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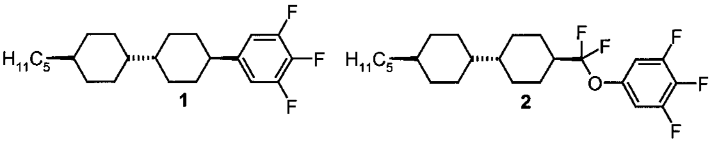
Difluorooxymethylene-Bridged Liquid Crystals: A Novel Synthesis Based on the Oxidative Alkoxydifluorodesulfuration of Dithianylium Salts**

Peer Kirsch,* Matthias Bremer, Andreas Taugerbeck, and Tilman Wallmichrath

Dedicated to Professor Heinz A. Staab
on the occasion of his 75th birthday

In our search for new, superior liquid crystals[1] for use in active-matrix liquid crystal displays[2] (AM-LCD or thin film transistor LCD, TFT-LCD) it was found that the insertion of a difluorooxymethylene bridge into a specific location of the mesogenic core structure of phenylbicyclohexyl-type liquid crystals (**1**)[3] results in a class of materials (**2**; Scheme 1)[4] that exhibits a surprising improvement of essentially all application-relevant properties (see Table 1). These include a broader nematic phase range, a higher dielectric anisotropy ($\Delta\varepsilon$), a lower rotational viscosity (γ_1),[5] but also a higher specific resistivity and voltage holding ratio.[6] Since the liquid crystals **1** are currently the most commonly used type of materials for all kinds of AM-LCDs, this fundamental improvement represents significant progress for LCD technology as a whole with regard to faster switching times and a broader operating temperature range.



Scheme 1. The liquid crystalline basic structure **1** and its analogue **2** which is extended by a difluorooxymethylene bridge.

Whilst there is a variety of methods reported for the preparation of aryl α,α-difluorobenzyl ethers,[7] the efficient synthesis of aryl and alkyl α,α-difluoroalkyl ethers has been an unsolved problem so far. The first small amounts of **2**[4b, 8] and its analogues were synthesized by the general methods depicted in Scheme 2. But both synthetic routes suffer from serious drawbacks, such as low yields and difficult purification of the intermediates **7**[4b, 8] and **8**,[9–11] and of the target compounds **9**. Therefore, it was our aim to develop a new,

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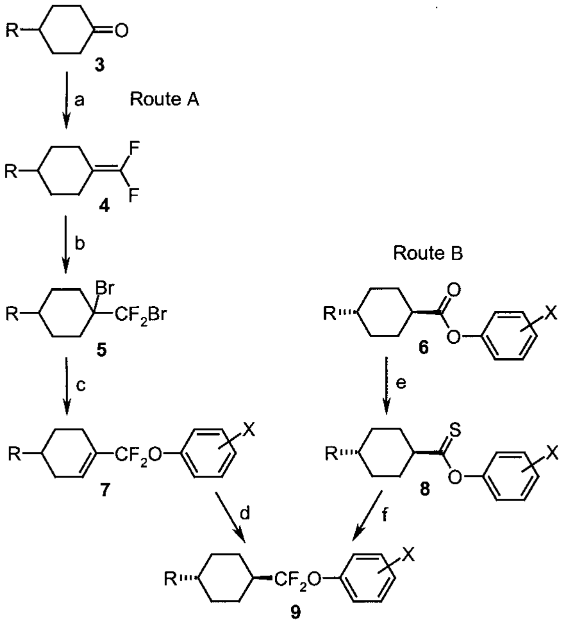
Table 1. Physical properties of liquid crystals (**1**, **2**, **26**–**32**) and chiral dopants (**33**, **34**)[19, 20] containing an α,α-difluoroalkyl ether bridge.[a]

Compound	Phase sequence	T_{NI}	$\Delta\varepsilon$	Δn	γ_1
1	C 88 N 102.4 I	82.8	8.4	0.0720	233
2	C 59 N 112.1 I	99.3	9.5	0.0688	184
26	C 67 N 116.5 I	108.2	11.8	0.0800	488
27	C 41 I	–31.7	19.0	0.1025	116
28	C 81 S_B 169 N 285.7 I	296.7	–0.2	0.0695	796
29	C 140 $S_?$ 150 S_B 169 N >325 I	333.2	–2.1	0.0626	2935
30	C 45 N (28.8) I	–8.4	17.0	0.1115	123
31	C 19 S_B 72 I	4.3	0.7	0.0500	93
32	C 47 I	–39.0	1.2	0.0488	–
33	T_g –76 I	–	–	–	–
34	T_g 27 I	–	–	–	–

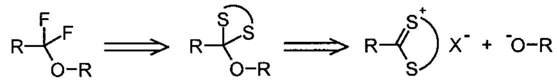
[a] "Virtual" clearing points (T_{NI}), dielectric anisotropies ($\Delta\varepsilon$), birefringences (Δn), and rotational viscosities (γ_1) are extrapolated from the Merck liquid crystal mixture ZLI-4792.[21] The temperatures are given in °C, the γ_1 values in mPa s. C = crystalline, S_x = smectic X, N = nematic, I = isotropic, T_g = glass transition. Numbers in parentheses denote monotropic phase transitions.



Scheme 2. Previously reported general synthetic routes to cyclohexyl-α,α-difluoromethyl phenyl ethers **9**.[4] The yields vary strongly depending on the phenol component: Route A: a) CF_2Br_2, $P(NMe_2)_3$, THF/dioxane 10/1; 0 °C → room temperature (RT), 18 h (80–90%); b) Br_2, Et_2O; 0 °C, 1 h (85–95%); c) 2.6 equiv XPhONa, DMF; 60 °C, 18 h (35–70%); d) 1. H_2, 5% Pd-C, THF; 60 °C, 60 bar; 2. preparative HPLC; 3. crystallization from *n*-pentane (25–35%). Route B: e) 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide (Lawesson's reagent),[9] chlorobenzene; reflux, 18 h (5–30%); f) DBH (1,3-dibromo-5,5-dimethylhydanthoin), 70% HF–pyridine, CH_2Cl_2; –70 °C → RT (5–40%).

universally applicable large-scale synthesis for α,α-difluoroalkyl ethers such as **2**, which does not require sophisticated purification steps and which is based on inexpensive and readily available precursors.

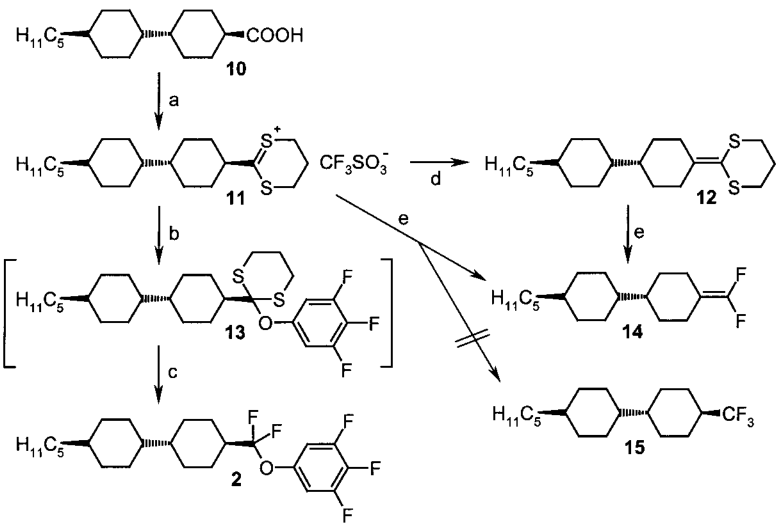
Oxidative fluorodesulfuration[11, 12] is one of the most versatile synthetic tools for the selective introduction of fluorine into complex organic molecules, which is also compatible with other sensitive functionalities. Since cycloaliphatic thionoesters (such as **8**) often suffer from poor stability, in this case a cyclic dithioorthoester seemed a more suitable alternative substrate for the fluorodesulfuration (Scheme 3). The results reported by Klaveness et al.[13] indicated that these dithioorthoesters might be obtained by reaction of a dithianylium salt[14] with a hydroxy compound in the presence of an auxiliary base.



Scheme 3. Retrosynthetic analysis of the formation of the difluorooxymethylene link.

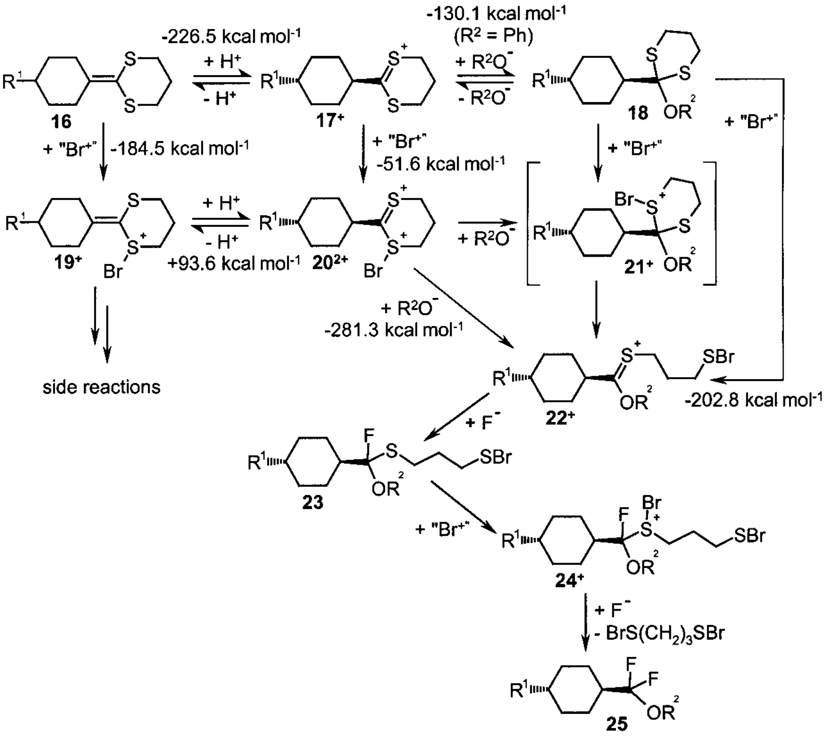
Putting these considerations into practice, we were able to convert the carboxylic acid **10** into the corresponding dithianylium triflate ($\mathbf{11}^{+}CF_3SO_3^{-}$) by condensation with 1,3-propanedithiol and trifluoromethanesulfonic acid under azeotropic water removal (Scheme 4; for details see Experimental Section). The same procedure can also be applied for the conversion of aromatic carboxylic acids. The resulting dithianylium salt $\mathbf{11}^{+}CF_3SO_3^{-}$ and its aromatic analogues are non-hygroscopic solids which can be stored for months at ambient temperature without special precautions. Some dithianylium salts with a shorter alkyl or 4-alkylcyclohexyl group are semi-solids at ambient temperature, without clearly defined melting points. These noncrystalline salts are best stored at –20 °C as a solution in dichloromethane to avoid their slow decomposition by elimination of trifluoromethanesulfonic acid.

First attempts to synthesize and purify the dithioorthoester **13** according to the procedure described in reference [13] only resulted in the exclusive isolation of the ketenedithioketal **12** (Scheme 4). However, conducting the whole reaction se-



Scheme 4. Synthesis of the liquid crystal **2** and conditions leading to the formation of **12** and **14**: a) 1. $HS(CH_2)_3SH$, CF_3SO_3H, toluene/isooctane 1/1; azeotropic removal of water; 2. crystallization by addition of methyl *tert*-butyl ether at 0 °C (90%); b) 3,4,5-trifluorophenol, NEt_3, CH_2Cl_2; –70 °C, 10 min; c) 1. $NEt_3\cdot 3HF$; –70 °C, 5 min; 2. Br_2; –70 °C → 0 °C (84%); d) NEt_3, CH_2Cl_2; RT, 1 h (39%); e) 1. $NEt_3\cdot 3HF$; –70 °C, 5 min; 2. *N*-bromosuccinimide; –70 °C → 0 °C (from $\mathbf{11}^{+}CF_3SO_3^{-}$ and **12**: complex mixture with **14** as main identifiable product, yield not determined).

quence—formation of the dithioorthoester and subsequent halonium-mediated fluorodesulfuration[11, 12] (triethylamine tris(hydrofluoride) ($NEt_3 \cdot 3HF$); 1,3-dibromo-5,5-dimethylhydanthoin (DBH), *N*-bromosuccinimide (NBS) or bromine)—as a one-pot procedure at −70 °C furnished the desired product **2** in good to excellent yields. The highest yields are obtained by using the phenol in an excess of about 0.5 equivalents with regard to the dithianylium salt.



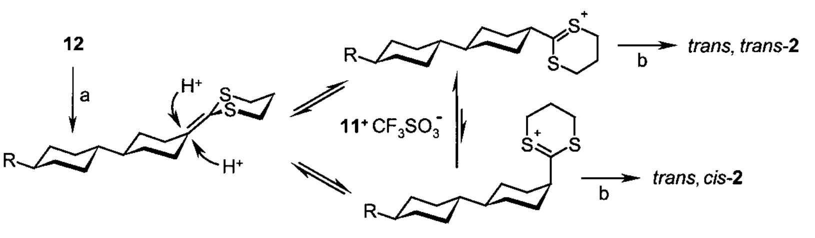
Scheme 6. Tentative mechanistic pathway for the observed reactivity of cycloaliphatic dithianylium salts (for related proposals see also ref. [12]).

Treatment of the dithianylium salt **11**$^+$ $CF_3SO_3^-$ with base (triethylamine) results in quantitative deprotonation of the cation to the ketenedithioketal **12**. Contrary to our expectations, direct fluorodesulfuration of **11**$^+$ $CF_3SO_3^-$, without prior addition of the phenoxide, does not lead to the trifluoromethylbicyclohexyl **15** but to a complex mixture containing **14** as the major identifiable component. A mixture of a similar composition is obtained by the fluorodesulfuration of **12** (Scheme 4).

The alkoxydifluorodesulfuration works not only in the presence of phenols but also with acidic alcohols such as trifluoroethanol, trichloroethanol, or even *S*-1,1,1-trifluorooctan-2-ol.[15] For aromatic dithianylium salts the use of less acidic alcohols, such as ethanol, is feasible in principle, but the resulting difluorobenzyl ethers are often sensitive towards hydrolysis under the work-up conditions and on contact with silica gel and can only be characterized as a transient species by GC-MS analysis of the primary reaction mixture.

The cyclohexyldithianylium triflate **11**$^+$ $CF_3SO_3^-$ can also be generated by protonation of the ketenedithioketal **12**[16] with trifluoromethanesulfonic acid.[17] The protonation is reversible at room temperature, which is indicated by the preferred formation of *trans,trans*-**2** (> 98 %) on applying the full fluorodesulfuration procedure, presumably via the thermodynamically more stable equatorial dithianylium cation *trans,trans*-**11**$^+$. Thus, also ketenedithioketals such as **12** can be converted into the corresponding α,α-difluoroalkylethers by the one-pot reaction sequence depicted in Scheme 5. This provides an attractive synthetic alternative if the dithianylium salt is not readily available from the corresponding carboxylic acid.

The experimental findings were condensed into a tentative mechanism (Scheme 6) which was additionally investigated by density functional theory (DFT) calculations (B3LYP/6-31G*//B3LYP/6-31G* level of theory including unscaled zero-point vibrational energy corrections;[18] for details see Supporting Information). Instead of the 4-alkylcyclohexylidene substructure, the 2-isopropylidene moiety was used to simplify the computational problem. The following discussion uses the numbering system of Scheme 6 but implies the isopropyl model systems. The proton affinity of **16** is −226.5 kcal mol^{-1}. Surprisingly, even the addition of a bromonium ion to the dithianylium salt **17**$^+$ results in the formation of the dication **20**$^{2+}$ with an exothermicity of −51.6 kcal mol^{-1}. The reaction of phenolate ($R^2 = Ph$) with **17**$^+$ gives **18** (−130.1 kcal mol^{-1}), and subsequent attack by Br^+ directly leads to the ring-opened product **22**$^+$. The primary addition product **21**$^+$ is not a stationary point at this level of theory. In the absence of a suitable nucleophilic reaction partner, **20**$^{2+}$ can loose a proton to furnish **19**$^+$. This process is endothermic by 93.6 kcal mol^{-1}. Alternatively, **19**$^+$ might be generated directly by bromination of the ketenedithioketal **16** (−184.5 kcal mol^{-1}). With regard to the experiments represented in Scheme 4, species **19**$^+$ might be considered as a possible starting point for a series of reactions leading among others to compound **14**.



Scheme 5. Direct selective conversion of the ketenedithioketal **12** ($R = C_5H_{11}$) to *trans,trans*-**2**: a) 1. CF_3SO_3H, CH_2Cl_2; 0 °C → 20 °C (1 h) → −70 °C; 2. 3,4,5-trifluorophenol, NEt_3; −70 °C; 3. $NEt_3 \cdot 3HF$; −70 °C; 3. DBH; −70 °C → −20 °C (*trans,trans*-**2**/*trans,cis*-**2** ~98/2; overall yield 93 %).

Application of the general methods described above offered an convenient access to a large variety of structurally diverse new liquid crystals and related compounds. The physical properties of a selection of the newly synthesized materials (Scheme 7) are listed in Table 1. The most striking result of the insertion of the difluorooxymethylene bridge into the basic phenyl-

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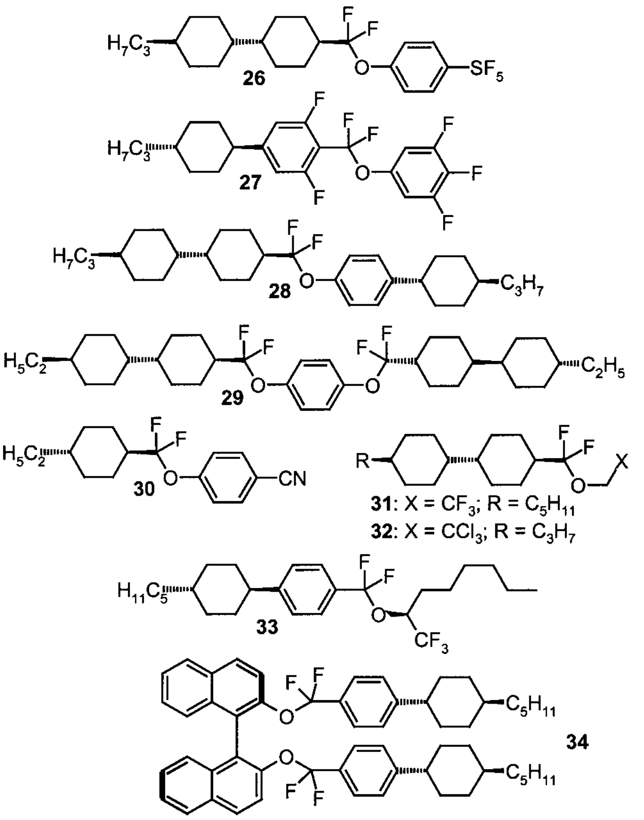

Scheme 7. Structures of liquid crystals (**26**–**32**) and chiral dopants (**33**, **34**) given in Table 1.

bicyclohexyl structure is the pronounced reduction of the rotational viscosity (γ_1) of **2** by 21 % compared to that of **1**. At the same time the clearing temperature is increased by 10 K and the melting point is decreased by 29 K. Similar effects are observed for most phenylcyclohexane-based materials. A detailed comparative discussion of the changes of physical properties induced by the insertion of highly fluorinated brige elements into different locations within the mesogenic core structure will be subject of a forthcoming publication.

Starting either from inexpensive carboxylic acids or carbonyl compounds the previously elusive α,α-difluoroalkyl ethers can be conveniently prepared in high yields. The uncomplicated preparation or in situ generation of the dithianylium salts as key intermediates as well as the easy purification of the final product makes this method a highly attractive choice for industrial-scale production of liquid crystals, pharmaceuticals, and a variety of other fine chemicals.

Experimental Section

Dithianylium triflate **11**$^+$CF$_3$SO$_3$$^-$: 1,3-Propanedithiol (125 g, 1.16 mol) was added to a suspension of **10** (250 g, 0.89 mol) in a mixture of toluene (250 mL) and isooctane (250 mL). The milky suspension was heated to 50 °C, and trifluoromethanesulfonic acid (173 g, 1.16 mol) was added over 30 min (slightly exothermic). The resulting solution was heated to 102–104 °C, and water formed during the reaction (28 mL) was removed azeotropically over 4 h. The solution was cooled to 90 °C, and methyl *tert*-butyl ether (1 L) was added over 45 min at 90–70 °C. The suspension was cooled to 0 °C and filtered under a dry nitrogen atmosphere. The crystals were washed with methyl *tert*-butyl ether (4 × 250 mL) and dried in vacuo to yield **11**$^+$CF$_3$SO$_3$$^-$ (402 g, 90 %) as pinkish crystals. The purity was estimated to be about 95 % by ^{1}H NMR spectroscopy, and was sufficient for the further reactions. The compound slowly decomposed at about 90–100 °C; ^{1}H NMR (250 MHz, CDCl$_3$, 303 K): $\delta = 3.75$ (t, 4H, $J = 5$ Hz), 3.15–2.95 (m, 2H), 2.60–2.45 (m, 2H), 2.17 (d, 2H, $J = 10$ Hz), 2.03–1.60 (m, 4H), 1.35–0.75 (m, 21H); ^{13}C NMR (60 MHz, CDCl$_3$, 303 K): $\delta =$ 203.4 (s, S-C=S$^+$), 121.1 (q, CF$_3$SO$_3$$^-$), 57.2, 53.5, 43.2, 42.3, 38.1, 37.7, 35.5, 33.8, 32.5, 30.3, 29.5, 27.1, 23.1, 17.3, 14.5; MS (EI): *m/z* (%): 352 [M^+ − CF$_3$SO$_3$H] (100).

Synthesis of **2** from the dithianylium salt **11**$^+$CF$_3$SO$_3$$^-$: A solution of 3,4,5-trifluorophenol (10 g, 68 mmol) in a mixture of triethylamine (7.33 g, 72 mmol) and CH$_2$Cl$_2$ (90 mL) was cooled to −70 °C. Then a solution of **11**$^+$CF$_3$SO$_3$$^-$ (30.9 g, 62 mmol) in CH$_2$Cl$_2$ (85 mL) was added over 45 min at the same temperature. After the mixture had been stirred for 1 h, NEt$_3$ · 3HF (50 mL, 310 mmol) were added over 5 min. Then, over a period of 1 h a solution of bromine (49.5 g, 310 mmol) in CH$_2$Cl$_2$ (20 mL) was added at −70 °C. The mixture was stirred for one more hour at −70 °C and then allowed to warm up to 0 °C. The solution was poured into a mixture of 32 % aqueous NaOH (107 mL) and ice (200 g). The pH was adjusted to 5–8 by addition of 32 % aqueous NaOH (ca. 28 mL). The aqueous layer was extracted with CH$_2$Cl$_2$ (50 mL), and the combined organic extracts were filtered through 2.5 g of celite, washed with water, and evaporated to dryness. The residue was dissolved in *n*-heptane (60 mL), stirred for 30 min with 5 g of silica gel, filtered, and evaporated to dryness. The crude product was chromatographed with *n*-heptane on silica gel to yield **2** (22.8 g; 84 %) as a nematic oil which slowly crystallized (purity 99.2 %, verified by GLC and HPLC). The sample was purified further by recrystallization from *n*-heptane at −20 °C (purity > 99.9 %; GLC and HPLC). For mesophases see Table 1; ^{1}H NMR (250 MHz, CDCl$_3$, 303 K): $\delta = 6.82$ (mc, 2H, Ar-2,6-*H*), 2.08–1.65 (m, 4H), 1.38–0.80 (m, 27H); ^{19}F NMR (280 MHz, CDCl$_3$, 303 K): $\delta = -165.3$ (mc, 1F; Ar-4-*F*), −133.8 (mc, 2F; Ar-3,5-*F*), −79.3 (d, $J = 8.4$ Hz, 2F; C*F*$_2$O); MS (EI): *m/z* (%): 432 [M^+] (25), 284 [M^+ − F$_3$PhOH] (50).

Synthesis of **2** from the ketenedithioketal **12**: Trifluoromethanesulfonic acid (0.25 mL, 2.84 mmol) was added dropwise at 0 °C to a solution of **12** (1.00 g, 2.84 mmol)[16] in CH$_2$Cl$_2$ (15 mL). The cooling bath was removed and the mixture was stirred for 30 min at room temperature. Then it was cooled down to −70 °C and a solution of 3,4,5-trifluorophenol (0.63 g, 4.25 mmol) in toluene and triethylamine (0.71 mL, 5.10 mmol) in CH$_2$Cl$_2$ (3 mL) was added. After the mixture had been stirred for 1 h at −70 °C, NEt$_3$ · 3HF (2.29 mL, 14.2 mmol) was added. After 5 min a suspension of DBH (4.05 g, 14.2 mmol) in CH$_2$Cl$_2$ (15 mL) was added portionwise over 30 min. After stirring for additional 60 min, the mixture was allowed to warm up to −20 °C and then poured into ice-cold 1N aqueous NaOH (50 mL). The organic layer was separated, and the aqueous layer was extracted with CH$_2$Cl$_2$ (3 × 30 mL). The combined organic extracts were stirred for 15 min with 5 g of celite, filtered, washed with brine (2 × 30 mL), dried over Na$_2$SO$_4$, and evaporated to dryness. The residue was dissolved in *n*-hexane and filtered through a short silica gel column. Yield: 1.14 g (93 %) of **2**, containing 96.9 % *trans,trans* and 2.2 % *trans,cis* isomer (GLC). Further purification to > 99.8 % (GLC) of *trans,trans*-**2** was accomplished by crystallization from *n*-heptane at −20 °C.

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[20] The values for the helical twisting power (HTP) of the newly synthesized compounds are as follows: **33**: −8.3 μm^{-1}; **34**: +35.0 μm^{-1} (determined from a 1% w/w solution in the Merck mixture MLC-6260 at 20 °C).

[21] The application-oriented evaluation of liquid crystals for use in LCDs is centered around "virtual" clearing temperatures, electrooptic parameters, and viscosities. These data are obtained by extrapolation from a standardized nematic host mixture: $T_{\mathrm{NI,extr}}$, $\Delta\varepsilon$, Δn, and γ_1 were determined by linear extrapolation from a 10% w/w solution in the commercially available Merck mixture ZLI-4792 ($T_{\mathrm{NI}} = 92.8\,^\circ\mathrm{C}$, $\Delta\varepsilon = 5.27$, $\Delta n = 0.0964$). The values thus obtained are empirically corrected for changes in the order parameter. For the pure substances the mesophases were identified by optical microscopy, and the phase transition temperatures by differential scanning calorimetry (DSC).

A Short Copper–Copper Distance in a (μ-1,2-Peroxo)dicopper(II) Complex Having a 1,8-Naphthyridine Unit as an Additional Bridge**

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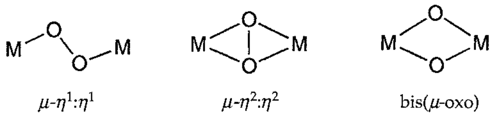
Keith O. Hodgson,* and Stephen J. Lippard*

Proteins that utilize transition metal ions to activate molecular oxygen perform a variety of functions.[1–4] Peroxo-bridged dimetallic species are important intermediates in these processes. The geometry of a bound peroxide group may play an important role in determining its reactivity and thus the function of the protein. Comparison of synthetic dinuclear peroxo complexes with the protein cores has helped elucidate the structures and properties of many such biological species. The μ-η^2:η^2 side-on geometry is presently known only in dicopper-containing proteins,[2] whereas the μ-η^1:η^1 (μ-1,2-peroxo)-bridged structure occurs in diiron-containing proteins (Scheme 1).[3]



Scheme 1. Selected geometric units formed upon the reaction of dioxygen with dimetallic transition metal centers.

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