A Highly Stereoselective Optical Switching Process Based on Donor-Acceptor Substituted Dissymmetric Alkenes

Jager, W.F.; de Jong, J.C.; de Lange, B.; Huck, N.P.M.; Meetsma, A.; Feringa, B.L.

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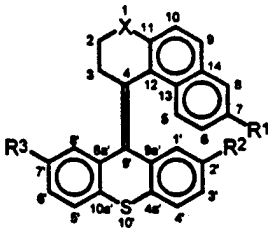
A Highly Stereoselective Optical Switching Process Based on Donor-Acceptor Substituted Dissymmetric Alkenes**

Wolter F. Jager, Johannes C. de Jong, Ben de Lange, Nina P. M. Huck, Auke Meetsma, and Ben L. Feringa*

The development of organic materials for optical data storage and molecular optical devices requires components whose physical properties can be modulated by light.[1] For a few bistable molecular systems based on photocyclization reactions impressive results have been obtained.[2] So far the bistable molecules are detected primarily by UV/Vis spectroscopy (photochromism),[1, 2] although detection based on changes in other properties such as refractive index[3] and conductivity [4] is also successfully employed.

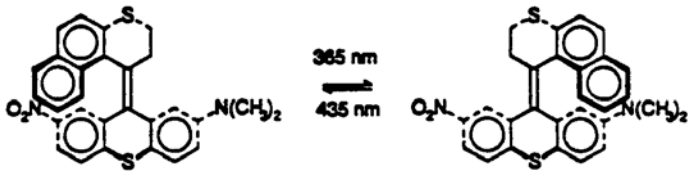
The first chiroptical molecular switch, based on the bistability of the helical *cis* and *trans* thioxanthenes **1** and **2**, was reported by our group.[5] These pseudoenantiomers[6] interconvert stereospecifically M-*cis* ⚬ P-*trans*; in other words the *cis-trans* isomerization of **1** and **2** is accompanied by a reversal of helicity. For these compounds a difference in the relative proportion of the two photostationary states of only 4 % was reached (irradiation with λ = 300 nm: 64 % M-*cis*, 36 % P-*trans*; irradiation with λ = 250 nm: 68 % M-*cis*, 32 % P-*trans*), whereas 10 % racemization (M-*cis* → P-*cis*; P-*trans* → M-*trans*) was observed after 20 switching cycles.[5]

We describe here a remarkably selective switching process based on the intrinsic chirality of donor-acceptor substituted



1 : X = CH_2, R^1 = CH_3, R^2 = OCH_3, R^3 = H
2 : X = CH_2, R^1 = CH_3, R^2 = H, R^3 = OCH_3
3 : X = S, R^1 = H, R^2 = NO_2, R^3 = N $(CH_3)_2$
4 : X = S, R^1 = H, R^2 = N $(CH_3)_2$, R^3 = NO_2

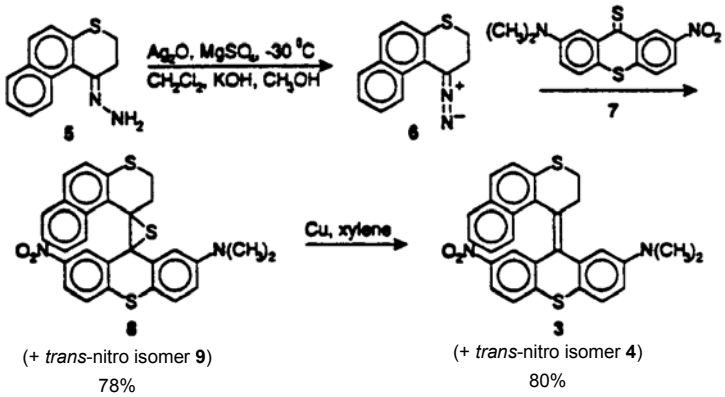
dissymmetric *cis* and *trans* **3** and **4**, respectively (Scheme 1). The absorption maxima of these compounds are red-shifted relative to those of **1** and **2**, allowing the switching process to take place in the visible. Moreover, increased thermal and photochemical stability towards racemization was obtained by the introduction of a sulfur atom at the 1-position.



Scheme 1. Chiroptical molecular switch based on the photoisomerization of P-**3** and M-**4**.

The photochemical isomerization P-**3** (*cis*-nitro) ⚬ M-**4** (*trans*-nitro) (Scheme 1) is detected by chiroptical techniques. Major advantages over other photochromic systems are: a) a more discriminative detection technique, since unlike UV spectra, circular dichroism (CD) and optical rotatory dispersion (ORD) spectra of both molecular forms P-**3** (*cis*-nitro) and M-**4** (*trans*-nitro) can reverse sign and are roughly mirror images; b) photochemical isomerization during readout[1] (fatigue) can be excluded by using ORD techniques employing a wavelength outside the absorption region.

The formation of the central double bond is the key step in the synthesis of **3** and **4** outlined in Scheme 2. Hydrazone **5** was



Scheme 2.

oxidized to the corresponding diazo compound **6** (Ag_2O, CH_2Cl_2, -30 °C), and subsequent 1,3-dipolar cycloaddition[7] with thioketone **7** was followed by extrusion of N_2 to provide the episulfides **8** (*cis*-nitro) and **9** (*trans*-nitro). The episulfides were desulfurized by reduction with copper powder to afford

[*] Prof. Dr. B. L. Feringa, Dr. W. F. Jager, Dr. J. C. de Jong, Dr. B. de Lange, Drs. N. P. M. Huck, Drs. A. Meetsma
Department of Organic and Molecular Inorganic Chemistry
Groningen Centre for Catalysis and Synthesis
University of Groningen
Nyenborgh 4, NL-9747 AG Groningen (The Netherlands)
Telefax: Int. code + (50)634296

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isomers **3** and **4** in a 60:40 ratio. The red *cis*-nitro isomer **3** (m.p. 212°C) and the yellow *trans*-nitro isomer **4** (m.p. 206 °C) were separated chromatographically.[8]

Recrystallization of **3** from ethanol afforded crystals suitable for X-ray analysis. The molecular structure of **3** is depicted in Figure 1.[9] The arrangement about the central double bond is

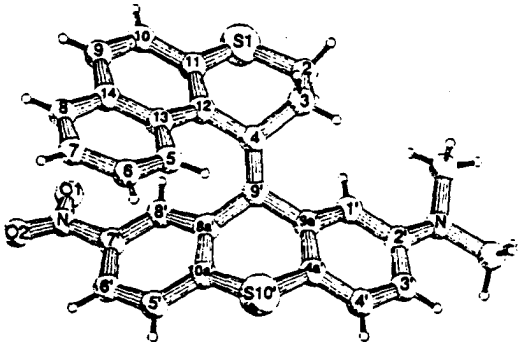

Fig. 1. X-ray crystal structure of **3** (PLUTO diagram).

nearly planar (dihedral angles 0.4-5.4°), and the bond length C4-C9′ has a normal value of 1.353 Å. The anti-folded helical structure, in which the top and bottom halves are tilted up and down, respectively, relative to the plane of the central double bond, and by which severe nonbonding interactions are avoided, is clearly shown. In **3** the nitroarene acceptor unit is located opposite the naphthalene moiety of the upper part of the molecule.

The enantiomers of **3** and **4** were resolved by chiral high-performance liquid chromatography (HPLC) with (+)-poly-(triphenylmethylmethacrylate) as a chiral stationary phase.[10] The configurations of all four stereo isomers M-**3**, P-**3**, M-**4**, and P-**4** were assigned by CD spectroscopy.[11] The enantiomers of **3** and **4** are perfectly stable under ambient conditions. The thermal racemization of P-**4** (*trans*-nitro) into M-**4** (*trans*-nitro), as determined by polarimetry at 85.0 and 90.0 °C, showed first-order kinetics with a barrier of 122.2 ± 0.5 kJ mol^{-1}. Introduction of a sulfur atom at the 1-position [12] increases the racemization barrier[13] by 12 kJ mol^{-1} relative to that of the carbon analogue **1**.[5] No thermal *cis-trans* isomerization (**3** ° **4**) occurs. In contrast. a stereospecific photochemical *cis-trans* isomerization (P-**3** ° M-**4**, λ = 300-435 nm, *n*-hexane) takes place readily and was monitored by CD, ^{1}H NMR spectroscopy, and HPLC analysis.

The UV/Vis spectra of **3** and **4** are clearly different (Fig. 2). Both compounds exhibit intense short-wavelength absorptions

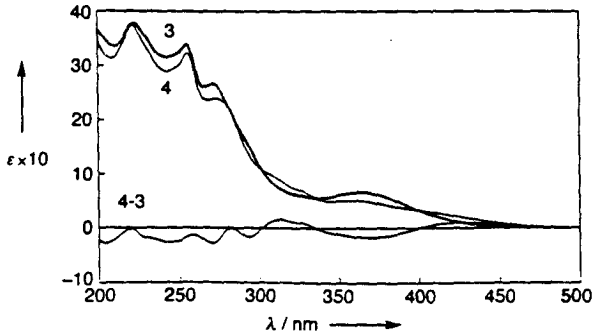

Fig. 2. UV spectra of **3** (dotted line) and **4** (solid line), and the difference spectrum (*n*-hexane).

at 220, 255, and 275 nm (ε = 25 000-40 000) and less intense long-wavelength absorptions. For **3** (*cis*-nitro) a well-defined absorption at 366 nm (ε = 7500) is observed, while **4** (*trans*-nitro) has a much broader, low-intensity absorption at 360 nm (ε = 5300). The CD spectra of P-**3** (*cis*-nitro) and M-**4** (*trans*-nitro) (Fig. 3) are roughly mirror images at most wavelengths. This is in accordance with the "pseudoenantiomeric nature"[6] of P-**3** and M-**4**, in which the chiral properties are mainly determined by the opposite helical structure.

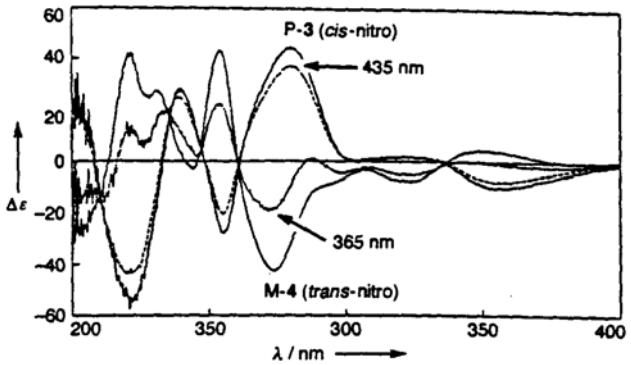

Fig. 3. CD spectra of M-**4**, P-**3**, and the photostationary states generated by irradiation at 365 and 435 nm (in *n*-hexane).

Irradiation of solutions of enantiomerically pure P-**3** (or M-**4**) in *n*-hexane at 300 and 350 nm for 10 s resulted in two distinct photostationary states. CD spectroscopy and chiral HPLC analysis revealed that at 300 nm the photostationary state was composed of 54 % M-**4** (*trans*-nitro) and 46 % P-**3** (*cis*-nitro), while the photostationary state at 350 nm was composed of 62 % M-**4** (*trans*-nitro) and 38 % P-**3** (*cis*-nitro). The P-**3** ° M-**4** interconversion is perfectly reversible showing no trace of racemization after 60 switching cycles. The results of several irradiation experiments compiled in Table 1 show that the compositions of the photostationary states are strongly dependent on the solvents and wavelengths applied.[14]

Table 1. Composition of the mixture of diastereomers for the different photostationary states determined by irradiation of M-**4** in different solvents with light of different wavelengths.

Entry	Solvent	λ [nm]	Proportion of diastereomers [%]		(M-**4** vs P-**3**) [%]
1	*n*-hexane [a]	300	54 M-**4**	46 P-**3**	8
2	*n*-hexane [a, b]	350	62 M-**4**	38 P-**3**	24
3	cyclohexane [b]	350	62 M-**4**	38 P-**3**	24
4	toluene [b]	350	73 M-**4**	27 P-**3**	46
5	dioxane [b]	350	83 M-**4**	17 P-**3**	66
6	*n*-hexane [a]	313	50 M-**4**	50 P-**3**	0
7	*n*-hexane [a]	365	70 M-**4**	30 P-**3**	40
8	*n*-hexane [a]	405	53 M-**4**	47 P-**3**	6
9	*n*-hexane [a]	435	10 M-**4**	90 P-**3**	-80

[a] CD measurements. [b] HPLC analysis.

The extrema in the UV/Vis difference spectra of **3** and **4** (Fig. 2) at 314, 365, and 435 nm represent wavelengths at which after irradiation large differences in the composition of photostationary states can be expected.[15] Irradiation of either enantiomerically pure M-**4** (*trans*-nitro) or P-**3** (*cis*-nitro) at 365 nm results in a photostationary state composed of 70 % M-**4** and 30 % P-**3**. Alternating irradiation with 365 and 435 nm light results in a highly diastereoselective interconversion between

photostationary states with ratios of M-**4** and P-**3** of 70:30 and 10:90, respectively (Table 1, Fig. 3). The results demonstrate that the photochemical isomerization of both P-**3** and M-**4** is stereospecific and also shows high wavelength-dependent diastereoselectivity. At the same time the photochemical and thermal stability of **3** and **4** towards racemization has greatly improved.

Unlike other known potential optical memory systems[1 - 4] the key feature of the bistable molecules described here is that switching is accompanied by inversion of the chirality. These chiral compounds are suited as optical write-read-erase information storage systems.[1, 16] Photochemical writing in the visible and reading by chiroptical means either in the visible (ORD) or in the UV (CD) may be possible. Furthermore an Erasable Direct Read After Write (EDRAW) process might be executed by using for instance 365 nm light for reading and erasing (P-**3** $\circ$ M-**4** isomerization). The fact that the switching process occurs between photostationary states in which either of the pseudoenantiomers P-**3** or M-**4** are present in large excess makes this switch relatively insensitive towards racemization or degradation processes, since these processes will lower the CD signals of these states but will not change their signs. Studies on incorporating the highly selective chiral switchable molecules in polymeric films or depositing them on surfaces to develop macroscopic information storage devices are currently in progress.

Experimental Procedure

8 and **9**: A stirred solution of hydrazone **5** (350 mg, 1.53 mmol) in anhydrous CH_2Cl_2 (40 mL) was cooled to -30 °C, whereupon $MgSO_4$ (approximately 1 g), Ag_2O (530 mg, 230 mmol, 1.5 equiv) , and a saturated solution of KOH in methanol (1.2 mL) were successively added. After 30 min the deep red solution was filtered into another ice-cooled flask, and the remaining residue was washed with cold CH_2Cl_2 (15 mL). To this clear solution was added thioketone **7** in small portions. Evolution of nitrogen was observed, and the deep red color slowly disappeared. The thioketone was added until the evolution of nitrogen had ceased; a total of 200 mg (0.63 mmol) was necessary. After 3 h of stirring and a standard workup, the red residue was purified by flash column chromatography (SiO_2 , CH_2Cl_2/pentane 1/1, R_f = 0.30). The orange crystalline product consisted of isomers **8** and **9** (60:40). Yield: 255 mg, 78 % (based on the amount of **7** added). HRMS calcd. 514.084, found 514.084; Elemental analysis calcd for $C_{28}H_{22}N_2O_2S_3$; C 65.34, H 4.31, S 18.69; found C 65.00, H 4.27, S 18.51.

8 (*cis*-nitro): ^{1}H NMR (200 MHz, TMS): δ = 2.40-2.70(m, 4 H), 3.10 (s, 6 H), 6.76 (dd, J = 8.55, 2.56 Hz, 1 H), 6.97 (d, J = 7.54 Hz, 1 H), 7.07 (d, J = 8.97 Hz, 1 H), 7.20-7.55 (m, 7 H), 7.86 (d, J = 2.56 Hz, 1 H), 9.03 (d, J = 7.69 Hz, 1 H).

9 (*trans*-nitro): ^{1}H NMR (200 MHz, TMS): δ = 2.17 (s, 6 H), 2.40-2.80 (m, 4 H), 6.27 (m, 2 H), 6.90 (d, J = 8.98 Hz, 1 H), 7.02 (d, J = 8.65 Hz, 1 H), 7.23-7.68 (m, 6 H), 8.13 (dd, J = 8.55, 2.56 Hz, 1 H), 8.89 (d, J = 8.97 Hz, 1 H).

3 and **4**: The mixture of episulfides **8** and **9** (95 mg, 0.18 mmol) was desulfurized as described in ref. [11b]. The red solid obtained (71 mg, 0.14 mmol, 80 %) consisted of the two isomers **3** and **4**, which were readily separated by flash column chromatography (SiO_2 , CH_2Cl_2/hexane 1/1, R_f = 0.57 and 0.67).

3 (*cis*-nitro): m.p. 212.2-212.6 °C; ^{1}H NMR (200 MHz, $CDCl_3$, TMS): δ = 3.07 (s, 6 H), 4.21 (dd, J = 7.58, 2.55 Hz, 4 H), 6.76 (dd, J = 8.55, 2.57 Hz, 1 H), 6.95-7.21 (m, 4 H), 7.29 (d, J = 2.57 Hz, 1 H), 7.36-7.76 (m, 6 H); HRMS calcd 482.110, found 482.112; UV (*n*-hexane λ_{max} (ε)): 220.8 (36700) 254.9 (34500) 272.0 (27700) 365.2 (7500): CD (P isomer, *n*-hexane, λ_{max} ($\Delta\varepsilon$)): 221 (- 57) 240 (28.3) 255.2 (-28) 281.4 (44) 356 (- 10).

4 (*trans*-nitro): m.p. 205.8-206.1 °C; ^{1}H NMR (200 MHz, $CDCl_3$, TMS): δ = 2.30 (s, 6 H), 3.45-3.72 (m, 4 H), 5.93 (d, J = 2.56 Hz, 1 H), 6.26 (dd, J = 8.76, 2.78 Hz, 1 H), 7.01-7.19 (m, 3 H), 7.39 (d, J = 8.4 Hz, 1 H), 7.48-7.69 (m, 4 H), 8.15 (dd, J = 8.55, 2.56 Hz, 1 H), 8.43 (d, J = 2.14 Hz, 1 H); UV (*n*-hexane, λ_{max} (ε)): 221.7 (37700) 252.2 (33900) 273.0 (25500) 360.0 (5300); CD (P isomer, *n*-hexane, λ_{max} ($\Delta\varepsilon$)): 221 (- 42) 226.6 (- 26) 244 (3.3) 254.2 (- 43.3) 274.2 (42.4) 323.2 (7.7) 348 (- 4.6).

Irradiations of 2×10^{-5} M solutions of enantiomerically pure **3** and **4** were performed in cylindrical quartz cells. Low-pressure mercury lamps (28 × 1 cm: 8 W) were used for irradiations at 300 and 350 nm, and the irradiation time was 10 s. For irradiations at 313, 365, 405, and 435 nm a 200 W high-pressure mercury lamp equipped with interference filters was employed. Typical irradiation times for this setup were 20 to 30 min.

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[8] Isomers **3** and **4** are readily distinguished by their ^{1}H NMR spectra, as the methyl singlet at δ = 3.07 for **3** (dimethylamino group in the *trans* position) is shifted upfield to δ = 2.30 for **4** (dimethylamino group in the *cis* position) owing to the shielding effect of the naphthalene moiety.

[9] Further details of the crystal structure investigation may be obtained from the Director of the Cambridge Crystallographic Data Centre, 12 Union Road, GB-Cambridge CB2 1EZ (UK), on quoting the full journal citation.

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[12] For the unsubstituted analogue of **4** (X = S, $R^1 = R^2 = R^3$ = H, Fig. 1) a racemization barrier of 120.9 ± 0.5 kJ mol^{-1} was determined, while for the unsubstituted analogue of **1** (X = CH_2 , $R^1 = R^2 = R^3$ = H, Fig. 1) a racemization barrier of 110.7 ± 0.5 kJ mol^{-1} was determined (see ref. [11 a]).

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[14] In ethanol and chloroform no photostationary state was reached after 30 min irradiation at 300 nm, which implies that the quantum yields for the isomerization processes that occur in these solvents is at least a factor 100 lower than in *n*-hexane.

[15] The isomeric composition of the photostationary state upon irradiation at a wavelength λ is given by: [**3**]/[**4**] = $\varepsilon_4\Phi_{4\rightarrow3}/\varepsilon_3\Phi_{3\rightarrow4}$.

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Asymmetric Syntheses of Stavudine (d4T) and Cordycepin by Cycloisomerization of Alkynyl Alcohols to Endocyclic Enol Ethers**

Frank E. McDonald* and Mark M. Gleason

Various deoxynucleosides[1] show potent antiviral activity, particularly against the human immunodeficiency virus (HIV), which is the causative agent for acquired immunodeficiency syndrome (AIDS). Stavudine (2′,3′-didehydro-3′-deoxythymidine; d4T) retains the high antiviral activity of 3′-azido-3′-deoxythymidine (AZT) while exhibiting significantly lower bone marrow toxicity and reduced inhibition of mitochondrial DNA synthesis.[2] Cordycepin (3′-deoxyadenosine) has been widely

[*] Prof. F. E. McDonald, M. M. Gleason
Department of Chemistry, Northwestern University
2145 Sheridan Road, Evanston, IL 60208-3113 (USA)
Telefax: Int. code + (708)491-7713

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