DNA and conclude that (i) an interstrand disulfide cross-link can significantly stabilize duplex DNA while causing little structural distortion; (ii) disulfide cross-links, unlike psoralen,[6b] do not perturb base pairing and the denaturation pathway of DNA; and (iii) it may be possible to drive structural transitions in DNA and to rationally engineer non-ground-state DNA structures by exploiting the favorable energetics associated with disulfide bond formation. Since these unstrained, intramolecular disulfide bonds are both kinetically and thermodynamically resistant to reduction,[27] such cross-linked oligonucleotides should facilitate studies of enzyme-mediated unpairing processes such as transcription, replication, and recombination.

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Supplementary Material Available: Complete experimental details for the synthesis of ϕdI phosphoramidite and oligonucleotides **1-7**, details and results of gel electrophoresis and the nucleoside composition analyses, selected CD, ^{31}P NMR, and ^{1}H NMR spectra of cross-linked oligonucleotides **6** and **7** and the unmodified decamer, and energy-minimized molecular models of disulfide cross-linked oligonucleotides **6** and **7** (15 pages). Ordering information is given on any current masthead page.

(27) In experiments to be reported elsewhere, we have determined that the disulfide bond of oligonucleotide **6** (74 μM) is virtually unaffected by 1 mM 2-mercaptoethanol, 25 °C, overnight. This thiol concentration is sufficient to maintain the enzymatic activity of most proteins. It should be noted, however, that **6** and **7** do not form stable duplex DNA at 25 °C, a factor that *facilitates* disulfide reduction. The corresponding cross-linked 12-mer, 5'-d(CGCGAATTCGCG), is completely resistant to 25 mM 2-mercaptoethanol.

Structure of a Free, Unassociated Alkyl-Substituted α-Sulfonyl Carbanion: Isolation and X-ray Crystal Structure Analysis of the Inclusive Lithium Cryptate (Me_2CSO_2Ph)(Li·[2.1.1]cryptand)†

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Recently we disclosed the enantioselective synthesis of a lithium α-sulfonyl carbanion salt which is optically stable at low temperatures.[1] In view of the new mechanistic and synthetic possibilities offered thereby, a deeper knowledge of the structure of α-sulfonyl carbanions and the Li^+ gegenion effect is desirable. Work from our laboratories and elsewhere has shown that alkali-metal salts of α-sulfonyl carbanions exist in the crystal[1-4] and in THF solution[1,2,5] as dimeric and monomeric contact ion pairs which are associated via the sulfonyl O atoms. We have previously probed the free, unassociated α-sulfonyl carbanion[6] and the gegenion effect in the case of the phenyl-substituted species $[PhCH_2(Ph)CSO_2CF_3]^-$ by determining inter alia the crystal structure of its tetrabutylammonium and lithium salt.[2] Surprisingly, here only a small static and dynamic Li^+ gegenion effect was found. Since the free α-sulfonyl carbanion is also of significant theoretical interest,[7] the attainment of the lithium salt of an alkyl-substituted α-sulfonyl carbanion with complete ion separation was an attractive goal. In this communication we report the isolation of the novel title compound (Me_2CSO_2Ph)(Li·[2.1.1]-cryptand) (**1**) and the determination of its crystal structure; that of the solvated dimeric O-Li contact ion pair $[(Me_2CSO_2Ph)$-Li·diglyme$]_2$ (**2**) is already known.[3c]

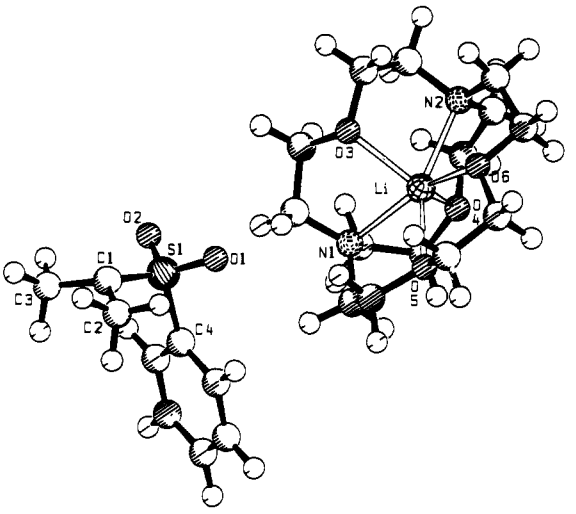

Figure 1. Molecular structure of **1** showing the atom-numbering scheme.[10] Selected bond lengths (Å) and angles (deg) of **1** and of **2** (values following the oblique lines): S1-O1 1.449 (2)/1.462 (2), S1-O2 1.456 (2)/1.454 (2), S1-C1 1.625 (3)/1.640 (3), S1-C4 1.795 (3)/1.794 (3), O1-S1-O2 116.7 (1)/116.6 (1), C1-S1-C4 111.3 (1)/111.8 (1), C3-C1-C2 116.7 (3)/115.5 (3), C3-C1-S1 117.6 (2)/115.7 (2), C2-C1-S1 117.5 (2)/115.3 (2), C1-S1-O1-O2 -128.7 (4)/-128.7 (4), C4-S1-C1-C3 -75.8 (4)/-72.8 (4), C4-S1-C1-C2 71.7 (4)/66.3 (4), O1-S1-C1-C2 42.2 (4)/48.0 (4), O2-S1-C1-C3 -38.6 (4)/-41.3 (4), C3-S1-C1-C2 147.5 (4)/139.2 (4).

Compound **1** was isolated as orange crystals by addition of an equimolar amount of [2.1.1]cryptand[8] to a solution of (Me_2CSO_2Ph)Li in THF and recrystallization of the solid formed from THF. A view of the molecular structure of **1** is depicted in Figure 1.[9] **1** is an inclusive cryptate with discrete

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$(Me_2CSO_2Ph)^-$ and [Li·[2.1.1]cryptand]$^+$ ions; the anionic centers are well separated from the Li^+ ion, and no unusual short intermolecular contacts are observed. Hence, **1** may be regarded as a model for a solvent-separated ion pair. The anion of **1** has, like that of **2**, a strongly pyramidalized anionic carbon atom (C_α atom) with the methyl groups bent away from the O atoms. It features the typical C_α–S conformation of α-sulfonyl carbanions[1-4,6,7] wherein the lone electron pair is almost exactly orientated gauche to both O atoms. This allows inter alia for a stabilization by negative hyperconjugation (n_C–σ_{SPh}^*).[7] A comparison of the bonding parameters of the unassociated anion of **1** and of the lithium-associated one of **2** reveals a close similarity except for one feature (Figure 1): the trigonal C_α atom in the cryptate **1** is significantly less pyramidalized than that in the contact ion pair **2** as shown by the pyramidalization angle χ[11] of 32.5° and 40.8°, respectively. There is much evidence from crystal structure analysis of acyclic O–M-associated α-sulfonyl carbanion alkali-metal salts that the pyramidalization of the alkyl-substituted C_α atom originates primarily from the minimization of torsional strain around the C_α–S bond whereas the planarization of the phenyl-substituted C_α atom stems from the maximization of stabilizing p_π–p_π overlap.[1-4] This, however, implies that electronically the energy difference between a pyrmidalized and planar (at the C_α atom) α-sulfonyl carbanion is only small, a conclusion that is supported by ab initio calculations.[7b] Thus, in dimeric solvated contact ion pairs like **2**, intramolecular packing forces could reinforce the pyramidalization of the C_α atom because of its shallow pyramidalization potential. A space-filling model of **2** (C_i) reveals indeed a packing that encompasses a close proximity of methylene and methyl groups of both diglyme molecules and the methyl groups at the C_α atom. The greater pyramidalization of the C_α atom in **2** therefore may be attributed to a steric intraaggregate chelate ligand/anion interaction. In dimeric solvated O–Li contact ion pairs of benzylic lithio sulfones,[1,2,3c,f,4a,c] manifestation of such an effect is not to be expected because of a steeper pyramidalization potential of the C_α atom bearing a phenyl group. Accordingly, the C_α atom of the analogous dimer {[Ph(Me)CSO_2Ph]Li·diglyme}$_2$ (C_i) is almost planar, and no close proximity exists between the diglyme molecules and the groups at the C_α atom.[3c]

The complex ion [Li·[2.1.1]cryptand]$^+$ has already been crystallographically characterized; its present structure shows no significant deviation.[12] Since with **1** the separation of an O–Li-associated lithium carbanion salt has been achieved in the solid state,[13] isolation of inclusive cryptates of other synthetically important lithium carbanion salts with O–Li and/or N–Li association[4c,14] may be feasible too.[15]

In summary, the Li^+ gegenion effect on an alkyl-substituted or benzylic α-sulfonyl carbanion in dimeric solvated lithium salts is apparently small. The extent of the pyramidalization of the C_α atom, however, can be determined in the former case to a certain degree by intraaggregate interactions.

A fair structural picture of the associated as well as the unassociated α-sulfonyl carbanion has now emerged. This should aid considerably an investigation of the asymmetric induction exerted by the sulfonyl group at the C_α atom which is now underway in our laboratories.

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Supplementary Material Available: Details of the X-ray structural analysis of **1** including tables of refined atomic coordinates, bond lengths and angles, calculated hydrogen atom coordinates, and anisotropic thermal parameters and figures showing space-filling models of the molecular structures of **2** and {[Ph(Me)CSO_2Ph]Li·diglyme}$_2$ (46 pages); listing of observed and calculated structure factors (18 pages). Ordering information is given on any current masthead page.

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Construction, DNA Binding, Two-Dimensional Nuclear Magnetic Resonance Spectrum, and Structure of a Mutant *lac* Repressor Headpiece

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The *lac* repressor–operator system has been the prototype for studying protein–DNA interactions.[1] While site-specific mutagenesis has provided information on the role of individual amino acids in recognition,[2,3] it is not understood at a detailed molecular level.[4,5] Many mutants have been generated by nonsense mutations[6,7] (although the substitutions are limited to amino acids whose codons have suppressible mutations) and cassette mutagenesis.[8] Here, we describe the secondary structure of a 56-residue *lac* repressor mutant headpiece studied by two-dimensional NMR. The tyrosine 7 to isoleucine (Y7I) mutant of the repressor has been designed to test the importance of proposed tyrosine 7–tyrosine 17 stacking in the stabilization of the protein and the role this might play in DNA recognition. This interaction reported by Jardetzky[9,10] remains one of the first NOEs observed for *lac* headpiece. While some NMR spectral differences have been reported for mutant repressors,[11,12] we believe this study to represent the first direct comparison of the structural and biological

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