

HIGHLY STEREOSELECTIVE ADDITIONS OF CERTAIN
2-LITHIO-1,3-DITHIANES TO CYCLOHEXANONES. SOLVENT EFFECTS

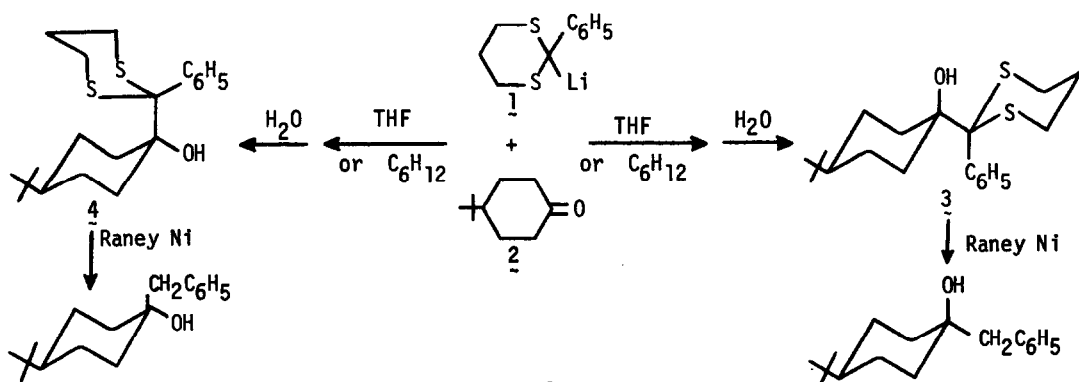
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In a series of important papers^{1,2} Nguyen Trong Anh and collaborators have discussed the importance of charge control *vs.* orbital control³ in reaction of nucleophiles with ambident⁴ substrates. Hard nucleophiles⁵ react in charge-controlled fashion whereas orbital control tends to prevail for soft nucleophiles.⁵ Thus the observation^{6,7} that hard bases attack anancomeric⁸ cyclohexanones predominantly from the axial side (unless steric effects are overwhelming) whereas soft bases lead to preferential equatorial attack has been explained by reasoning⁹ that charge control should be operative mainly in axial approach whereas equatorial approach should be orbital-controlled.

In previous work¹⁰ we had obtained spectral evidence that 2-phenyl-2-lithio-1,3-dithiane (**1**, Scheme 1) exists as a tight ion pair in tetrahydrofuran (THF) or cyclohexane (C₆H₁₂) but as a solvent-separated, delocalized ion pair in hexamethylphosphoric triamide (HMPTA). On the reasonable assumption that the delocalized species should be the softer base and therefore yield more equatorial attack,^{6b} we proceeded to study its reaction with the anancomeric 4-*t*-butylcyclohexanone (**2**). The results are presented here and compared with results involving the parent 2-lithio-1,3-dithiane for which previous work¹⁰ had suggested that it was probably a tight ion pair in all



Scheme 1

solvents studied. As it turns out, our findings provide little evidence in favor of or against the theoretical prediction, because other events (thermodynamic vs. kinetic control, enolate formation) determine the reaction course.

The outcome of the reaction of **1** with **2** as initially observed is summarized in Table 1.

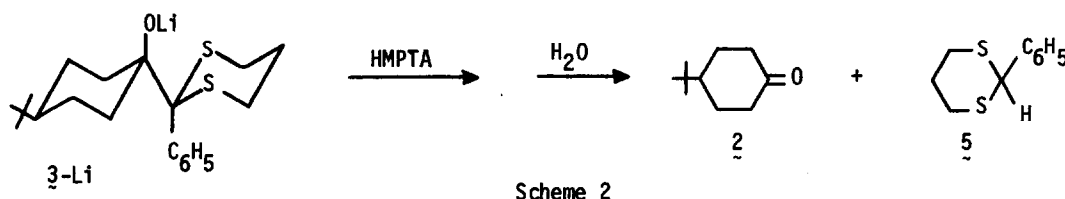
Table 1. Reaction of 4-*t*-Butylcyclohexanone with 2-Phenyl-2-lithio-1,3-dithiane.

Solvent	Yield, %	3:4
C ₆ H ₁₂ ^a	90	82:18
THF ^b	75	100:0
HMPA ^c	0	-

^a2 hr at 25°C. ^b2 hr at -20°C plus 15 hr at 25°C. ^c1.5 hr at 0°C plus 15 hr at 25°C.

Analysis of the product mixture was effected by a combination of proton and ¹³C NMR. Configuration was ascertained by hydrogenolysis of the products to the known^{11,12} 1-benzyl-4-*t*-butylcyclohexanols (Scheme 1) whose proportion, determined by gas chromatography, also provided a check on the original product composition.

The reaction in THF is totally stereoselective, contrary to that in C₆H₁₂. No reaction occurs in HMPA. Our suspicion that, in the latter solvent, the reaction proceeds in the reverse direction was confirmed when we converted the equatorial adduct (axial alcohol) **3** to its lithio derivative in HMPA. Upon quenching, starting materials **2** and **5** were recovered (Scheme 2).



This finding suggested that addition in the other two solvents was also reversible but with the equilibrium largely on the side of the adducts. This hypothesis was confirmed when the product composition in the addition of **1** to **2** in THF and C₆H₁₂ was followed as a function of time (Table 2). The thermodynamically controlled product **3** accumulates more rapidly in the more polar solvent THF.^{13,14}

Table 2. Products of Reaction of **1** with **2** as a Function of Reaction Time.

Solvent	THF	THF	THF	C ₆ H ₁₂	C ₆ H ₁₂	C ₆ H ₁₂	C ₆ H ₁₂
Time, hr	"zero" ^a	1.5 ^a	4 ^b	"zero" ^c	2 ^c	20 ^c	48 ^c
Product Ratio, 3 : 4	79:21	86:14	100:0	76:24	82:18	95:5	98.2:1.8

^aAt -20°C. ^b1.5 hr at -20°C plus 2.5 hr at 25°C. ^cAt 25°C.

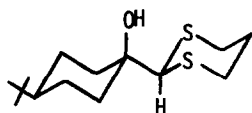
Little if any stereoselectivity was found in any of the solvents studied when the parent compound, 2-lithio-1,3-dithiane (**6**) (cf. Scheme 3) was allowed to react with **2**, nor was there any change of composition with time (Table 3).

Table 3. Products of Reaction of **2** with **6** in Various Solvents.

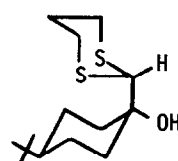
Solvent	C ₆ H ₁₂	THF	TMEDA ^a	THF/2 TMEDA	THF/2 HMPTA	HMPTA
Yield, %	71	99	8	38	26	0
7 : 8 ^b	49:51	40:60	58:42	37:63	61:39	-

^aTetramethylethylene diamine.

^b**7** =

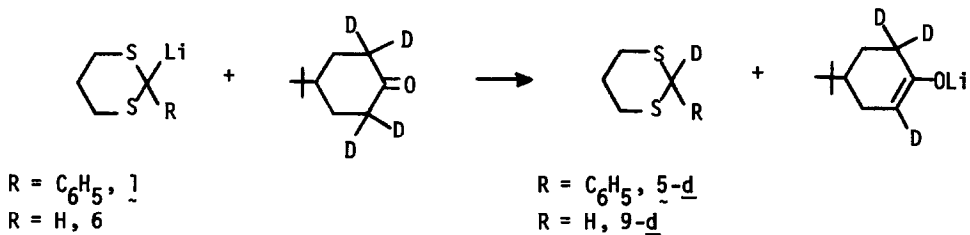


8 =



Product composition in Table 3 was determined by gas chromatography and ¹H NMR, and configuration of epimers was assigned by Raney-Ni hydrogenolysis to the known^{12,15} 1-methyl-4-*t*-butylcyclohexanols. In view of the sometimes low yields, the (minor) product variations may not be significant, but it is significant that the reaction with **6**, like that with **1**, fails to give adduct in HMPTA but that, unlike that with **1**, it is irreversible. The latter point was confirmed by converting a mixture of **7** and **8** to its lithio derivative in HMPTA: upon quenching, the unchanged mixture was recovered.

We were interested to determine what happens in HMPTA. When **2** is treated with **1** in HMPTA and the mixture is quenched in D₂O, the products are **5** (cf. Scheme 2), rather than **5-d**, and **2-d** (95.2% **d**₁ by mass spectrometry). Similarly, **6** and **2** in HMPTA yielded 1,3-dithiane (**9**), rather than **9-d**, after quenching in D₂O. The logical conclusion is that **1** and **6** react with **2** in HMPTA not by addition but by enolate formation. This hypothesis was confirmed as shown in Scheme 3.



(Analysis after quenching with CH₃CO₂H)

Scheme 3

The following two interesting conclusions emerge: 1) The reaction of **1** with **2** at room temperature in THF is thermodynamically controlled. Equilibrium lies entirely on the side of the lithio derivative of **3**; thus **3** can be synthesized in a totally stereoselective reaction. (High stereoselectivity of nucleophilic attack on cyclohexanones is normally found only with very bulky reagents.¹⁶) 2) In HMPTA, addition to **2** is supplanted by enolate formation. Since, in the addition of **1** to **2**, thermodynamic control obtains, the enolate is evidently more stable than the

adduct in HMPTA but not in THF or C_6H_{12} . In the case of **6**, since addition is irreversible, exclusive formation of the enolate in HMPTA must indicate that the transition state to enolate formation is of substantially lower energy than that to addition; thus the energies of the transition states reflect those of the products.

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References and Footnotes

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14. In an even more closely parallel situation, **1** adds (reversibly) to cyclohexenones largely 1,2 in hexane-THF mixtures at $-78^\circ C$ whereas in pure THF substantial amounts of 1,4 adduct are formed (irreversibly) even at $-78^\circ C$; at room temperature, only the thermodynamically controlled 1,4-addition product is found: V. V. Kane, Ortho Pharmaceutical Co., personal communication.
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