Organosulfur Chemistry. 3. NMR Spectra of Carbanions Derived from 1,3-Dithianes as Related to the High Stereoselectivity in their Reactions with Electrophiles[1,2]

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Abstract: ^1H and ^{13}C NMR spectra of 2-lithio and 2-potassio derivatives of 2-phenyl-1,3-dithiane in various solvent mixtures have been recorded. These species exist as two distinct types of anions or ion pairs, one in THF and the other in HMPA. The former species appears to involve substantial association between carbanion and metal cation, whereas the latter type shows little such interaction; both species exhibit high stereoselectivity in reactions with electrophiles. This suggests that neither lithium–sulfur interactions[1a,2] nor the concomitant intimate ion pairing, but rather an intrinsically preferred equatorial orientation of the lone pair in carbanions derived from 1,3-dithianes, may be responsible for such stereoselectivity.

In the previous paper in this series[1a] reactions of the lithium derivatives of anancomeric 1,3-dithianes with electrophilic reagents such as DCl, methyl iodide, formaldehyde, etc., were shown to proceed with high stereoselectivity to give virtually exclusively equatorial substitution products (Scheme I). As a part of this general scheme, "contrathermodynamic" equatorial → axial isomerization of a group as large as *tert*-butyl was shown to provide an estimate of >6 kcal/mol for the equatorial preference of lithium (presumably in the form of an ion pair) in the intermediate lithiodithianes[1a] (Scheme II).

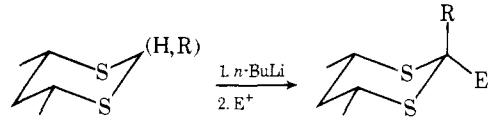
To account for this high degree of stereoselectivity, an ion pair structure for the intermediate lithium compound was postulated in which the lithium ion is held in the equatorial position by the cooperative effect of the carbanion and one of the unshared electron pairs of each of the two sulfur atoms[1a] (Scheme III). This explanation was favored over the alternative possibility that the equatorial orientation of the carbanion itself might be substantially more stable, for stereoelectronic reasons, than the axial orientation as depicted in Scheme IV.

However, the latter hypothesis is supported by several recent quantum mechanical computations.[3] Thus the calculations of Lehn and Wipff[3a] indicate that a carbanion adjacent to two sulfurs is 9 kcal/mol more stable in the equatorial-like than the axial-like position. These computations also suggest that ion pairing of the carbanion with the lithium cation actually lowers the equatorial–axial energy difference to as little as 3.5 kcal/mol. Such calculations, of course, strictly apply only to the gas phase for simple dithiane carbanions.

In an effort to gain further understanding of the nature of 2-lithio-1,3-dithianes in solution and to determine the influence of Li–S interactions on the stereochemical properties of these compounds, we have investigated their structure in solution utilizing ^{13}C and ^1H NMR spectroscopy. Our spectral studies, in conjunction with investigation of reaction stereoselectivity, now suggest (in accord with theoretical arguments) that Li–S coordination and concomitant ion pairing are not required for the high stereoselectivities exhibited by lithiodithianes.

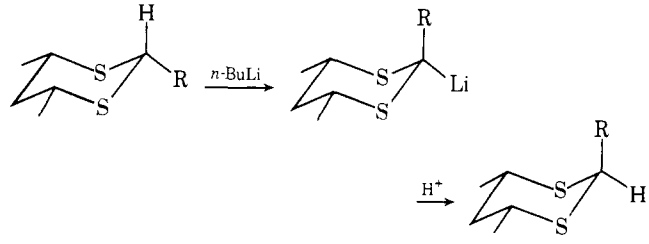
Spectral Studies. The first[2] and, thus far, most informative compound subjected to NMR analysis is **3**, prepared from **1** or **2** with *n*-butyllithium. The phenyl portion of the ^1H NMR spectrum of **3** in tetrahydrofuran (THF) (Figure 1) is very similar to that of triphenylmethyllithium.[4] The marked upfield shifts of the aromatic protons of **3** in comparison to the corresponding chemical shifts in **1** or **2** suggest substantial delocalization of negative charge into the phenyl ring of **3** (see Table I). Analogous shift differences are observed in the carbon spectra of **1**, **2**, and **3** (see Table II). The demethyl compound **5**, prepared from **4** with *n*-butyllithium, exhibits spectral properties very similar to those of **3** (see Tables I and II).

Scheme I



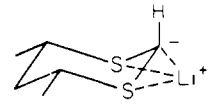
R = H, CH_3, C_6H_5

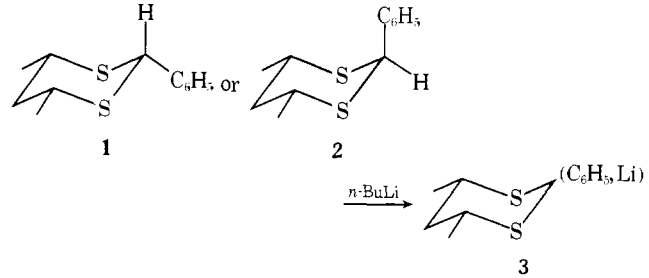
Scheme II



R = D, CH_3, C_6H_5, $C(CH_3)_3$, CH_2OH, $C(CH_3)_2OH$, $CHOHC(CH_3)_3$

Scheme III





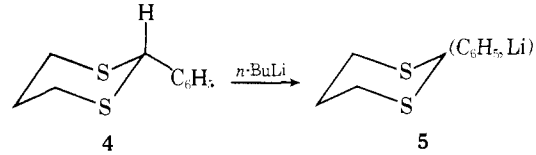


Table I. Chemical Shifts for the Aromatic Protons of **1**, **2**, and **4** and Their 2-Lithio Derivatives in Various Solvents

Compd	Solvent	$\delta(H_{ortho})^a$	$\delta(H_{meta})^a$	$\delta(H_{para})^a$
1	THF	~7.23	~7.23	~7.23
2	THF	7.75	7.22	7.22
4	THF	~7.27	~7.27	~7.27
3	THF	7.63 (−0.12)	6.93 (−0.29)	6.27 (−0.95)
5	THF (2 M)	7.50 (−0.25)	6.84 (−0.38)	6.18 (−1.04)
5	THF (0.03 M)	7.58 (−0.17)	6.88 (−0.34)	6.22 (−1.00)
3	THF-TMEDA[b]	7.63 (−0.12)	6.95 (−0.27)	6.25 (−0.97)
5	THF-TMEDA[b]	7.57 (−0.18)	6.87 (−0.35)	6.20 (−1.02)
5	TMEDA[c]	7.60 (−0.15)	6.94 (−0.28)	6.27 (−0.95)
5	THF-HMPA[d] (0.03 M)	6.86 (−0.89)	6.44 (−0.78)	5.39 (−1.83)
5	THF-HMPA[e] (1 M)	6.78 (−0.97)	6.41 (−0.81)	5.39 (−1.83)
5	HMPA[c]	6.79 (−0.96)	6.37 (−0.85)	5.32 (−1.90)

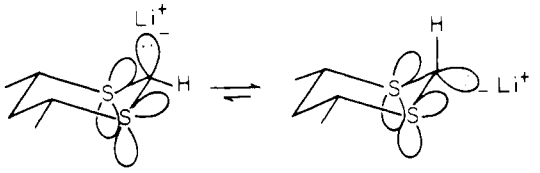
[a] Chemical shifts are in parts per million downfield from tetramethylsilane. Estimated error limits ±0.04 ppm, ±0.1 ppm where indicated ~. Data in parentheses are shift differences relative to **2**. [b] Organolithium concentration ca. 2 M, TMEDA 2.5 M. [c] Sample contained a small amount of THF. [d] Sample contained ca. 8 molar equiv of HMPA. [e] Sample contained ca. 3 molar equiv of HMPA.

Table II. Chemical Shifts for the Aromatic Carbons of **1**, **2**, and **4** and Their 2-Lithio Derivatives in Various Solvents

Compd	Solvent	$\delta(C_{ortho})^a$	$\delta(C_{meta})^a$	$\delta(C_{para})^a$
1	THF	128.9	128.3	128.5
2	THF	129.0	128.6	127.1
4	THF	129.0	128.3	128.6
3	THF	122.5 (−6.5)	127.5 (−1.1)	113.4 (−13.7)
5	THF	122.5 (−6.5)	127.3 (−1.3)	113.1 (−14.0)
5	THF-TMEDA (1:1)	122.8 (−6.2)	127.5 (−1.1)	113.8 (−13.3)
5	THF-HMPA (2:1)	117.5 (−11.5)	127.3 (−1.3)	104.1 (−23.0)

[a] Chemical shifts are in parts per million downfield from internal tetramethylsilane. Data in parentheses: shift differences relative to **2**.

Scheme IV



The ^1H and ^{13}C NMR signals of the aromatic protons and carbon atoms in **3** and **5** in THF are unaffected by tetramethylethylenediamine (TMEDA), a solvent known to disaggregate tetrameric *n*-butyllithium[5] and concomitantly cause substantial changes in its NMR properties.[6] TMEDA is apparently complexed to the lithiodithiane in THF because the methyl resonance of TMEDA is shifted ca. 0.1 ppm downfield from its normal value.[7] Such a shift has been shown to be characteristic of organolithium-TMEDA complexes.[6] Nonetheless, this complexation has no palpable effect on the carbanion portion of **3** and **5**. Crystallization of the **5**-TMEDA complex can be induced from THF-hexane solution and the isolated colorless crystals show a ratio of 1:1.26 for **5**:TMEDA as found by integration of the ^1H NMR spectrum of the crystals dissolved in THF.

The aromatic ^1H and ^{13}C chemical shifts of **3** and **5** in THF are moved dramatically upfield upon addition of hexamethylphosphoramide (HMPA) (see Tables I and II), suggesting ion pair separation resulting in increased charge delocalization into the phenyl ring. Changes in the ^1H NMR spectrum of **5** were followed as a function of HMPA concentration. Small amounts of HMPA were added to a 2 M solution of **5** in THF, and spectra were recorded after each addition. A plot of change in chemical shift for the aromatic protons of **5** vs. molar equivalents of HMPA is shown in Figure 2a. As indicated there, the maximum shift is reached after addition of 3 molar equiv of HMPA (see also Table I).

Results from an analogous HMPA titration of the **5**-TMEDA 1:1.26 complex, 2 M in THF, are shown in Figures 2b and 2c. Chemical shift changes as well as individual shift

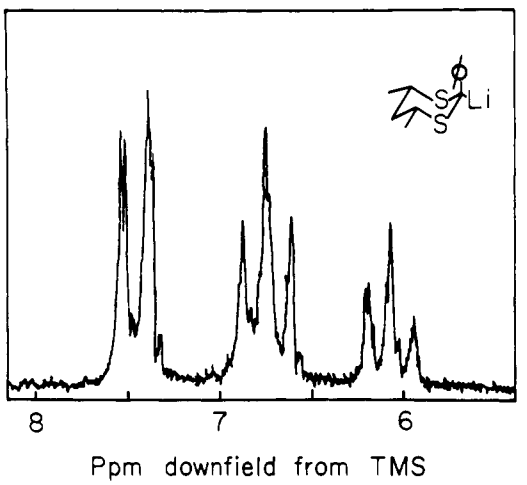


Figure 1. ^1H NMR spectrum of 2-phenyl-2-lithio-*cis*-4,6-dimethyl-1,3-dithiane (**3**) in THF.

values observed for the aromatic protons of **5** during the HMPA titration of the **5**-TMEDA complex (Figure 2b) are almost identical with those obtained for **5** in THF alone (Figure 2a). Figure 2c shows the effect of HMPA on the chemical shift of the TMEDA methyl resonance. As HMPA concentration increases, the methyl resonance moves from the deshielded position of the **5**-TMEDA complex to the normal chemical shift observed for TMEDA in THF in the absence of **5**, suggesting that TMEDA is being displaced from the solvent sphere of **5** by HMPA.

A similar titration was performed on a dilute (0.03 M) solution of **5** in THF (see Figure 2d). Upfield shifts are again observed, but approximately 8 molar equiv of HMPA is required to produce the maximum change in chemical shift. These data suggest the existence of an equilibrium between the contact ion pair (A) and solvent-separated ion pair (B) con-

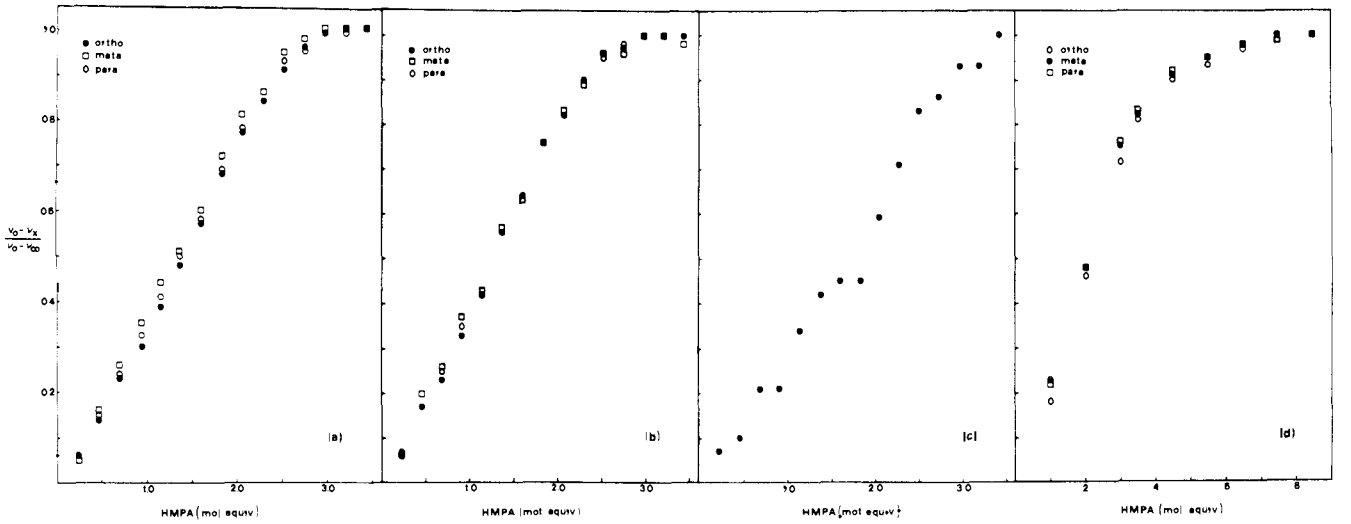
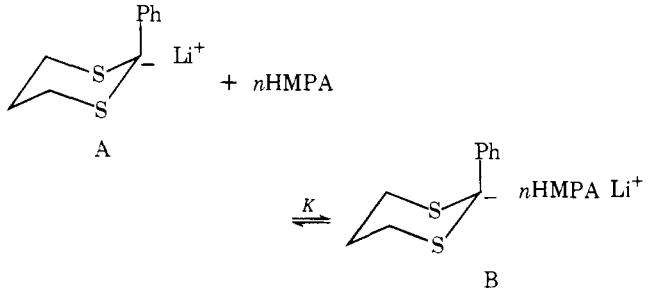


Figure 2. Chemical shift changes for solutions of **5** as a function of the number of added molar equivalents of HMPA, where ν_0 is the chemical shift in THF, ν_∞ is the maximum high field shift reached during the titration, and ν_x is the chemical shift at intermediate titration points. (a) The aromatic protons of **5**, initially 2 M in THF. (b) The aromatic protons of **5**, initially 2 M in THF containing 1.25 molar equiv of TMEDA. (c) The TMEDA methyl protons of the **5**–TMEDA complex, initially 2 M in THF. (d) The aromatic protons of **5**, initially 0.03 M in THF.

Scheme V



taining n molecules of HMPA as shown in Scheme V. Such an equilibrium can be described by the relationship

$$\log ([B]/[A]) = n \log [HMPA] + \log K \qquad (1)$$

If it is assumed that only A is present in THF and only B is present in the solution containing 8 molar equiv of HMPA, then the two corresponding chemical shift values can be used to calculate molar proportions of A and B at any point in the above titration from eq 2, where m_A and m_B are the molar proportions of A and B, respectively, ν_A and ν_B are the assigned chemical shifts for A and B respectively, and ν_{obsd} is the observed chemical shift for each titration point.

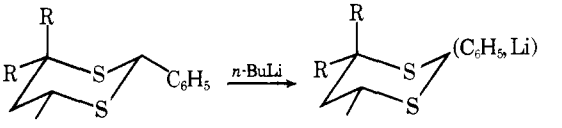
$$m_A = 1 - m_B = \frac{\nu_{obsd} - \nu_B}{\nu_A - \nu_B} \qquad (2)$$

Thus [B]/[A] ($= m_B/m_A$) can be determined for each titration point. The initial concentration of HMPA, $[HMPA]_0$, requires adjustment for those n molecules of HMPA which become bound in the solvent-separated ion pair, i.e., $[HMPA] = [HMPA]_0 - n[B]$. For the correct value of n a plot of log [B]/[A] vs. log ($[HMPA]_0 - n[B]$) should then yield a straight line with slope equal to n. A series of such plots using, initially, assumed values of n led to a consistent value when $n = 2.25$. The fact that n is not an integer may be due to experimental error or may indicate that the process is more complicated than that shown in Scheme V.

Application of this analysis to the titration experiments with 2 M initial concentrations of **5** is unsatisfactory, probably owing to substantial changes in the macroscopic properties of such solutions during the titration. In the course of these experiments, the solvent becomes quite concentrated in HMPA which, in turn, may lead to formation of free ions and/or change the K in Scheme V during the titration. (The minute quantities of HMPA added to the 0.03 M solution would not be expected to induce such effects.) Nonetheless, if $n = 2$ (or 2.25) it is reasonable that in relatively concentrated HMPA solution, the maximum upfield NMR shifts are attained upon addition of 2.8 (i.e., somewhat more than 2 or 2.25) mol of HMPA.

Hogen-Esch and Smid[8] have performed a similar analysis of lithium fluorenyl from changes in its optical spectrum from a dioxane solution caused by addition of small quantities of dimethyl sulfoxide (Me_2SO). In that case only one molecule of Me_2SO is needed for the formation of the solvent-separated ion pair.

Low-temperature ^{13}C NMR spectra were recorded for **7** in various THF–HMPA mixtures. Solutions (1–2 M) of **7** in THF alone or with 1 molar equiv of HMPA showed no sig-



6, R = H
8, R = CH_3

7, R = H
9, R = CH_3

nificant overall changes in the NMR spectrum down to a temperature of −100 °C. However, a solution of **7** in THF containing 2 molar equiv of HMPA showed separation of the resonance of the ortho carbon atoms of the phenyl ring into two equally intense signals at −80 °C. These two resonances coalesced at −62 °C. Addition of another equivalent of HMPA to this solution raised the coalescence temperature to −21 °C. Energy barriers for these two coalescence phenomena were calculated to be 11.5 and 13.3 kcal/mol, respectively, from coalescence temperatures and line separations.[9]

Such low-temperature ^{13}C NMR experiments were even more informative when conducted with compound **9**. The ^{13}C spectrum of **9** at −50 °C exhibits two meta carbon signals of equal intensity, as well as two ortho carbon resonances, even in THF (1 M), presumably because of the additional steric hindrance of phenyl rotation afforded by the syn-axial methyl group. The ortho carbon signals coalesce at −5 °C, corresponding to an energy barrier to rotation of 13.0 kcal/mol. Similar measurements for THF solutions of **9** containing 1, 2,

Table III. Chemical Shifts of the Aromatic Protons of **10** in Various Solvents

Solvent	$\delta(H_{ortho})^a$	$\delta(H_{meta})^a$	$\delta(H_{para})^a$
THF	7.18	6.67	5.84
THF-(18-C-6)[b]	7.04	6.60	5.63
THF-2(18-C-6)[c]	6.99	6.57	5.54
HMPA[d]	6.79	6.37	5.34

[a] Chemical shifts are in parts per million downfield from Me_4Si. Estimated error limits ±0.04 ppm. [b] Sample contained 1 molar equiv of 18-crown-6. [c] Sample contained 2 molar equiv of 18-crown-6. [d] Sample contained a small amount of THF.

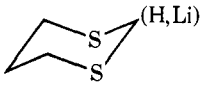
and 3 molar equiv of HMPA led to energy barriers 13.6, 14.4,[10] and 16.4 kcal/mol, respectively.

Analogous coalescence behavior has been observed for other benzylic systems,[11] and such phenomena have been explained in terms of ion pair equilibria. Our results can be rationalized in similar fashion as shown in Scheme VI. Rotation is relatively fast for the tight ion pair (in THF) but slower for the solvent-separated and hence more delocalized anion.

Shifts of the aromatic protons in the ^1H NMR spectrum of potassiodithiane **10,** readily prepared from **4** and potassium hydride in THF (Scheme VII),[12] are shown in Table III. Also shown there are the corresponding shifts of the potassiodithiane in HMPA and in the presence of 18-crown-6; these species are even more facile to obtain from KH and **4** in HMPA[12] or in THF in the presence of 18-crown-6,[13] respectively.

The aromatic proton resonances of **10** in THF are similar to those of **5** in THF but are at higher field (see Tables I and III). Upfield shifts for other systems have been observed previously as the ion is changed from lithium to the larger potassium.[14] Addition of 1 molar equiv of 18-crown-6 to **10** in THF leads to a further upfield shift of the aromatic signals which is but slightly enhanced upon addition of a second molar equivalent of the crown ether. Addition of HMPA to **10** in THF leads to substantially larger shifts of the phenyl protons to high field, the shifts being approximately the same as those observed for the lithium analogue **5** in HMPA (see Tables I and III).

Several other 2-lithio-1,3-dithianes have been studied by NMR spectroscopy. However, compound **11,** which contains

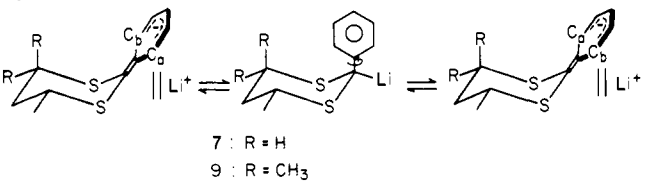


11

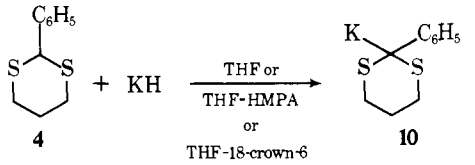
no carbanion-stabilizing substituent, such as the phenyl group in **3, 5,** and **7,** shows little variation of spectroscopic behavior with solvent. Thus ^{13}C and ^1H NMR spectra of **11** in THF are very similar to those recorded in THF-HMPA solutions (see Table IV).

Stereoselectivity Studies. Quenching of **3** in THF with HCl (or DCl) gives >99% of **2,** but the same reaction of **3** in concentrated (>1 M) solutions of THF-HMPA produces a ca. 85:15 mixture of **2** and **1,** respectively. These results were initially thought[2] to provide evidence for a large difference in stereoselectivity for the two types of ion pairs of **3** (vide supra).

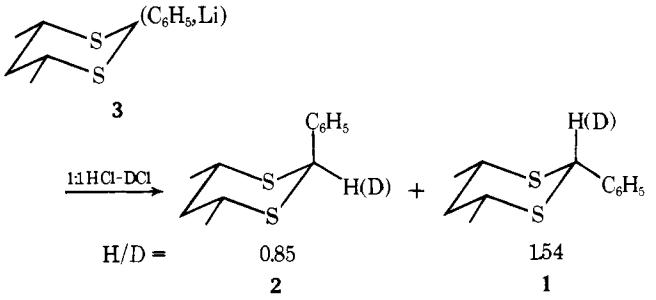
Scheme VI



Scheme VII



Scheme VIII



However, subsequent experiments have shown these quenching data to be misleading. Quenching of **3** in THF-HMPA with 1:1 HCl-DCl and mass spectroscopic determination of the H/D ratio in the separated products **2** and **1** revealed that significantly more deuterium was present in **2** than in **1**[15] (see Scheme VIII). The possibility of incomplete metalation of **1** as the source of proton-rich **1** was ruled out by quenching a portion of the reaction mixture with deuterium oxide. Mass spectrometric analysis of the quenched products showed 98.5% deuterium incorporation.

These results can be explained by invoking an intermolecular exchange during the quenching process in which **2,** formed as the initial quenching product, is epimerized to the thermodynamically more stable **1** via **3** (see Scheme IX).

Since, because of an isotope effect, proton exchange is faster than deuteron exchange, **1** will have a higher H/D ratio than the initially formed **2**. Either equilibrium during HCl-DCl quenching is established more rapidly in the presence of HMPA than in pure THF, or quenching occurs more slowly in the more basic and more viscous HMPA-containing solvent. In any case, the evidence is that **1** is *not* formed in a kinetically controlled quenching reaction. (Partial equilibration during quenching is not an uncommon occurrence in carbanion chemistry.)

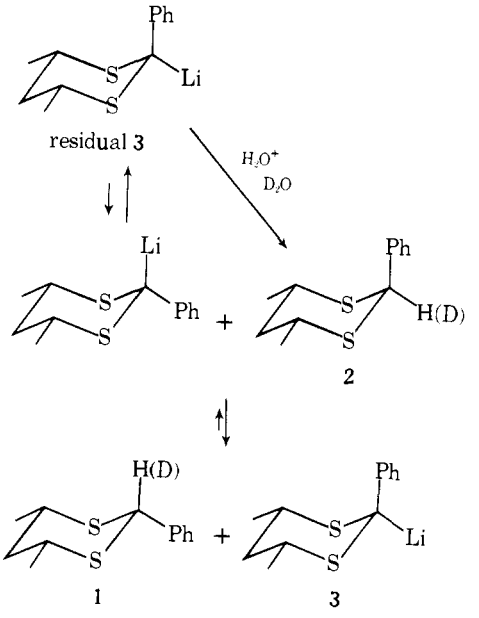
To reduce the effects of this intermolecular equilibration pathway, the reaction mixture was diluted to 0.03 M and only 3 molar equiv of HMPA was added. Acid quenching of this dilute solution gave a reproducible 96:4 ratio of **2:1,** but mass spectral analysis of the products from reaction of **3** with 1:1 HCl-DCl showed that the equilibration pathway had not been

Table IV. ^1H and ^{13}C Chemical Shifts[a] for 1,3-Dithiane and Its 2-Lithio Derivative **11** in THF and THF-HMPA

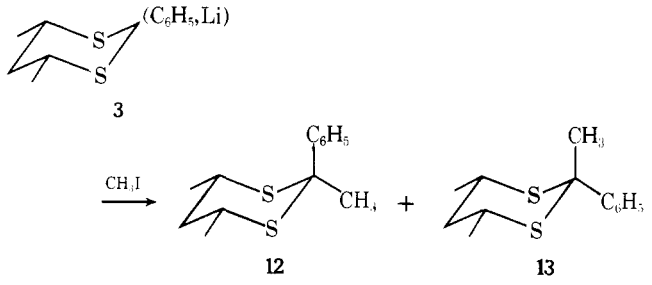
Compd	Solvent	C(2)-*H*	C(2)	C(4,6)	C(5)
1,3-Dithiane	THF	3.68[b]	32.2	30.4	26.3
1,3-Dithiane	HMPA		31.7	29.7	27.2
9	THF-d_8	2.78	26.7	34.1	31.2
9	THF-d_8-HMPA-d_{18}	2.77	27.8	34.3	31.3

[a] Chemical shifts in parts per million downfield from internal tetramethylsilane. [b] Obtained from deuteriochloroform solution.

Scheme IX



Scheme X



Solvent		
THF	>99.9%	<0.1%
THF–HMPA	99.9	0.1

eliminated. The H/D ratio for **2** was 0.99 and that for **1** was 2.08.

Because kinetic control could not be attained, the acid-quenching experiments were abandoned. The results obtained, however, do imply that even in HMPA **3** reacts kinetically in a highly stereoselective manner (>96%).

The problem of equilibration can be circumvented by quenching **3** with an alkylating agent such as methyl iodide. There is in principle a drawback to this approach since methylation is probably not diffusion controlled. If a finite equilibrium of axial and equatorial carbanions exists for **3,** as shown in Scheme IV, a sluggish quenching reaction might not be expected to provide a reliable measure of the equilibrium constant (Curtin–Hammett principle[16]).

Fortunately, reaction of **3** in THF or THF–HMPA with methyl iodide gave over 99.9% of the equatorial substitution product **12.** Compound **13** could not be detected in the reaction in THF, and only 0.1% of **13** was found in the reaction in THF–HMPA (see Scheme X). This result means either that essentially only the equatorial carbanion is present to be alkylated, or, if both carbanions coexist or the carbanion is planar, equatorial approach is much more facile than axial approach in methylation. However, steric causes alone cannot account for exclusive equatorial alkylation, as shown by the sterically analogous case of *N*-alkylpiperidines where quaternization with methyl iodide leads mainly to axially methylated products.[17]

Configurational Assignments. Assignment of configuration for **1, 2, 6, 12,** and **13** is straightforward from ^{1}H NMR data from these compounds. Configurational diagnostics for anancomeric 4,6-dimethyl-1,3-dithianes are available from chemical shift differences for C(2) protons—equatorial protons resonate upfield from axial protons[1a,18]—and the characteristic long-range (J^5) coupling of the C(2) equatorial proton with the equatorial proton at C(5).[1a,19] Compound **1** exhibits a sharp downfield (δ 5.11) singlet for its C(2) hydrogen, and **2** shows a broad upfield (δ 5.00) singlet for the corresponding proton. Isomers **1** and **2** also differ noticeably in chemical shift in the aromatic region. Phenyl signals of **1** appear as a close multiplet centered at δ 7.5, whereas **2** shows two sets of aromatic multiplets centered at δ 7.4 and 8.0 with an integrated area ratio of 3:2, respectively. Kalff and Havinga[18b] have observed similar differences for the aromatic resonance of 2,2-diphenyl-1,3-dithiane at −90 °C, a temperature at which the conformer equilibrium is slow on the NMR time scale. The resonances observed farthest downfield were assigned to the ortho protons of the axial phenyl group, and the deshielding effect was ascribed to interaction with the lone pairs of electrons on sulfur for a conformation in which the plane of the phenyl ring is perpendicular to the bisecting plane of the dithiane ring. Langer and Lehner have reported analogous results.[20] A similar rotational preference has been observed for *r*-2-(*p*-trifluoromethylphenyl)-*t*-4,*t*-6-dimethyl-1,3-dioxane in the crystal.[21] Such an orientation of the phenyl ring is compatible with the observed shielding of the C(4,6) hydrogens (δ 2.83) in **2** as compared to the corresponding hydrogens (δ 2.94) in **1**. Isomer **1** is expected to adopt the conformation in which the phenyl-ring plane lies in the bisecting plane of the dithiane ring, similar to that found for *r*-2-(*p*-bromophenyl)-*c*-4,*c*-6-dimethyl-1,3-dioxane in the crystal.[21]

Isomers **12** and **13** both show two sets of aromatic resonances in their ^{1}H NMR spectra (cf. ref 18b) but are configurationally distinguishable by the chemical shifts of the C(4,6) hydrogens and the C(2) methyl hydrogens. The C(4,6) hydrogens of **12** resonate at much higher field (δ 2.63) than the corresponding hydrogens of **13** (δ 3.16), owing, presumably, to shielding by the axial aromatic ring in **12.** A chemical shift difference also exists for the C(2) methyl proton of **12** and **13** as expected. In general the protons of an axial methyl group in 2-methyl-1,3-dithianes resonate at lower field than those of an equatorial methyl,[18a] presumably due at least partly to steric compression. Thus the C(2) methyl proton signal for compound **13** (δ 2.18) is found substantially downfield from that in **12** (δ 1.68). The configurational assignment was confirmed by nuclear Overhauser effect (NOE) experiments. Irradiation of the C(2) methyl group in **13** produced an 8.2–9.2% enhancement in the (proximal) H(4,6)'s as well as a 24.8–24.9% enhancement in H(ortho) of the phenyl ring. By way of control, irradiation of C(2) methyl in **12** produced a 6.5% decrease in the H(4,6) signal and a 6.1% increase in H(ortho). Irradiation of H(ortho) in **13** produced no significant NOE; similar irradiation in **12** led to a 5.5% increase in H(4,6).

The configuration of **6** can be readily assigned from the chemical shift and splitting patterns of the protons at carbons, 4, 5, and 6, and from comparison of its ^{1}H NMR properties with those of the conformationally heterogeneous stereoisomer *trans*-2-phenyl-4-methyl-1,3-dithiane (**14**).

The above configurational assignments are in accord with the expected[1b] isomerizations **1** → **2** and **6** → **14** which were effected by the lithiation–protonation procedure, and the conversion of **1** or **2** to **12** via lithiation and subsequent methylation.

Conclusion

The NMR results presented above suggest the existence of two types of ion pairs for **3, 5,** and **7,** one in THF (or THF–TMEDA) and the other in solutions containing HMPA. These

two species appear to be contact and solvent-separated ion pairs, respectively. While the presence of free ions cannot be conclusively ruled out, their existence in dilute THF solutions containing only small amounts of HMPA seems quite unlikely.

Both kinds of ion pairs react with electrophiles in a highly stereoselective fashion, implying that intimate ion pairing and the previously suggested concomitant lithium–sulfur interactions are not required for the observed stereoselectivity. Rather, the preferred equatorial orientation of the lone pair in carbanions derived from 1,3-dithianes suggested by molecular orbital calculations[3] appears to be responsible for the high stereoselectivity observed upon electrophilic substitution.[29] To be sure, these calculations refer to simple dithiane carbanions, such as **11**, and not to the 2-phenyl analogues, such as **3** and **5**. But even if delocalization of unshared electrons into the phenyl ring makes **3** and **5** planar,[22] the deplanarization which must occur in the transition state for electrophilic substitution will be presumably attained more readily with bond formation on the equatorial rather than on the axial side. However, the fact that the barrier in **9** (16.4 kcal/mol) is higher than that in **7** (13.3 kcal/mol) in THF–3HMPA suggests the solvent separated ion to be still largely pyramidal, for in a planar ion (Scheme VI) it is difficult to see how the axial methyl group can enhance the barrier of **9** over that of **7**.

Experimental Section

High-vacuum manipulations of organolithium compounds were performed in a high-vacuum glass line equipped with a two-stage oil diffusion pump backed by a Precision Scientific Vac-Torr Model 150 two-stage oil pump, monitored with a GPH-320B Penning high-vacuum gauge. The high-vacuum line was equipped with a hypodermic needle outlet for use with septum-capped vessels. Operating pressures were $7–9 \times 10^{-6}$ Torr.

Tetrahydrofuran (THF) was predried by distillation from lithium aluminum hydride and distilled from sodium benzophenone ketyl[23a] or sodium anthracenide[23b] immediately before use. Hexamethylphosphoramide (HMPA) was freshly distilled from calcium hydride at reduced pressure under nitrogen. Tetramethylethylenediamine (TMEDA) was distilled from barium oxide or calcium hydride, degassed, and stored over barium oxide on the high vacuum line. Hexane was predried over calcium hydride and stored over sodium benzophenone ketyl on the high-vacuum line. Concentrations of *n*-butyllithium in hexane were monitored[24] periodically. Bench-top transfers of air-sensitive solutions and purified solvents were accomplished by syringe or double-ended needle techniques.[25]

1,3-Butanedithiol. The previous procedure[18a] was modified as follows. 1,3-Dibromobutane (100 g, 0.456 mol) was added slowly to a stirred solution of 71 g (0.93 mol) of thiourea in 40 mL of water heated on a steam bath under nitrogen. The mixture was stirred with heating until homogeneous (ca. 3 h), cooled in ice water, treated dropwise with 60 g (1.0 mol) of ethylenediamine, and heated on a steam bath for 1 h. It was then cooled to room temperature, poured into 500 mL of degassed water, extracted with three 100-mL portions of ether, and worked up in standard fashion to give 44 g (80%) of 1,3-butanedithiol as a light tan liquid, bp 60 °C (9 Torr) (lit.[18a] bp 64–67 °C (10 Torr)).

2-Phenyl-1,3-dithiane (4)[26] melted at 71–73 °C (lit.[26] mp 69.0–69.8 °C) and was sublimed before use.

***cis*-2-Phenyl-4-methyl-1,3-dithiane (6).** The general procedure of Seebach et al.[26] was followed to condense 1,3-butanedithiol and benzaldehyde, providing **6** in 59% yield as colorless microneedles, mp 54–60 °C. Two recrystallizations from methanol and sublimation afforded the analytical sample: mp 56.5–58 °C; IR (KBr) 1007 (m), 1121 (m), 1250 (s), 1286 (m), 1410 (s), 1440 (s), 1475 (m), 2813 (m), 2888 (s), 2925 (s), 2961 cm^{-1} (s); NMR ($CDCl_3$) δ 1.20 (d, $J = 7$ Hz, 3 H), 1.30–1.77 (A part of AB, m, 1 H), 2.01, 2.16 (B part of AB, apparent d of q, $J_{gem} = -15$, $J_{vic} = 3$ Hz, 1 H), 5.16 (s, 1 H), 7.20–7.59 (m, 5 H). Anal. Calcd for $C_{11}H_{14}S_2$: C, 62.81; H, 6.71. Found: C, 62.86; H, 6.96.

***trans*-2-Phenyl-4-methyl-1,3-dithiane.** A solution of 210 mg (1.00 mmol) of **6** in 5 mL of THF was cooled to −25 °C and 0.60 mL (1.3 mmol) of 2.2 M *n*-butyllithium in hexane was added with stirring under nitrogen. The yellow solution was stirred at −25 °C for 0.5 h and 0.5 mL of water was added. The mixture was poured into 25 mL of water and extracted with 30 mL of hexane. The extract was dried over magnesium sulfate, and solvent was evaporated at reduced pressure to leave 205 mg (98%) of a clear, colorless liquid which soon crystallized. Two recrystallizations from methanol provided **6** as colorless needles: mp 57–58 °C; NMR ($CDCl_3$) δ 1.47 (d, $J = 7$ Hz, 3 H), 1.53–3.35 (m, 5 H), 5.23 (s, 1 H), 7.10–7.70 (m, 5 H). Anal. Calcd for $C_{11}H_{14}S_2$: C, 62.81; H, 6.71. Found: C, 63.02; H, 6.98.

***r*-2-Phenyl-*c*-4,*c*-6-dimethyl-1,3-dithiane (1).** The general procedure[27] employing formic acid was used to condense *meso*-2,4-pentanedithiol[28] and benzaldehyde, affording a 9:1 mixture of **1** and **2** as a yellow oil which crystallized upon cooling. Recrystallization from ethanol gave **1** in 70% yield as large, colorless prisms, mp 65–72 °C. A further recrystallization from ethanol and subsequent sublimation afforded pure **2**: mp 73–75 °C; IR (CCl_4) 1030 (s), 1075 (m), 1155 (s), 1185 (s), 1230 (m), 1250 (m), 1300 (m), 1320 (m), 1420 (m), 1450 (s), 1490 (m), 1595 (m), 2820 (m), 2880 (s), 2920 (s), 2960 (s), 3025 (m), 3060 (m), 3080 cm^{-1} (m); NMR (CCl_4) δ 1.23 (d, $J = 7$ Hz, 6 H), 1.45 (part of A portion of AB), 1.95, 2.18 (B part of AB, $J_{gem} = -14$, $J_{vic} = 2.5$ Hz, 1 H), 2.60–3.23 (m, 2 H), 5.11 (s, 1 H), 7.25–7.71 (m, 5 H). Anal. Calcd for $C_{12}H_{16}S_2$: C, 64.27; H, 7.19. Found: C, 64.19; H, 7.05.

***r*-2-Phenyl-*t*-4,*t*-6-dimethyl-1,3-dithiane (2).** A solution of 112 mg (0.5 mmol) of **1** in 15 mL of THF was cooled to −25 °C and 0.35 mL (0.77 mmol) of 2.2 M *n*-butyllithium in hexane was added. The pale yellow solution was stirred at −25 °C for 1.5 h and transferred dropwise with a double-ended needle under nitrogen pressure to a vigorously stirred solution of 1 mL of concentrated hydrochloric acid, 5 mL of water, and 15 mL of THF. The solution was poured into 25 mL of water and extracted with 50 mL of hexane. The extract was washed with 25 mL of 5% sodium hydroxide and 25 mL of water, and dried over magnesium sulfate. Removal of solvent at reduced pressure left 101 mg (90%) of a clear, colorless oil. GLC analysis on a 20-ft aluminum column (i.d. $\frac{1}{8}$ in.) of 25% QF-1 on 80/100 mesh Chromosorb W (column A) at 150 °C revealed a ratio of 99:1 of **2:1**. In other experiments this ratio varied from 97:3 to 99.5:0.5. In one case a portion of the reaction mixture was quenched with methyl iodide and the remainder with HCl. The methylated mixture showed <0.1% of **1** while the HCl-quenched portion gave 1% of **1**. These results suggest that **1** results from partial equilibration of **2** (see analogous experiments with HMPA as solvent) and not from residual starting **1**.

A similar preparation as described above with recrystallization from methanol provided the analytical sample of **2**: mp 43–45 °C; IR (CCl_4) 700 (s), 1035 (s), 1160 (s), 1255 (s), 1330 (m), 1380 (s), 1425 (m), 1450 (s), 1490 (s), 1590 (m), 2820 (m), 2880 (s), 2925 (s), 2965 (s), 3020 (m), 3060 cm^{-1} (s); NMR (CCl_4) δ 1.20 (d, $J = 7$ Hz, 6 H), 1.45, 1.67 (part of A portion of AB), 1.87, 2.10 (B part of AB, $J_{gem} = -14$, $J_{vic} = 3$ Hz, 1 H), 2.50–3.17 (m, 2 H), 5.00 (broad s, 1 H), 7.20–7.61 (m, 3 H), 7.80–8.10 (m, 2 H). Anal. Calcd for $C_{12}H_{16}S_2$: C, 64.27; H, 7.19. Found: C, 64.19; H, 7.05.

2-Phenyl-*r*-2,*t*-4,*t*-6-trimethyl-1,3-dithiane (13). The formic acid procedure[27] was used to condense acetophenone and *meso*-2,4-pentanedithiol over a period of 15 min to afford a 70% yield of a 9:1 mixture of **13** and **12**, as indicated by GLC analysis on column A at 160 °C. Three recrystallizations from hexane provided **13** as colorless needles: mp 81–83 °C; IR (CCl_4) 1030 (s), 1040 (m), 1065 (s), 1155 (m), 1250 (s), 1325 (m), 1380 (s), 1420 (m), 1450 (s), 1455 (s), 1485 (m), 1495 (m), 1595 (m), 2820 (m), 2880 (s), 2930 (s), 2970 (s), 3060 cm^{-1} (m); NMR (CCl_4) δ 1.23 (d, $J = 7$ Hz, 6 H), 1.55 (part of A portion of AB), 2.01, 2.25 (B part of AB, $J_{gem} = -14$, $J_{vic} = 3$ Hz, 1 H), 2.18 (s, 3 H), 2.83–3.50 (m, 2 H), 7.25–7.56 (m, 3 H), 7.70–8.00 (m, 2 H). Anal. Calcd for $C_{13}H_{18}S_2$: C, 65.53; H, 7.61. Found: C, 65.53; H, 7.66.

On other occasions, where reaction times were prolonged beyond 15 min, larger proportions of **12** (e.g., **13:12** = 1:2 after 24 h) were obtained. This is clearly a matter of partial thermodynamic control; equilibration of either **12** or **13** with trifluoroacetic acid leads to a 1:4.5 ratio of **13:12**.

A 5% solution of **13** in $CDCl_3$ was carefully degassed and sealed under vacuum for the NOE experiments. Irradiation of the 2-methyl singlet (δ 2.18) produced an 8.2–9.2% area enhancement of the multiplet at δ 3.16 (4,6-H), an increase of 24.8–24.9% in the area of the

multiplet corresponding to the phenyl ortho protons (δ 7.85), and a 2.2–4.4% increase in the area of the meta and para proton resonances (δ 7.40). Irradiation at δ 7.85 had no effect on the 2-methyl signal and caused only a 1.3% increase of the 4,6-H signal area. In both cases the area of the signals centered at δ 1.23 (4,6-methyls and one of H-5 protons) was taken as the standard.

2-Phenyl-*r*-2,*c*-4,*c*-6-trimethyl-1,3-dithiane (12). A solution of 56 mg (0.25 mmol) of **1** in 5 mL of THF was treated with 0.12 mL (0.26 mmol) of 2.2 M *n*-butyllithium in hexane with stirring at −25 °C. The pale yellow solution was stirred at −25 °C for 1 h, and 0.1 mL of methyl iodide was added. The solution was poured into 25 mL of water and extracted with 50 mL of hexane. The extract was dried over magnesium sulfate. Removal of solvent at reduced pressure left 55 mg (92%) of a pale yellow solid. GLC analysis on a 6-ft stainless steel column (i.d. 1/8 in.) of 10% UCW98 on 80/100 mesh Chromosorb W (column B) at 185 °C showed one major product, that corresponding to **12**. None of **13** or **1** could be detected. A similar preparation with recrystallization of the product from hexane and subsequent sublimation provided analytically pure **12**: mp 122.5–124.5 °C; IR (CCl_4) 1035 (s), 1070 (m), 1150 (m), 1185 (m), 1255 (m), 1370 (m), 1380 (m), 1420 (m), 1445 (s), 1455 (m), 1490 (s), 1590 (m), 2820 (m), 2880 (s), 2925 (s), 2970 (s), 3060 cm^{-1} (m); NMR (CCl_4) δ 1.20 (d, J = 7 Hz, 6 H), 1.53 (part of A portion of AB), 1.68 (s, 3 H), 1.80, 2.01 (B part of AB, J_{gem} = −14, J_{vic} = 3 Hz, 1 H), 2.30–3.00 (m, 2 H), 7.16–7.60 (m, 3 H), 7.88–8.23 (m, 2 H). Anal. Calcd for $C_{13}H_{18}S_2$: C, 65.53; H, 7.61. Found: C, 65.70; H, 7.48.

A 5% solution of **12** in $CDCl_3$ was carefully degassed and sealed under vacuum for the NOE experiments. Irradiation at δ 1.68 (2-methyl) caused a 6.1% signal enhancement of the phenyl ortho proton resonance (δ 8.06) and a 6.5% decrease in area for signals of 4,6-H (δ 2.65), based on the area of signals for H(meta) and H(para). Irradiation at δ 8.06 resulted in a 5.5% enhancement of the 4,6-H multiplet and a 3.4% decrease in area for the 2-methyl resonance. The signals centered at δ 1.20 (4,6-methyls and one of 5-H) served as standards for area measurements in the latter experiment.

Methylation of 3 in HMPA. A solution of 56 mg (0.25 mmol) of **1** in 5 mL of THF was cooled to −25 °C and 0.12 mL (0.26 mmol) of 2.2 M *n*-butyllithium in hexane was added. The pale yellow solution was stirred at −25 °C for 0.25 h and 0.20 mL (1.1 mmol) of HMPA was added. The solution was stirred at −25 °C for 1 h, quenched with 0.1 mL of methyl iodide, poured into 25 mL of water, and extracted with 50 mL of pentane. The extract was washed with three 25-mL portions of water and dried over magnesium sulfate. Concentration at reduced pressure left 52 mg (88%) of a pale yellow solid. GLC analysis on column B at 185 °C showed a ratio of 99.9:0.1 ± 0.1 for **12:13**. This ratio was verified with known mixtures of **12** and **13**. Coinjection experiments supported assignment of the minor peak to **13**. Reaction mixtures containing larger amounts of HMPA give similar results. For example, when the same procedure was applied to 2 mmol of **1** in 25 ml of 2:1 THF–HMPA, none of **13** could be detected.

Quenching of 3 in HMPA with 1:1 HCl–DCl. A solution of 2.24 g (10.0 mmol) of **1** in 300 mL of THF was treated with 4.4 mL (10.1 mmol) of 2.3 M *n*-butyllithium in hexane with stirring under nitrogen at −25 °C. The yellow solution was stirred at −25 °C for 0.2 h, 5.25 mL (30.0 mmol) of HMPA was added, and stirring was continued at −25 °C for 1.5 h. Approximately 30 mL of the solution was quenched by inverse addition to deuterium oxide under nitrogen. The remainder of the solution was transferred dropwise with a double-ended needle to a vigorously stirred solution of 1:1 HCl–DCl (prepared by addition of 10 mL of freshly distilled acetyl chloride to 20 mL of 1:1 H_2O–D_2O). The D_2O-quenched solution was poured into 25 mL of 5% hydrochloric acid and extracted with three 35-mL portions of pentane. The combined extracts were washed with three 30-mL portions of water and dried over magnesium sulfate. Removal of solvent at reduced pressure left 230 mg of a colorless, crystalline solid. GLC analysis on column A at 150 °C showed a 96:4 ratio of **2:1**. Low-voltage mass spectral analysis showed 100% deuterium incorporation.

The HCl–DCl-quenched solution was washed with two 50-mL portions of 5% sodium bicarbonate. The combined washings were extracted with 100 mL of pentane, and the extracts were concentrated at reduced pressure, poured into 100 mL of water, and extracted with three 100-mL portions of pentane. The combined pentane solution was washed with three 50-mL portions of water, dried over magnesium sulfate, and concentrated to yield 1.97 g of a colorless, crystalline solid. GLC on column A at 150 °C showed a ratio of 96:4 for **2:1**. Two recrystallizations from methanol gave 815 mg of pure **2** as colorless needles, mp 42–43 °C. Low-voltage mass spectral analysis indicated 50.2% deuterium incorporation. The minor isomer **1** was isolated from the mother liquor by preparative GLC on a 20-ft aluminum column (i.d. 3/8 in.) of 25% QF-1 on 60/80 mesh Chromosorb W at 180 °C, and recrystallization from methanol gave **1** as colorless needles, contaminated (7%) with **2**. Low-voltage mass spectral analysis showed 32.5% deuterium incorporation.

Titration of 5 (2 M in THF) with HMPA. (Figure 2a). A dry 10-mm NMR tube containing 784 mg (4.00 mmol) of **4** and capped with two rubber septa was attached to the high-vacuum line, and ca. 2 mL of THF was distilled in. The tube was filled with nitrogen and removed from the vacuum line. The solution was cooled to −20 °C under nitrogen and 2.5 mL (4.0 mmol) of 1.6 M *n*-butyllithium in hexane was added with a syringe. The yellow solution was kept at −20 °C for 0.5 h, frozen with liquid nitrogen, and attached to the high-vacuum line. Two degassing cycles were performed and the solvent was smoothly distilled. The residual off-white solid was taken up in 2.0 mL of THF, and the tube was filled with nitrogen and removed from the vacuum line. Tetramethylsilane was distilled from calcium hydride under N_2 into the tube through a double-ended needle, and the tube was capped with a third septum. HMPA was added in 160-μL portions, and ^1H NMR spectra were recorded at 0 °C after each addition.

Titration of 5–TMEDA Complex (2 M in THF) with HMPA (Figures 2b,c). Solid **5** (4.00 mmol) was prepared in a 10-mm NMR tube as described in the previous procedure. This off-white solid was taken up in a solution of 0.75 mL (5.0 mmol) of TMEDA and 1.0 mL of THF. HMPA was added in 160-μL portions, and ^1H NMR spectra were recorded at 8 °C after each addition. The THF resonances, which remained unchanged with respect to Me_4Si in the previous titration, were taken as internal references.

Titration of 5 (0.03 M in THF) with HMPA (Figure 2d). A solution of 163 mg (0.833 mmol) of **4** in slightly less than 25 mL of THF contained in a dry, septum-capped 25-mL volumetric flask under nitrogen was treated with 0.37 mL (0.85 mmol) of 2.3 M *n*-butyllithium in hexane with stirring at −25 °C. A 2.0-mL portion was transferred with a double-ended needle to a dry, nitrogen-flushed septum-capped 10-mm NMR tube containing a sealed 5-mm NMR tube filled with deuterium oxide for a lock signal. HMPA was added in 10-μL portions, and ^1H NMR spectra were recorded at 8 °C after each addition. The THF resonances were used as internal references.

Measurement of TMEDA:5 Ratio in the Crystalline Complex. A solution of 196 mg (1.00 mmol) of **4** in 1 mL of THF, 3 mL of hexanes, and 0.30 mL (2.1 mmol) of TMEDA was cooled to −25 °C and 0.50 mL (1.0 mmol) of 2.0 M *n*-butyllithium in hexane was added. The yellow solution was kept at −25 °C for 0.25 h. Cooling the solution to −50 °C induced crystallization and the mother liquor was removed through a double-ended needle. The colorless crystals were washed with hexane, taken up in 1 mL of THF, and transferred to a dry, nitrogen-flushed, septum-capped NMR tube. Integration of the ^1H NMR spectrum showed a ratio of 1.26:1 for TMEDA:**5**.

2-Potassio-2-phenyl-1,3-dithiane (10). A solution of 196 mg (1.00 mmol) of **4** in 3 mL of THF was added to 3.9 mmol (470 mg of a 35% suspension which was washed with THF) of potassium hydride under nitrogen, and the mixture was stirred at room temperature for 5 h. The potassium hydride was allowed to settle, and the yellow supernatant liquid was transferred to a dry, nitrogen-flushed, septum-capped NMR tube. Similar procedures with much shorter reaction times (<1 h) were employed for preparing solutions of **10** in HMPA or in THF with 18-crown-6.

Preparation of Other 2-Lithiodithiane NMR Samples. Procedures similar to those described above were used for preparing all other NMR samples described in the text.

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Electron Paramagnetic Resonance Study of Inversion Barriers and Conformations in Substituted Cyclopentyl Radicals

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Abstract: The cyclopentyl (I), methylcyclopentyl (II), fluoromethylcyclopentyl (III), chloromethylcyclopentyl (IV), and isocyanatocyclopentyl (V) radicals have been prepared by x-irradiation of the substituted cyclopentane in adamantane. By computer analysis of the temperature dependences of the line widths in their EPR spectra, the activation energies for interchange of the ring β protons were obtained and conclusions were drawn about the lowest energy geometry and the mode of inversion for each radical. The activation energies are (kcal/mol): radical I, 1.3; II, 3.2; III, 2.4; IV, 5.3; V, 1.9.

I. Introduction

There has been a long-standing interest in the study of dynamic processes in alicyclic molecules and a vast literature has developed concerning the application of NMR techniques to the determination of conformations and inversion barriers in such systems.[2] The use of EPR for similar investigations in cyclic radicals is much less common, however, even though the same information can be learned about their structures and conformational preferences. Much of the present knowledge is based on the results of organic reaction studies, which do not directly probe radical intermediates.[3a] EPR has been mostly used to examine six-membered rings, such as the cyclohexyl radical for which an activation energy for chair-to-chair inversion has been obtained by the analysis of the temperature dependence of line widths.[3b,4,5]

The dynamics of five-membered rings are considerably more complicated than for six-membered rings because the ring atoms are in general not equivalent and there are more than two different positions that a substituent may occupy. There is in addition the possible existence of pseudorotation as the lowest energy inversion process in any five-membered ring. Thus it is not surprising that only a few such radicals have been studied by EPR. In general, four magnetically equivalent ring β protons are observed in the solution spectra of α-substituted cyclopentyl radicals,[6] implying either that they are inverting rapidly between equivalent nonplanar forms or that they are planar.

One prominent exception is the cyclopentyl radical itself. Line width alternation was some time ago observed in the solution spectrum of this radical, presumably the result of ring