Synthesis of optically pure 3-(1n.pi.\-\textdagger)-\((1S,6R)\)-bicyclo[4.4.0]decane-3,8-dione, a molecule which is chiral in the excited state only

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Synthesis of Optically Pure
3-(1nπ*)-(1S,6R)-Bicyclo[4.4.0]decane-3,8-dione, a Molecule Which is Chiral in the Excited State Only

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Abstract: Low-temperature photooxygenation of (1S,6R)-3-((E,Z)-methoxymethylene)bicyclo[4.4.0]decane-8-one (7), prepared in 10 steps from 2,6-dimethoxynaphthalene (5), yields a mixture of four isomeric 1,2-dioxetanes (8a–d) with ee > 98%. Upon thermal decomposition, these 1,2-dioxetanes are all precursors for 3-(1nπ*)-(1S,6R)-bicyclo[4.4.0]decane-3,8-dione (1*), an optically active diketone in its locally excited 1nπ* state. The optical activity of this molecule is evidenced by the nonvanishing circular polarization in the chemiluminescence of 8a–d. The degree of polarization (g) at 420 nm equals (1.5 ± 0.3) × 10−3, a value which is similar to that of the regular fluorescence of optically active (1S,6R,8S)-8-hydroxybicyclo[4.4.0]decane-3-one (6). This similarity implies the absence of substantial racemization in the excited state, whence one concludes that the rate constant for intramolecular 1nπ* energy transfer in 1* is ≤109 s−1. The chiroptical results show that localization of excitation energy at the carbonyl at the 3-position of 1* can be achieved by the synthetic route applied, yielding enantiomerically pure 3-(1nπ*)-(1S,6R)-bicyclo[4.4.0]decane-3,8-dione (1*), an optically active molecule whose chirality is due solely to the presence of localized electronic excitation energy.

Introduction

Molecules in which chirality is due solely to small differences between the discriminating groups have always fascinated stereochemists. Striking examples are chiral tetraalkylmethanes and fullerenes and molecules which are chiral due to isotopic substitution. One of the smallest deviations from achirality is found in systems in which the chirality is due solely to the presence of localized electronic excitation energy. This can arise in centrosymmetric or meso compounds with two remote enantiomeric chromophores, as shown in Figure 1 for 1, 1*, and related structures 2–4. In the ground state these diketones (R,S) are achiral, while in the excited state two enantiomeric forms (R*,S) and (S*,R) are present, providing the excitation energy is localized.

The excited state can be formed by the irradiation of R,S with circularly polarized light. The difference in concentration of R*,S and S*,R is then governed by the dissymmetry factor in absorption (g = AOD/OD); in fact, the resultant enantiomeric excess (ee) equals g/2. The optical activity of the excited-state species is evidenced by a nonvanishing degree of circular polarization of luminescence (CPL). Such excited-state chirality has experimentally been demonstrated in the 1,7-diketone 2*. In the case of the 1,5-diketone 3*, a zero CPL has been found which is ascribed to a fast racemization in the singlet excited state (lifetime τ) due to 1nπ* energy transfer. In the absence of energy transfer, the circular polarization, as measured in these experiments, equals g/2. Energy transfer reduces the ee, and thus the CPL signal, by a factor of (2kΔτ + 1)−1.

Since in photoselection experiments the ee is governed by g (which, for the n→π* band of ketones, will give an ee of at most ~10%), a major improvement of selectivity has been foreseen by using chemoselection to produce R*,S, potentially with an ee of 100%. According to this approach, singlet-excited-state

Figure 1. Meso diketones that contain two carbonyl moieties of opposite chirality. All structures are achiral in the ground state but chiral in the excited state, provided excitation energy is localized at one carbonyl group.

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2,4-adamantanediene (4*) has been prepared by the thermolysis of the corresponding optically active 1,2-dioxetanes. These four-membered rings are known to dissociate into two carbonyl fragments accompanied with chemiluminescence. Upon thermal decomposition, one of the carbonyls is produced in its (singlet or triplet) excited state by a nonadiabatic process (chemiexcitation). The radiative transition from the singlet excited state to the ground state following chemiexcitation accounts then for the chemiluminescence. Despite the fact that the excitation is directed chemically to one of the carbonyls only, a vanishingly small circular polarization in chemiluminescence of the 1,2-dioxetanes has been detected. A complete loss of optical activity occurred within the lifetime of 2 ns of 4*; due to the close proximity of both carbonyls in 4, energy transfer is extremely fast.

In this paper we describe the synthesis and the circular polarization of the chemiluminescence of optically pure 3-(1m*).-(1S,6R)-bicyclo[4.4.0]decane-3,8-dione (1*), a diketone in which both carbonyls are more remote. The synthetic route is based on our previous work for the chemiexcitation of 4.6,8 Via thermal decomposition of the optically active 1,2-dioxetanes 8a-d, enantiomerically pure 1* is obtained together with ground-state methyl formate (Scheme 1).

Results and Discussion

Synthesis. The optically active precursor of 1* is synthesized starting from 2,6-dimethoxynaphthalene (5), as outlined in Scheme 2. In six steps and an overall yield of 15%, 5 has been transformed into optically pure (ee > 98%) (1S,6R,8S)-8-hydroxybicyclo[4.4.0]decane-3-one (6) using in the last step the HLADH-reduction of 1 as pioneered by Jones et al.8 The conversion of 6 into (1S,6R)-3-(E,E)-methoxymethylene)bicyclo[4.4.0]decane-8-one (7) is achieved in a four-step procedure. Protection of the alcohol with an acetyl group followed by the Wittig reaction with 1.1 equiv of (methoxymethylene)phosphorane in THF gives the E- and Z-isomers of (1S,6R,8S)-3-(methoxymethylene)bicyclo[4.4.0]dec-8-yl acetate in a 1:1 ratio in 25% yield. Hydrolysis of the acetyl group with LiOH and a pyridinium chlorochromate oxidation of the alcohol yielded optically pure enol ether (1S,6R)-7. Photooxygenation of 7 with singlet oxygen in dichloromethane at -80 °C, using methylene blue as sensitizer, gives a mixture of four isomeric 1,2-dioxetanes 8a-d (60%) and allylic hydroperoxides 9a-d (40%) as byproducts.9 The ratio of 8 to 9 is strongly influenced by temperature and solvent, as reported for model compounds.10 The 1,2-dioxetanes are purified (removal of byproducts 9a-d) by using low-temperature (-30 °C) column chromatography. The four isomeric (1S,6R)-1,2-dioxetanes 8a-d are formed in approximately equal amounts by the 1O2 attack of both enol ethers at both sides of the molecule, as is concluded from NMR spectra.

Thermolysis and Chiroptical Properties. In order to investigate the rates of decomposition of the four individual isomeric 1,2-dioxetanes, we have monitored the thermolysis of 8a-d with 1H NMR spectroscopy. First-order rate constants of k1 = 9.6 × 10^-4 s^-1 and k2 = 6.5 × 10^-4 s^-1 for two pairs of 1,2-dioxetanes are estimated from kinetic studies at 60 °C in toluene-d8 (Figure 2).

The difference in stability for the two pairs is thought to arise from the difference in steric interactions in the equatorial and axial positions of the oxygen atoms of the four-membered rings, while no difference is expected for the E- and Z-stereoisomers. The unequal rate constants give rise to a nonexponential decay of the chemiluminescence intensity (Figure 3) as well as the circular dichroism signal at 295 nm (Figure 4). The CD data have been taken on a dilute sample of (1S,6R)-8a-d in bis(2-methoxyethyl) ether (diglyme). After thermolysis at 80 °C, only a trace amount of optically active impurity (probably a trace of one product) gives rise to a small negative residual CD of 8a-d at λmax = 295 nm.

The thermolysis of 8a-d in diglyme at 80 °C is accompanied with chemiluminescent emission, the spectrum of which (Figure 3) closely resembles the fluorescence spectra of 1 and 6. As expected, 1m* species formed in the decomposition reaction are effectively quenched under the experimental conditions used.
Collecting the emission at 430 nm, we observe\(^{11}\) for 8a–d a dissymmetry factor of chemiluminescence \(g_{\text{chem}} = -(1.5 \pm 0.3) \times 10^{-3}\). The effect cannot be due to a CD artifact, because in the original sample (i.e., before thermolysis) we observe a zero CD signal at 430 nm.

Thermolysis of the optically active dioxetanes 8a–d furnishes initially the excited diketone in its locally excited \(\pi^*\) state. The optical activity of this molecule is evidenced by the nonvanishing circular polarization in the chemiluminescence. In the absence of racemization, the circular anisotropy in emission of the hydroxy ketone 6, \(g_{\text{chem}}\), should be similar to \(g_{\text{chem}}\) of the chemiluminescent diketone \(1^*\). The fact that the dissymmetry factor in the chemiluminescence has the same order of magnitude as the dissymmetry factor of the \((\text{photoexcited})\) fluorescence of optically pure hydroxy ketone 6 (\(g_{\text{chem}} = -(0.9 \pm 0.2) \times 10^{-3}\) at the same wavelength) implies that racemization due to energy transfer is relatively small: \(k_{\text{ET}} \leq 10^9 \text{s}^{-1}\), calculated with \(\tau_1 = 2 \text{ ns}\).\(^{12}\) This result for the 1,6-diketone 1 is in line with the available data on the energy transfer for ketones 2–4. The distance between both carbonyl carbons in 1, \(R_{ab}\), as found from X-ray analysis,\(^{13}\) amounts to 5.25 Å (Figure 5).\(^{14}\) For the 1,7-diketone 2, energy transfer is relatively slow (\(k_{\text{ET}} \leq 10^7 \text{s}^{-1}\)) for an estimated \(R_{ab}\) of 6.95 Å PM3 calculation\(^{15}\), while for the 1,5-diketone 3 and the 1,3-diketone 4, having estimated \(R_{ab}\) values of 4.47 and 2.50 Å, respectively, the energy transfer is fast (\(k_{\text{ET}} \approx 10^{10} \text{s}^{-1}\)).

The chiroptical results indicate that the value of \(g_{\text{chem}}\) for \(1^*\) is determined only by optical activity due to the presence of a locally excited state in a high enantiomeric excess, equally to the >98% ee and de of the hydroxy ketone 6.

**Concluding Remarks**

In conclusion, the results presented in this paper show the successful synthesis and detection of CPL of enantiomerically pure \(1\pi^*\)-excited \(1^*\), whose chirality is due solely to the presence of localized excitation energy. The localization of excitation energy on the carbonyl at the 3-position of 1 has been accomplished by enantioselective chemiexcitation of enol ethers 7 to 1,2-dioxetanes 8a–d, which by decomposition are all isomeric precursors of 3-\((\pi\pi^*)\)-1*. The optical activity was established from the CPL in the chemiluminescence of the 1,2-dioxetanes. No racemization, due to relatively slow intramolecular energy transfer (\(k_{\text{ET}} \leq 10^9 \text{s}^{-1}\)) with respect to the singlet-excited-state lifetime (2 ns), was observed. Furthermore, this concept of excited-state chirality of ground-state meso molecules can be used to observe second harmonic generation (SHG) in centrosymmetric molecules and assemblies by using a circularly polarized excitation laser.
was prepared according to ref 9b. A 0.1 M phosphate buffer (400 mL, pH 6.5), prepared from 0.1 M NaH2PO4 and 0.1 M Na2HPO4 solutions in Millipore water, was sterilized for about 30 min. Diketone 1 (1 g, 6.02 mmol) and rotary evaporation of the dried (MgSO4) CHCl3 solution. The crude product was purified by slow evaporation. Tetrahydrofuran (THF) was distilled under dry argon atmosphere was added to the buffer, and the mixture was kept in the dark at room temperature. After 8 days maximum reaction time, the mixture was diluted with 250 mL of dichloromethane. The reaction mixture was poured into 100 mL of dry diethyl ether. The dark brownish liquid was washed again with water (2X, 10 mL), dried (MgSO4), and rotary evaporation of the organic layer afforded a dark red residue. Column chromatography on silica gel (hexane/ethyl acetate, 92:8 elution) gave 1.25 g of (1S,6R,8S)-3-((E,Z)methoxymethylene)bicyclo[4.4.0]decan-8-01 as a colorless oil (yield 54%). The reaction was monitored by TLC (hexane/ethyl acetate, 80:20 elution), Rf = 0.15, [α]D23 = −28.8° (c 0.052, EtOH). 1H NMR (CDCl3): δ 5.8 (2H, s, H1), 5.25 (2H, d, OCH3), 2.85–2.95 (1H, dd, H2), 2.75–2.85 (1H, H4), 2.0–2.4 (2H, H2, H7), 1.75–1.90 (2H, m, H3, H5), 1.5–1.65 (2H, H6, H8). 13C NMR (CDCl3): δ 208.86 (s, C6), 207.49 (t, C4), 144.11 (d, C2, C3), 40.27 (t, C7, C8), 33.06 (t, C9, C10). IR (KBr): v 1710 (C=O stretch, saturated). Anal. Caled for C30H38O2: C, 82.88; H, 9.03. Found: C, 82.76; H, 9.01.

(1S,6R,8S)-3-(E,Z)-methylenecycloalkanone (7) was prepared according to ref 9b. A 0.1 M phosphate buffer (400 mL, pH 6.5), prepared from 0.1 M NaH2PO4 and 0.1 M Na2HPO4 solutions in Millipore water, was sterilized for about 30 min. Diketone 1 (1 g, 6.02 mmol) and rotary evaporation of the dried (MgSO4) CHCl3 solution. The crude product was purified by slow evaporation. Tetrahydrofuran (THF) was distilled under dry argon atmosphere was added to the buffer, and the mixture was kept in the dark at room temperature. After 8 days maximum reaction time, the mixture was diluted with 250 mL of dichloromethane. The reaction mixture was poured into 100 mL of dry diethyl ether. The dark brownish liquid was washed again with water (2X, 10 mL), dried (MgSO4), and rotary evaporation of the organic layer afforded a dark red residue. Column chromatography on silica gel (hexane/ethyl acetate, 92:8 elution) gave 1.25 g of (1S,6R,8S)-3-((E,Z)methoxymethylene)bicyclo[4.4.0]decan-8-01 as a colorless oil (yield 54%). The reaction was monitored by TLC (hexane/ethyl acetate, 80:20 elution), Rf = 0.15, [α]D23 = −28.8° (c 0.052, EtOH). 1H NMR (CDCl3): δ 5.8 (2H, s, H1), 5.25 (2H, d, OCH3), 2.85–2.95 (1H, dd, H2), 2.75–2.85 (1H, H4), 2.0–2.4 (2H, H2, H7), 1.75–1.90 (2H, m, H3, H5), 1.5–1.65 (2H, H6, H8). 13C NMR (CDCl3): δ 208.86 (s, C6), 207.49 (t, C4), 144.11 (d, C2, C3), 40.27 (t, C7, C8), 33.06 (t, C9, C10). IR (KBr): v 1710 (C=O stretch, saturated). Anal. Caled for C30H38O2: C, 82.88; H, 9.03. Found: C, 82.76; H, 9.01.

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Optically Pure 3-(\(\pi^*\))-\((1S,6R)\)-Bicyclo[4.4.0]decane-3,8-dione blue (10 mg) were dissolved in 600 mL of dichloromethane and photooxygenated for 1 h at -80 °C. The irradiations were carried out with a Hanau TQ78 500-W medium-pressure mercury lamp through quartz, using a sheet of brownish polyimide (Kapton 500H, du Pont de Nemours) wrapped around the lamp compartment as short wavelength filter (cutoff 550 nm). Cooling of the lamp and primary cooling of the reaction vessel were accomplished by means of a closed circuit filled with methanol from a cryostat. The temperature of -80 °C was reached by extra external cooling baths of ethanol and liquid nitrogen. Column chromatography at -30 °C using dichloromethane/ethyl acetate, 60:40 elution, resulted in removal of the sensitizer, yielding a mixture of dioxetanes and allylic hydroperoxides in a ratio of 60:40. Pure dioxetane was obtained by concentrating 700 mL of the crude dioxetane solution to ~250 mL and subsequent column chromatography at -30 °C using dichloromethane/acetonitrile, 96:4 as eluent. The initially low-boiling solvents, dichloromethane, acetone, and ethyl acetate, were removed in the presence of an appropriate high-boiling solvent, bis(2-methoxyethyl) ether (diglyme) or toluene-d₈. CPL measurements were carried out using a concentrated dioxetane solution (a solution of 550 mL of 1,2-dioxetane was concentrated into 20 mL of diglyme). For recording \(^1\)H and \(^{13}\)C NMR spectra, an aliquot of the dioxetane solution was concentrated at 0 °C. During evaporation, cold CDCl₃ or toluene-d₈ was added in such a way that the 1,2-dioxetane was always present in solution. The 1,2-dioxetane was stored as a solution in dichloromethane below -20 °C. \(^1\)H NMR (toluene-d₈, \(T = 25\) °C): \(δ 5.26, 5.22, 5.20, 5.18 (4 × 1H, s, H₁₁), 3.28, 3.26 (2 × 3H, s, OCH₃), 3.16 (6H, s, OCH₆), 2.7-0.7 (envelope). \(^{13}\)C NMR (CDCl₃, \(T = -20\) °C): \(δ 211.28, 211.08 (s, 2 × C₁), 109.60, 109.44 (d, 2 × C₁), 89.54, 89.51, 89.43, 89.34 (s, 4 × C₆), 56.04, 55.99, 55.69, 55.62 (q, 4 × OCH₃), 47.98, 47.25, 46.91, 46.74 (t, 4 × C₇), 41.16, 40.92, 40.67, 40.52, 40.16, 40.92, 40.67, 40.06, 39.37, 38.02, 37.11, 35.70, 35.38, 34.94, 33.79, 33.52, 32.64, 32.44, 32.28, 30.23, 29.2, 28.04, 27.7, 26.27.