Esch, J. H.; Hulst, R.; Kellogg, R. M.; Feringa, B. L. *Chem. Eur. J.* **2000**, *6*, 2633-2640.

(9) van Esch, J. H.; Feringa, B. L. *Angew. Chem. Int. Ed.* **2000**, *39*, 2263-2266.

(10) de Loos, M.; vanEsch, J.; Kellogg, R. M.; Feringa, B. L. *Angew. Chem. Int. Ed.* **2001**, *40*, 613-616.

(11) Scoonbeek, F. S.; van Esch, J. H.; Wegewijs, B.; Rep, D. B. A.; de Haas, M. P.; Klapwijk, T. M.;Kellogg, R. M.; Feringa, B. L. *Angew. Chem. Int. Ed.* **1999**, *38*, 1393-1397.

(12) Gesser, H. D.; Goswami, P. C. *Chem. Rev.* **1989**, *89*, 765-788.

(13) a) Shi, C.; Huang, Z.; Kilic, S.; Xu, J.; Enick, R. M.; Beckman, E. J.; Carr, A. J.; Melendez, R. E.; Hamilton, A. D. *Science* **1999**, *286*, 1540-1543. b) Abdallah, D. J.; Weiss, R. G. *Adv. Mater.* **2000**, *12*, 1237-1247.

(14) de Loos, M.; van Esch, J.; Stokroos, I.; Kellogg, R. M.; Feringa, B. L. *J. Am. Chem. Soc.* **1997**, *119*, 12975-12676.