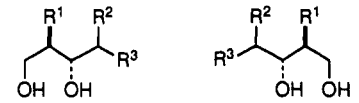
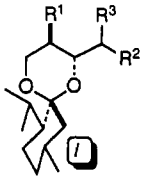
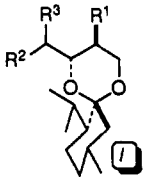


14 (14a; R¹ = Me, R², R³ = -(CH₂)₅-)

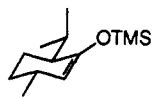
ent-14



15 (15a; R¹ = Me, R², R³ = -(CH₂)₅-)



16 (16a; R¹ = Me, R², R³ = -(CH₂)₅-)



17

More conveniently, kinetic acetalization was accomplished by treating the diol with *l*-menthone enol silyl ether (17) in the presence of triflic acid in THF (entry 7).[17] Formation of $(TMS)_2O$ may account for the facile, kinetic acetalization under these conditions.

The enantiodifferentiating transformation of *meso*-tetrol 8 was achieved successfully by employing the kinetic acetalization with *d*-menthone.[18] Treatment of 8 with 2 equiv of *d*-menthone enol TMS ether in the presence of TfOH (0.2 equiv) in THF at −40 °C for 2 h afforded a 4.5:1 mixture of menthonides 9 and 10 (61%) together with bis-menthonide 11 (12%) and recovered tetrol (10%).[19] Conversion of the mixture of 9 and 10 to the bis-TMS derivatives followed by separation by flash chromatography and subsequent desilylation gave pure 9 (mp 129–131 °C) (72%).

Selective protection of the primary hydroxy group of 9 as the TBDPS ether and subsequent hydrolysis of the menthonide gave triol 12. Finally, debenzylation followed by protection of the tetrol as its bis-acetonide and subsequent desilylation afforded 13 ($[\alpha]_D^{25}$ −5.07° (*c* 1.10, $CHCl_3$), >95% ee[20]), an intermediate in Kishi's synthesis of rifamycin S which had ^{1}H-NMR and specific rotation data in agreement with those reported previously.[2c,3k,l]

The studies reported herein not only serve as an illustration of the potential of the two-directional chain synthesis but also provide a new method for the enantiodifferentiating transformation of 1,3-polyols utilizing kinetically controlled acetalization with menthone.

Acknowledgment. This work was supported partially by Grant-in-Aid on Priority Areas from Japan Ministry of Education, Science, and Culture (No. 01649510).

Supplementary Material Available: Experimental details and spectral data for 4, 5, 7, 8, 9, 12, and 13 (9 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(17) In this reaction, (*R*)-14a of 70% ee was recovered in 44% yield.
(18) Acetalization of tetrakis-TMS ether of 8 with *l*-menthone under thermodynamic conditions (TMSOTf (0.3 equiv), toluene, −30 °C, 7 days) afforded a 53% yield of 9 and 10 in a 2.0:1 ratio.
(19) Higher selectivity (6.5:1) for 9 was observed in the lower conversion (51%) of 8.
(20) The value was determined by ^{1}H NMR analysis of (+)-MTPA ester of 13.

Transmission of Recognition Information to Other Sites in a Molecule: Proximity of Two Remote Sites in the Spirobenzopyran by Recognition of Alkali-Metal Cations

Masahiko Inouye,* Masaru Ueno, and Teijiro Kitao

Department of Applied Chemistry, University of Osaka Prefecture, Sakai, Osaka 591, Japan

Received January 2, 1992

Summary: A new spirobenzopyran was synthesized, in which recognition of alkali-metal cations induced a structural change in the molecule accompanying coloration that resulted in a proximity of two remote sites in the molecule.

We report an advanced artificial receptor in which recognition induces a structural change in the molecule accompanying coloration that results in a proximity of two remote sites in the molecules. Transmission of recognition information to other sites in the molecules is crucial in many biological systems,[1] such as enzyme and nervous systems, so that mimic of the process using simple and artificial molecules may be a worthwhile subject in its own right.

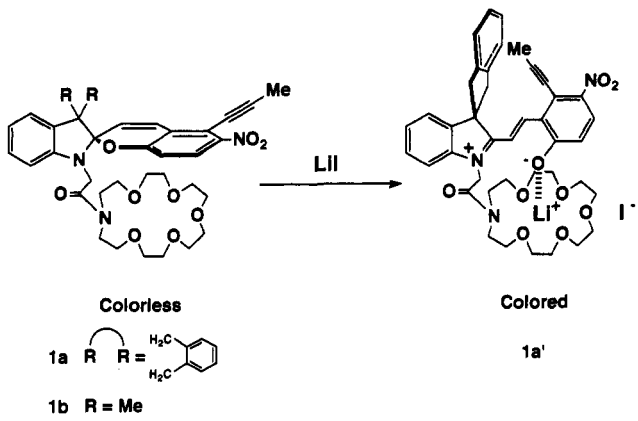
Our strategy utilizes the fact that isomerization of the spirobenzopyrans possessing a monoaza-crown ring as a recognition site to the open colored merocyanines is induced by recognition of alkali-metal cations.[2] We expected that the isomerization of a rationally designed new spirobenzopyran (1a) possessing a monoaza-crown ether, propynyl, and indane groups might have propynyl-Me groups approach the π-electrons of the indane–benzene ring, and any change in the microscopic environment of the Me groups could be easily detected by NMR (Scheme I). This new type of receptor is different from the artificial

(1) For reviews: Williams, R. J. P. *Chem. Soc. Rev.* **1980**, 281–364. Fersht, A. In *Enzyme Structure and Mechanism*, 2nd ed.; W. H. Freeman: New York, 1985; pp 263–291. Alberts, B.; Bray, D.; Lewis, J.; Raff, M.; Roberts, K.; Watson, J. D. In *Molecular Biology of the Cell*, 2nd ed.; Garland Publishing: New York, 1989; Chapters 12 and 19.

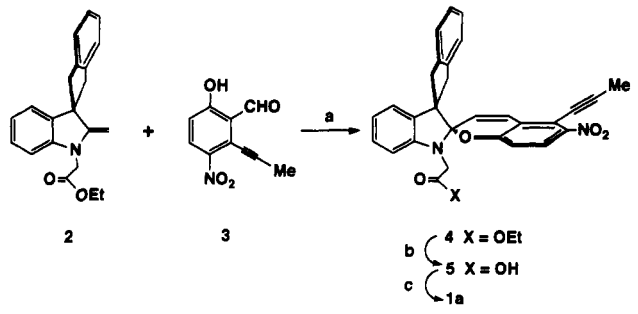
(2) Inouye, M.; Ueno, M.; Kitao, T.; Tsuchiya, K. *J. Am. Chem. Soc.* **1990**, *112*, 8977–8979. Inouye, M.; Ueno, M.; Tsuchiya, K.; Nakayama, N.; Konishi, T.; Kitao, T. *Ibid.*, submitted for publication.

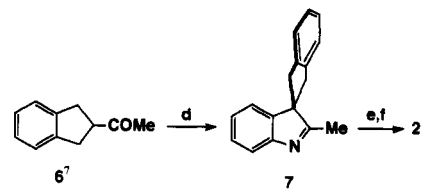
0022-3263/92/1957-1639$03.00/0

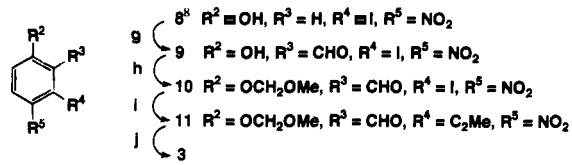
Scheme I



Scheme II[a]







[a] Key: (a) EtOH, reflux, 0.5 h; (b) NaOH, THF, H_2O, rt, 6 h; (c) monoaza-18-crown-6, 2-chloro-1-methylpyridinium iodide, *n*-Bu_3N, CH_2Cl_2, reflux, 2 h; (d) $PhNHNH_2$, AcOH, reflux, 3 h; (e) $BrCH_2CO_2Et$, CH_3CN, 60 °C, 6 h; (f) NaOH, H_2O, rt, 0.5 h; (g) hexamethylenetetramine, CF_3CO_2H, 80 °C, 12 h; (h) NaH, $ClCH_2OCH_3$, THF, rt, 6 h; (i) $PdCl_2(PPh_3)_2$, *n*-Bu_3SnC_2Me, PhMe, 70 °C, 2 h; (j) HCl, H_2O, rt, 3 h.

allosteric receptors so far synthesized because in the latter cases transmission of recognition information to the second recognition site is carried out through only a conformational change in the molecules.[3]

The new spirobenzopyran **1a** was synthesized from two key intermediates, **2** and **3**. The aldol-type cyclization of **2** with **3** gave spirobenzopyran **4** bearing ester groups, which was hydrolyzed to **5**, followed by condensation with monoaza-18-crown-6 by Mukaiyamas' method to **1a**.[4] The

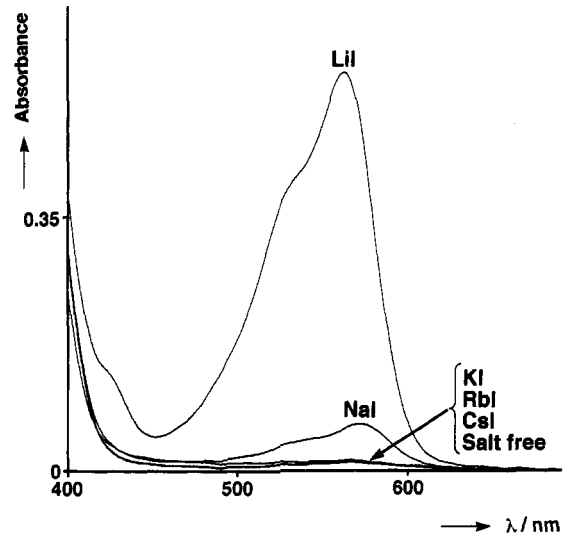


Figure 1. Electronic absorption spectra of the $CHCl_3$ solutions of **1a**.[9]

key intermediates, **2**[5] and **3**,[6] were prepared by standard synthetic methods (Scheme II).

The receptor **1a** thus prepared showed no absorption bands above 400 nm in nonhydroxylic solvents, indicating the closed spiropyran form. When a 5-fold molar quantity of LiI was added to the $CHCl_3$ solution of **1a**, however, new absorption bands appeared (λ_{max} = 562 nm, ϵ = 2270), while only negligible or no changes were observed upon addition of other alkali-metal iodides (Figure 1). In the ^1H NMR spectrum, the propynyl-Me protons of **1a** (20 μmol in 0.8 mL $CDCl_3$) appeared at 2.19 ppm, a normal position. After LiI (300 μmol) was added to the solution, initially, only the downfield shifts and broadening of the signals in the aza-crown ring were observed, which indicated that the lithium cations were bound to the macrocycle. With the elapse of time, however, new resonances began to appear. The new resonances were assigned as those of a merocyanine (**1a'**),[2] and noteworthy is that the Me protons of **1a'** were largely shifted upfield by 0.90 ppm, reflecting that the Me groups of **1a'** were placed on the center of the indane–benzene ring, as expected (Figure 2). This upfield shift was shown to be unambiguously due to the diamagnetic anisotropy of the indane ring by comparison of its NMR spectrum with that of **1b**, in which the

(3) Rebek, J., Jr. *Acc. Chem. Res.* **1984**, *17*, 258–264. Beer, P. D.; Rothin, A. S. *J. Chem. Soc., Chem. Commun.* **1988**, 52–54. Ebmeyer, F.; Rebek, J., Jr. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1148–1150. Schneider, H.-J.; Ruf, D. *Ibid.* **1990**, *29*, 1159–1160. Sijbesma, R. P.; Nolte, R. J. M. *J. Am. Chem. Soc.* **1991**, *113*, 6695–6696.

(4) **1a**: mp 63–65 °C; IR (KBr) 2900, 2200, 1650, 1480, 1450, 1320, 1290, 1100, 950, 800, 750 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 2.19 (s, 3 H), 2.86 (d, *J* = 15.3 Hz, 1 H), 3.23 (s, 2 H), 3.50–3.79 (m, 25 H), 4.14 (s, 2 H), 6.11 (d, *J* = 11.0 Hz, 1 H), 6.51 (d, *J* = 7.9 Hz, 1 H), 6.66–6.69 (m, 2 H), 6.74 (d, *J* = 9.2 Hz, 1 H), 7.11–7.17 (m, 5 H), 7.27 (d, *J* = 11.0 Hz, 1 H), 7.88 (d, *J* = 9.2 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 5.06, 38.62, 42.42, 45.25, 47.01, 48.93, 64.44, 69.81, 69.95, 70.42 - 70.84, 71.37, 72.64, 100.26, 104.95, 107.01, 114.73, 117.34, 119.56, 121.04, 121.20, 122.59, 124.15, 124.82, 126.49, 126.74, 126.82, 128.17, 135.01, 141.31, 141.62, 143.35, 146.85, 157.99, 169.19.

(5) **2**: mp 99–100 °C; IR (KBr) 2900, 1750, 1605, 1480, 1340, 1200, 1010, 750 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 1.26 (t, *J* = 7.3 Hz, 3 H), 3.33 (d, *J* = 15.9 Hz, 2 H), 3.34 (d, *J* = 15.9 Hz, 2 H), 3.80 (d, *J* = 2.4 Hz, 1 H), 3.92 (d, *J* = 2.4 Hz, 1 H), 4.21 (q, *J* = 7.3 Hz, 2 H), 4.25 (s, 2 H), 6.52 (d, *J* = 7.3 Hz, 1 H), 6.69 (t, *J* = 7.3 Hz, 1 H), 6.87 (d, *J* = 7.3 Hz, 1 H), 7.12 (t, *J* = 7.3 Hz, 1 H), 7.23–7.32 (m, 4 H); ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 14.26, 44.46, 50.16, 54.49, 61.28, 74.99, 105.17, 119.54, 121.70, 124.53, 126.82, 127.89, 136.89, 142.06, 145.60, 160.98, 168.89.

(6) **3**: mp 145–147 °C (sublim); IR (KBr) 3400, 2200, 1660, 1610, 1520, 1450, 1350, 1330, 1300, 1180, 1080, 930, 850, 780 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 2.38 (s, 3 H), 7.11 (d, *J* = 9.2 Hz, 1 H), 8.33 (d, *J* = 9.2 Hz, 1 H), 10.68 (s, 1 H), 12.49 (s, 1 H); ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ 5.21, 76.58, 104.48, 117.82, 119.30, 124.51, 132.68, 143.05, 165.89, 197.27.

(7) Moss, R. A.; Mallon, C. B. *J. Am. Chem. Soc.* **1975**, *97*, 344–347.

(8) Hodgson, H. H.; Moore, F. H. *J. Chem. Soc.* **1927**, 630–635.

(9) The absorption spectra were measured for 0.25 mM $CHCl_3$ solutions of **1a** in the presence or absence of alkali-metal iodides after the solutions had been allowed to stand in the dark for 12 h.

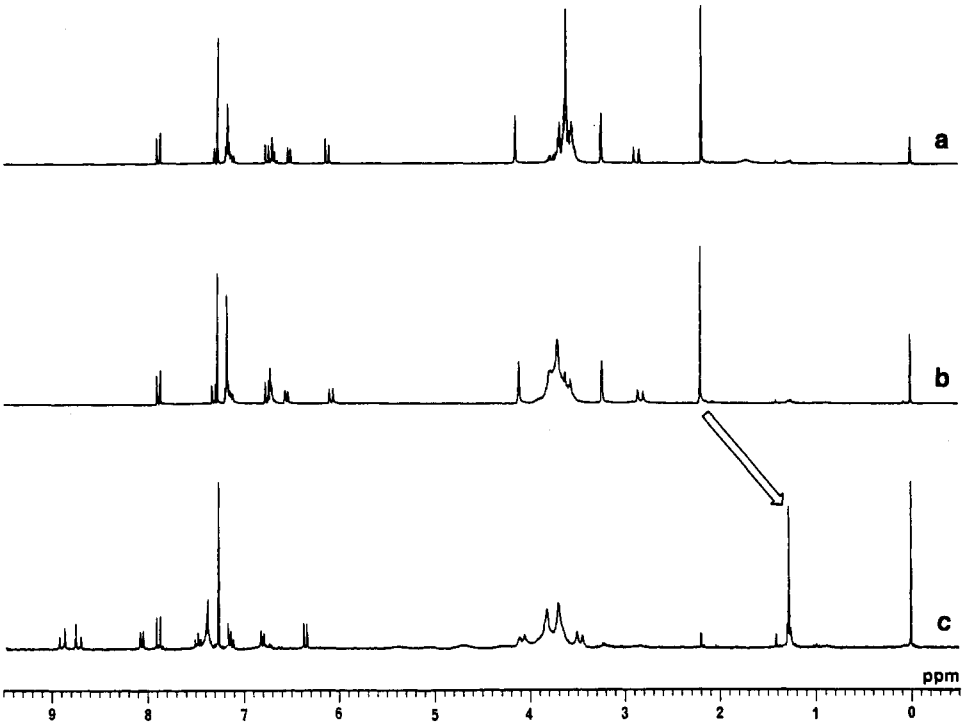


Figure 2. ^1H NMR spectra (270 MHz) of **1a** in $CDCl_3$ (a) before addition of LiI, (b) almost immediately after the addition, and (c) after 20 h.

Me groups of the open colored merocyanine (**1b'**) appeared at 2.35 ppm.

In conclusion, the present work demonstrates that recognition of lithium cations causes the spirobenzopyran to isomerize to the merocyanine, which results in a proximity of the two remote sites in the molecules. In future investigations, the design of molecules which possess reacting groups and/or a second recognition site in the transmitted parts shows further development for the multi-functional artificial receptors.

On the Solvent Dependence of *cis*-Diazene Inversion[1]

Robert C. Neuman, Jr.,* and Howard J. Gunderson[2]

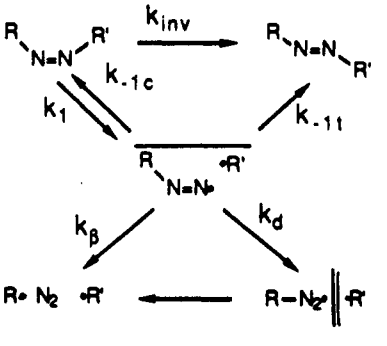
Department of Chemistry, University of California, Riverside, California 92521

Received September 24, 1991

Summary: Solvent dependence of nonradical inversion rates of *cis*-diazenes cannot be due to viscosity variation because these rates are too slow. For *cis*-azoadamantane, in a variety of aromatic and nonaromatic hydrocarbons, they show a correlation with solvent internal pressure giving an approximate activation volume of +7 cm^3/mol.

We have proposed that thermal decomposition of both symmetrical and unsymmetrical *cis*-diazenes follows the mechanisms outlined in Scheme I based on the pressure[1,3] and solvent[4] dependences of their decomposition rates. Pressure retards the rates of both deazatization and isomerization, and the resulting positive activation volumes are consistent with one-bond scission deazatization (k_1) and isomerization by inversion (k_{inv}).[5] The deazatization rates

Scheme I



(1) High Pressure Studies. 29. Part 28: Neuman, R. C., Jr.; Berge, C. T.; Binegar, G. Al.; Adam, W.; Nishizawa, Y. *J. Org. Chem.* **1990**, *55*, 4564.

(2) Gunderson, H. J., Ph. D. Dissertation, University of California, Riverside, Aug 1990.

(3) Neuman, R. C., Jr.; Binegar, G. Al. *J. Am. Chem. Soc.* **1983**, *105*, 134.

(4) Neuman, R. C., Jr.; Grow, R. H.; Binegar, G. Al.; Gunderson, H. J. *J. Org. Chem.* **1990**, *55*, 2682.

(5) k(N) and k(I) are observed rate constants for deazatization and isomerization, respectively; k_1 and k_{inv} are the specific rate constants shown in Scheme I.

0022-3263/92/1957-1641$03.00/0