On the Origin of the Stereoselectivity of Hydrazone Alkylations. Investigation of Aggregation Effects and Solution Kinetics

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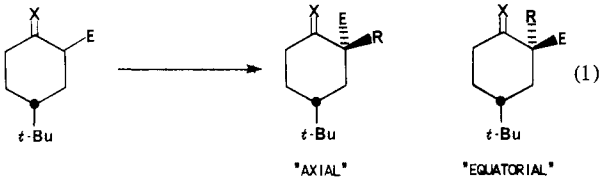
Abstract: Studies to elucidate the origin of the stereoselectivities of lithiated hydrazone alkylations are described. Failure to effect stereochemical changes through attempts to change anion aggregate structures casts doubt on mechanisms involving direct alkylation of aggregates. Solution alkylation kinetics support a mechanism involving a preequilibrium of organolithium trimers or tetramers with bis-solvated monomers, followed by rate-determining monomer alkylation. A working model to explain the observed alkylation stereoselectivities is proposed. Data contrasting the stereoselectivity of the alkylation and the corresponding aldol condensation of lithiated cyclohexanone dimethylhydrazones are provided in light of the proposed model.

Alkylations of conformationally anchored cyclohexanone enolates (eq 1: X = O; E = H, CN, CO_2Me, Me) exhibit modest selectivities for axial entry of the electrophile.[1] In contrast, the corresponding Schiff's base derivatives (including hydrazones, oximes, oximino ethers, and simple imines) exhibit axial alkylation preferences often exceeding 98%.[2,3] Although axial selectivity



(1)

is maintained when the carbanionic carbon is substituted with cyano or methylthio moieties (**1**; E = CN, SMe), alkylation of the corresponding ester derivative (**1**; E = COOMe) exhibits low selectivity more characteristic of ketone enolate alkylations.[2b,4]

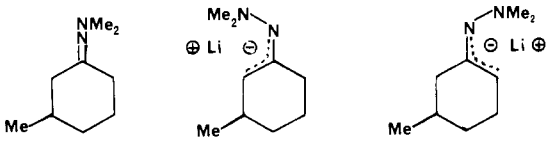
We recently reported that the solid-state structure of lithiated cyclohexanone *N,N*-dimethylhydrazone (**2**) was a solvent-free polymer (Figure 1).[4] Although the structure of **2** hinted at some interesting explanations for the observed alkylation selectivities, solution molecular weight determination implicated tetramers as the predominant species in THF at 25 °C. The relationships between the solid-state and solution structures of hydrazone anions, and the structures of the actual species being alkylated, were left ill-defined.

Described herein are studies to elucidate the origins of the observed alkylation stereoselectivities. We conclude that the dramatic hydrazone alkylation stereoselectivities do *not* derive from aggregation effects but possibly from modest steric and stereoelectronic effects working in concert.

Results

Combining the solid-state structural information on **2** with the solution molecular weight data, solvent-free cyclic tetramers appeared to be plausible solution structures (Figure 2). Direct alkylation of such species could explain a number of curious observations including the dramatic alkylation face selectivities and the relative insensitivity of the stereoselectivities to solvent effects.

We investigated the alkylation of 3-methylcyclohexanone *N,N*-dimethylhydrazone (**3**). *If aggregates were the actual species being alkylated, we surmised that the alkylation stereoselectivity could be altered through changes in the aggregate structures.* The



3 i ii

following experiments were designed to effect aggregate structural changes. (1) Solutions of anions derived from (±)-**3** were generated at different temperatures, cooled to −78 °C, and alkylated with methyl iodide under identical conditions. If the aggregates in solution were formed *kinetically*, one might expect to obtain different aggregation stereoselectivities. (2) Solutions of anions derived from (±)-**3** were generated at room temperature and cooled to the alkylation temperature (−78 °C) at differing rates. If equilibration of aggregate structures was rapid at ambient temperatures but slow at the low reaction temperatures, then varying degrees of equilibration would generate variations in the distribution of aggregates. (3) Solutions of anions derived from (±)-**3** were generated in the presence of excesses (3.5 equiv) of other hydrazones in order to generate hybrid aggregates. (4) By using different lithium amide bases, we varied the ratio of regioisomeric anions i and ii between 2:1 and 9:1 and (presumably), in turn, the aggregate distribution. (5) The anion derived from optically active (+)-**3** was generated and alkylated analogously. Although the anions derived from racemic (±)-**3** could alkylate from heterochiral aggregates, the anions derived from (+)-**3** must be homochiral or have diastereomeric subunits.[5]

(1) (a) Huff, B. J. L.; Tuller, F. N.; Caine, D. *J. Org. Chem.* **1969**, *34*, 3070. (b) House, H. O.; Umen, M. J. *J. Org. Chem.* **1973**, *38*, 1000. (c) Howe, R.; McQuillin, F. J. *J. Chem. Soc.* **1958**, 1194. (d) Kuwajima, I.; Nakamura, E. *J. Am. Chem. Soc.* **1975**, *97*, 3257. (e) Djerassi, C.; Osiecki, J.; Eisenbraun, E. J. *J. Am. Chem. Soc.* **1961**, *83*, 4433. (f) House, H. O.; Tefertiller, B. A.; Olmstead, H. D. *J. Org. Chem.* **1968**, *33*, 935. (g) Kuehne, M. E. *J. Org. Chem.* **1970**, *35*, 171. (h) Kuwajima, I.; Nakamura, E.; Shimizu, M. *J. Am. Chem. Soc.* **1982**, *104*, 1025.

(2) (a) Corey, E. J.; Enders, D. *Chem. Ber.* **1978**, *111*, 1337. (b) Corey, E. J.; Knapp, S. *Tetrahedron Lett.* **1976**, 4687. (c) Fraser, R. R.; Banville, J.; Dhawan, K. L. *J. Am. Chem. Soc.* **1978**, *100*, 7999. (d) Fraser, R. R.; Dhawan, K. L.; Taymaz, K. *Org. Magn. Reson.* **1978**, *11*, 269. (e) Fraser, R. R.; Dhawan, K. L. *J. Chem. Soc., Chem. Commun.* **1976**, 674. (f) Lyle, R. E.; Saavedra, J. E.; Lyle, G. G. Fribush, H. M. Marshall, J. L.; Lijinski, W.; Singer *Tetrahedron Lett.* **1976**, 4431.

(3) Reviews of the chemistry of metalated Schiff's bases: Hickmott, P. W. *Tetrahedron* **1982**, *38*, 1975. Enders, D. in "Current Trends in Organic Synthesis"; Nozaki, H., Ed.; Pergamon Press: New York, 1983. Whitesell, J. K.; Whitesell, M. A. *Synthesis* **1983**, 517. Fraser, R. R. In "Comprehensive Carbanion Chemistry"; Elsevier: New York, 1980.

(4) Collum, D. B.; Kahne, D.; Gut, S. A.; DePue, R. T.; Mohamadi, F.; Wanat, R. A.; Clardy, J.; Van Duyne, G. *J. Am. Chem. Soc.* **1984**, *106*, 4865.

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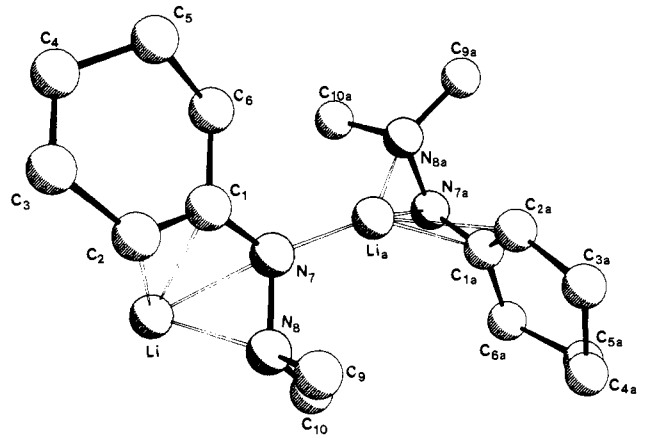
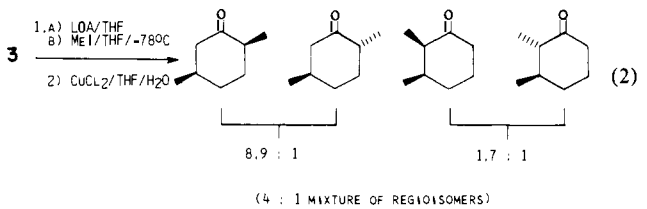


Figure 1. Molecular structure of the asymmetric unit of lithiated cyclohexanone dimethylhydrazone polymer **2** (ref 4).

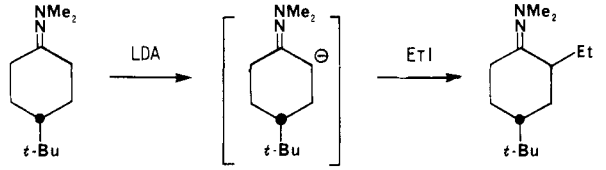
The results from alkylation of **3** are illustrated in eq 2. One significant observation made was that the major stereoisomeric 2,3-dimethylcyclohexanone hydrazone was the cis isomer; the corresponding alkylations of the 3-substituted ketone enolate provide the trans isomers as the major products.[6] However, all



(2)

the experiments designed to produce detectable changes in the alkylation diastereoselectivity failed. We *tentatively* concluded, therefore, that any model dependent on aggregation effects to explain hydrazone alkylation stereoselectivities was invalid. Additional support for this conclusion was obtained from the alkylation kinetics described below.[7]

Kinetics. We investigated the kinetics of the alkylation of 4-*tert*-butylcyclohexanone dimethylhydrazone (**4**) with ethyl iodide (EtI). Convenient anion solubility properties were obtained by generating the anion of **4** (referred to as **4**-Li) with lithium diisopropyl amide as a 0.01 M solution in 30:70 hexane/benzene. In order to minimize temperature fluctuations during quenching, the alkylations were run at ice bath temperature (0 ± 0.2 °C).



The reaction proved to be high order in ethereal donor solvent (vide infra) and the generated lithium iodide appeared to scavenge the donor solvents.[8] Therefore, the reactions defined as pseudo first order in ethereal solvent contained ≥30 mol equiv. The most convenient reaction rates were obtained by using 2-methyltetrahydrofuran (MeTHF) as the donor solvent and large molar excesses of ethyl iodide (pseudo first order). The alkylations were monitored by quenching aliquots of the reactions with ethanol and following loss of starting hydrazone relative to a tetradecane internal standard by gas chromatography.[9]

Dependence of Alkylation Rate on Hydrazone Anion Concentration. A plot of ln ([**4**-Li]/[**4**-Li]$_o$) vs. time exhibited a negative curvature characteristic of a fractional order dependence on anion concentration (Figure 3). The reaction was calculated to be 0.30 ± 0.04 order in anion up to three half-lives.[10,11]

Dependence of Alkylation Rate on Electrophile Concentration. A plot of ln k_{obsd} vs. ln [EtI] (Figure 4) illustrates the dependence of the pseudo-first-order rate constants on the ethyl iodide concentration over a 6-fold range. The reaction was found to be approximately first order in ethyl iodide (1.14 ± 0.03 order).[11]

Dependence of Alkylation Rate on 2-Methyltetrahydrofuran Concentration. The alkylation was monitored as a function of the concentration of MeTHF. From a plot of the ln k_{obsd} vs. ln [MeTHF], the reaction was found to be 2.14 ± 0.05 order in MeTHF (Figure 5).[11] The high order in MeTHF did not appear to arise from changes in the dielectric constant of the medium. The following approximate relative rates (k_{rel}) were obtained: MeTHF = 1, THF = 15, and DME = 225. We attribute the relatively large alkylation rate in DME to its capacity to act as a chelating ligand.

Stereochemistry of Addition of 4-Li to Formaldehyde. A model to explain the stereochemistry of hydrazone alkylation proposed and discussed in the forthcoming text led to the curious prediction that 1,2 additions of cyclohexanone dimethylhydrazone anions to ketones or aldehydes[12] would proceed with dramatically eroded

(5) (a) Lithiated (+)-**3** exhibited the following ^{13}C NMR spectrum in THF-d_8 at 32 °C: 152.09, 70.81, 47.81, 47.51, 39.51, 34.44, 31.22, 23.13 ppm. The ^{13}C NMR spectrum of racemic sample (±)-**3** exhibited the same resonances within 0.5 ppm precision. The notable similarities could implicate homochiral aggregates as the predominant species in solution or simply be a coincidental insensitivity of the spectra to structural changes. (The possibility that we were observing monomers seems unlikely based on both the kinetic studies and solution molecular weight determination[4] of related anions.) Although some structural information of hybrid alkyllithium aggregates in solution has been obtained spectroscopically,[5b] the complexity of the regioisomeric mixture of anions and considerable peak broadening below room temperature precluded a more detailed investigation. (b) Leading references: Brown, T. L. *Adv. Organometal. Chem.* **1965**, *3*, 365. Brown, *Pure Appl. Chem.* **1970**, *23*, 447. Brown, T. L. *Acc. Chem. Res.* **1968**, *1*, 23. Jackman, L. M.; Szeverenyi, N. M. *J. Am. Chem. Soc.* **1977**, *99*, 4954.

(6) For example see: Coates, R. M.; Ofenshain Sandefur, L. *J. Org. Chem.* **1974**, *39*, 275. Posner, G. H.; Sterling, J. J.; Whitten, C. E.; Lentz, C. M.; Brunelle, D. J *J. Am. Chem. Soc.* **1975**, *97*, 107. Boeckman, R. K., Jr. *J. Org. Chem.* **1973**, *38*, 4450. Evans, D. A.; Sims, S. L.; Andrews, G. C. *J. Am. Chem. Soc.* **1977**, *99*, 5453. Stork, G.; Danheiser, R. L.; Ganem, B. *J. Am. Chem. Soc.* **1973**, *95*, 3414. Piers, E.; Britton, R. W.; de Waal, W. *Can. J. Chem.* **1969**, *47*, 831. Kametani, T.; Nemoto, H.; Ishikawa, H.; Shiroyama, K.; Fukumoto, K. *J. Am. Chem. Soc.* **1976**, *98*, 3378.

(7) (a) Although direct aggregate functionalizations have been implicated through nonstoichiometric effects on stereochemical outcomes of organolithium reactions,[7b] definitive mechanistic studies implicating aggregate reactivity are quite rare.[7c] (b) Seebach, D. In "Proceedings of the Robert A. Welch Foundation Conferences on Chemistry and Biochemistry"; Wiley: New York, in press. (c) Al-Aseer, M. A.; Smith, S. G. *J. Org. Chem.* **1984**, *49*, 2608 and references cited therein.

(8) (a) When the alkylation of lithiated hydrazone **4**-Li was effected in the presence of 1 mol equiv of tetrahydrofuran, the reaction approached 50% conversion asymptotically. Addition of a second equivalent of tetrahydrofuran allowed the reaction to resume and proceed to complete conversion. This effect was observed even though the reaction remained homogeneous. Although concentrations of THF (12–40 equiv) that afforded reasonable reaction rates under the described conditions also caused significant deviations from pseudo-first-order behavior, by accounting for the consumption of THF (presumably in the form of bis-solvated lithium iodide dimer[8b]) as a function of percent conversion, we obtained a rate equation analogous to that derived from MeTHF. (b) Talalaeva, T. V.; Rodionov, A. N.; Kocheshkov, K. A. *Dokl. Akad. Nauk. SSSR* **1964**, *154*, 174; **1961**, *140*, 847.

(9) Similar results were obtained by monitoring the formation of the alkylation product but with slightly deminished precision.

(10) Although kinetic data reported are for conversion to three half-lives, all alkylation kinetic runs were shown to proceed to at least 96% conversion.

(11) (a) From the general rate equations[11b] $d[\mathbf{4}\text{-Li}]/dt = C[\mathbf{4}\text{-Li}]^X$ and $\ln(d[\mathbf{4}\text{-Li}]/dt) = \ln C + X \ln[\mathbf{4}\text{-Li}]$, a plot of $\ln(\Delta[\mathbf{4}\text{-Li}]/\Delta t)$ vs. ln [**4**-Li] affords a line with slope X, in which X corresponds to the reaction order in anion. The reported value, $X = 0.30 \pm 0.04$, was obtained from five independent data collections. Figure 3A is one representative data set. The orders in ethyl iodide and MeTHF (Figures 4 and 5, respectively) were obtained from the equations $k_{obsd} = k'[Y]^Z$ and $\ln k_{obsd} = \ln k' + Z \ln [Y]$. (b) Frost, A.; Pearson, R. In "Kinetics and Mechanism", 2nd ed.; Wiley: New York, 1961; Chapter 3.

(12) For previous reports of condensation of metalated Schiff's bases with aldehydes or ketones see: Wittig, G. *Rec. Chem. Progr.* **1967**, *28*, 45. Wittig, G. Hesse, A. *Org. Synth.* **1970**, *50*, 66. Wittig, G.; Reiff, H. *Angew Chem., Int. Ed. Engl.* **1968**, *7*, 7. Dauben, W. G.; Beasley, G. H.; Broadhurst, M. D.; Muller, B.; Peppard, D. J.; Pesnelle, P.; Suter, C. *J. Am. Chem. Soc.* **1975**, *97*, 4973. Büchi, G.; Wüest, H. *J. Org. Chem.* **1969**, *34*, 1122. Corey, E. J.; Enders, D.; Bock, M. G. *Tetrahedron Lett.* **1976**, *7*. Corey, E. J.; Enders, D. *Chem. Ber.* **1978**, *111*, 1362. Eichenauer, H.; Friedrich, E.; Lutz, W.; Enders, D. *Angew Chem., Int. Ed. Engl.* **1978**, *17*, 206. Reference 2a.

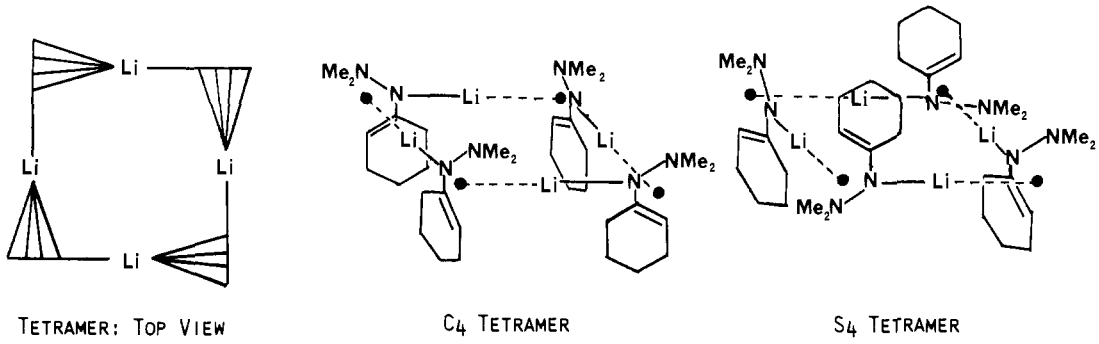
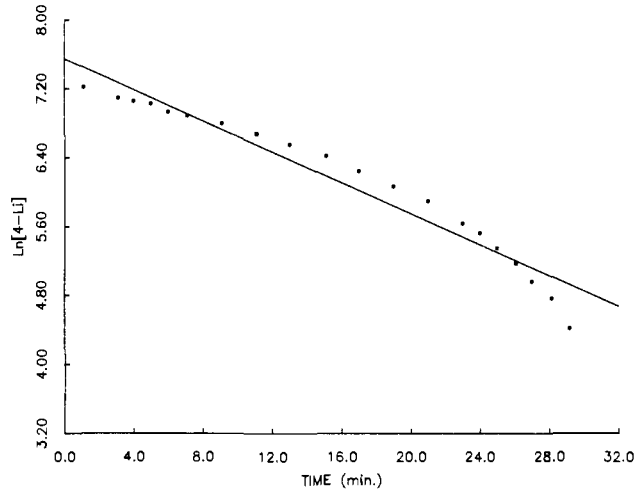


Figure 2.



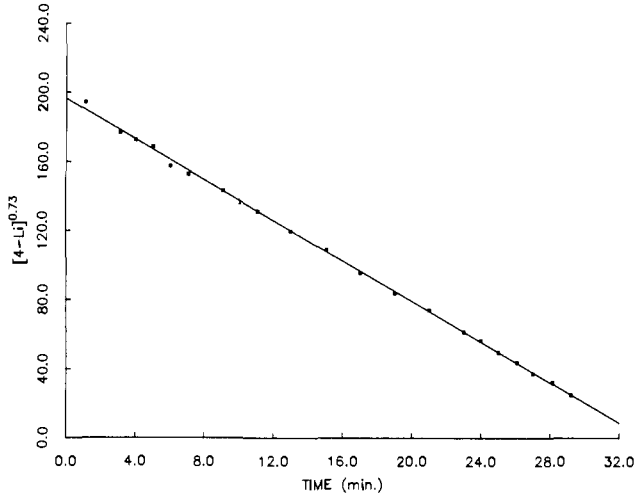


Figure 3. Alkylation rate dependence on [**4**-Li] plotted at (top) first order, (bottom) the calculated value of 0.27 order (see ref 11). Conditions: $[\mathbf{4}\text{-Li}]_0$ = 0.01 M; [EtI] = 0.25 M; [MeTHF] = 0.49 M; T = 0 °C.

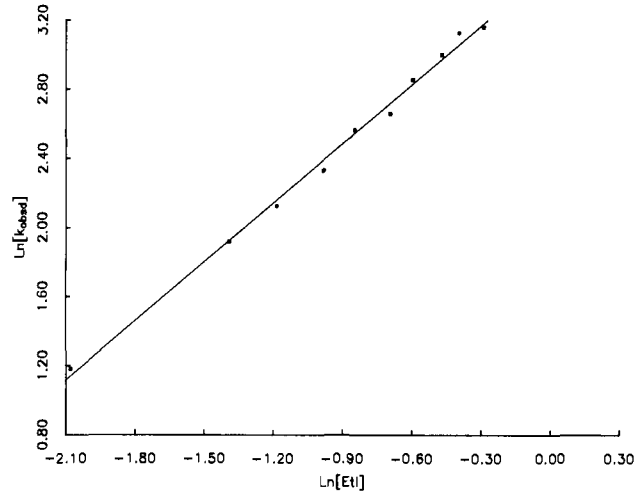


Figure 4. Observed 0.30 order rate constants as a function of [EtI]: $[\mathbf{4}\text{-Li}]_0$ = 0.01 M; [MeTHF] = 0.49 M; T = 0 °C. The slope of 1.14 ± 0.02 is the order in EtI (ref 11).

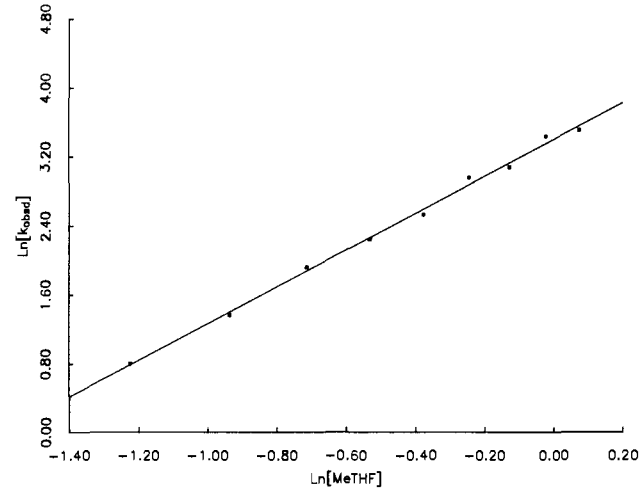
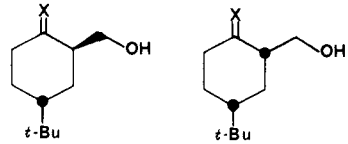


Figure 5. Observed 0.30 order rate constants as a function of [MeTHF]: $[\mathbf{4}\text{-Li}]_0$ = 0.01 M; [EtI] = 0.25 M; T = 0 °C. The slope of 2.14 ± 0.05 is the order in MeTHF (ref 11).

preference for axial attack. When hydrazone **4** in THF was treated with LDA following by gaseous formaldehyde at −78 °C, a chromatographically separable 1.7:1 mixture of hydrazones **5a** and **6a** was obtained in 81% combined yield. The isomers were



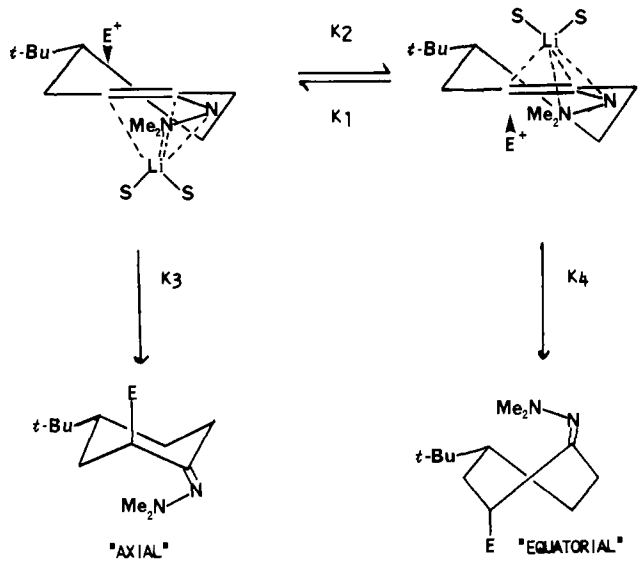
5a; X = $NNMe_2$ 6a; X = $NNMe_2$
5b; X = O 6b; X = O

shown to be stable to retro-aldol condensation and to epimerization upon treatment with varying quantities of LDA in THF at 25 °C.

Approximately 10% epimerization could be observed when pure **5a** or **6a** was left at room temperature for several days. Hydrazones **5a** and **6a** were independently hydrolyzed to the corresponding hydroxymethyl ketones **5b** and **6b** by using $CuCl_2$ in wet THF[2b] without epimer cross-contamination. Carbon-13 NMR spectroscopic analysis of **5b** and **6b** with comparison to the spectra of the corresponding stereoisomeric 4-*tert*-butyl-2-methylcyclohexanones[13] allowed for a reasonably secure structural assignment; the major isomer **5b** exhibited upfield steric compression shifts

(13) Stothers, J. B.; Tan, C. T. *Can. J. Chem.* **1974**, *52*, 308. Pfeffer, P. E.; Osman, S. F. *J. Org. Chem.* **1972**, *37*, 2425.

Scheme I



of the C_4 and C_6 resonances attributable to the axial substitutent.[13]

Discussion

The alkylation kinetic study afforded the following rate equation:

$$d\text{4-Li}/dt = k_{obsd}[\text{4-Li}]^{0.30\pm0.04}[\text{EtI}]^{1.14\pm0.03}[\text{MeTHF}]^{2.14\pm0.05}$$

This rate equation is consistent with the mechanism depicted in eq 3 and 4.

$$(\text{4-Li})_x + 2x(\text{solvent}) \rightleftharpoons x\text{4-Li(solvent)}_2 \quad (3)$$

$$\text{4-Li(solvent)}_2 + \text{EtI} \rightarrow \text{product} \quad (4)$$

$$x = 3 \text{ or } 4$$

Spectroscopically invisible bis-solvated monomers appear to be the species undergoing alkylation. However, we must still confront the problem of elucidating their structures and determining the origins of the dramatic hydrazone alkylation diastereoselectivities. Although the previously postulated[2a,15] η^4 face coordination of the metal counterion clearly could preclude entry of the electrophile from one of the two possible directions, the energetic differences between bis-solvated monomers of opposite face coordination (cf. iii and iv; Scheme I) might be expected to be small.

We would like to put forth the model illustrated in Scheme I to account for the hydrazone alkylation stereoselectivities observed to date.[2-4] Although the model is speculative, it is also experimentally testable.

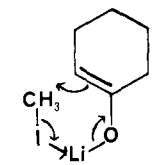
In the extreme, despite rapid aggregate–monomer preequilibrium, equilibration of face coordination isomers iii and iv could be slow relative to the rate of the alkylation. However, since the stereoselectivities of hydrazone alkylations are dependent on the size of the alkylating agent,[16] at least partial equilibration of iii and iv occurs on the time scales of the alkylations. Furthermore, our complete failure to detect aggregation effects in the alkylation of hydrazone **3** indicates that complete equilibration probably occurs. Accordingly, the overall stereoselectivity of hydrazone alkylation can be represented as in eq 5. Equation 5 is a statement

$$\text{axial/equatorial selectivity} = k_3/k_4 \times k_1/k_2 \quad (5)$$

of the Curtin–Hammett principle and has been discussed by Perrin and Seeman in its most general form.[17]

To explain dramatic axial alkylation selectivities, we need only to invoke the modest contributions from stereoelectronic preferences for chairlike transition states[18] (reflected in the k_3/k_4 term of eq 5) that afford the small axial selectivities observed in ketone enolate alkylations. Limited data prevent us from providing a discussion of steric and electronic factors that would bias the diastereofacial π complexation of the lithium and in turn the relative magnitudes of k_1 and k_2. However, it is notable that even a slight preference for isomer iii ($k_1/k_2 > 1$) could cause a considerable magnification of the observed axial alkylation selectivities relative to the corresponding ketone- and ester-substituted hydrazone derivatives that may not exhibit such π complexation.[4,19] Furthermore, the initially surprising tendency of sterically biased hydrazones to alkylate from the *more* hindered face (cf. ref 2c, 2d, and 4, and eq 2) can now be attributed to the preferred coordination of the lithium counterion to the *less* hindered face.

Substitutions of alkyllithiums with retention of configuration at the lithium-bearing carbon are documented.[20] Although it might prove tempting to invoke a mechanism involving precoordination of the alkyl iodide to the lithium counterion with an ensuing cyclic transition state[21] (e.g. vii), this would require displacement of the iodide with retention of configuration at the electrophilic carbon. That is not to say, however, that the alkylating agent cannot directly attack the π system from the face containing the lithium counterion. We developed the working hypothesis invoking attack of the alkylating agent from the face opposite to the π-complexed lithium for the simple reason that it successfully accounted for the tendency of 2- and 3-substituted cyclohexanone hydrazone anions to alkylate from the more hindered direction. However, since our concerns about such an assumption were understandably shared by both referees, we sought supportive evidence from a comparison of the stereochemistry of hydrazone alkylation with the hydrazone-directed Aldol condensation.[12]



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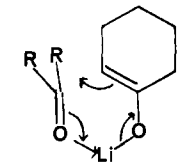

viii

Stereochemical results[22] and molecular orbital calculations[23] strongly suggest that Aldol condensations of ketone enolates with aldehydes proceed by intramolecular delivery of the electrophile via a chelated transition state of type viii. (Unlike alkylation transition state vii, transition state viii would be geometrically acceptable.) If we assume that the corresponding hydrazone-stabilized anions also condense with aldehydes via cyclic transition states, we find that the model described by Scheme I and eq 5 leads to a curious prediction. The proposed model implies that isomer iii predominates over isomer iv in solution (i.e., $k_1/k_2 > 1$). If at least one of the solvent molecules (designated as "S") in iii

(14) The cumulative effects of small deviations from pseudo-first-order conditions can account for at least some of the systematic overestimates of reaction orders. Therefore, it might be *inferred* that tetramer-to-monomer rather than trimer-to-monomer equilibria are involved. Similar overestimation of reaction orders in organolithium kinetic analyses have been noted: Waack, R.; West, P.; Doran, M. A. *Chem. Ind.* **1966**, 1035. Roovers, J. E. L.; Bywater, S. *Macromolecules* **1968**, *1*, 328. Holm, T. *Acta Chem. Scand.* **1969**, *23*, 1829; **1971**, *25*, 833. Johnson, A. F.; Worsfold, D. J. *J. Polym. Sci.* **1965**, *A3*, 449. Waack, R.; West, P. *J. Organometal. Chem.* **1966**, *5*, 188.

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(16) The stabilized anion derived from 4-*tert*-butyl-2-cyanocyclohexanone dimethylhydrazone in THF alkylates at −78 °C with selectivities varying from 14 to 26:1 depending on the structure of the alkylating agent.[4] Furthermore, ethylation of hydrazone **4** in neat THF at −78 °C provided significantly reduced (14:1) axial selectivity compared to the corresponding methylation.[2a,b]

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and iv represents the precoordinated carbonyl-containing electrophile, then internal delivery of the aldehyde moiety in the predominant isomer iii would have to proceed via an *unfavorable* twistboatlike transition state.[21] The corresponding reaction of the minor isomeric azaallyllithium–aldehyde complex corresponding to iv would react via a *favorable* chairlike transition state. Therefore, *whereas stereoelectronic preferences and face coordination preferences are believed to work in concert to afford high axial alkylation selectivities, they should be in opposition in the corresponding condensation of hydrazone 4-Li with aldehydes to afford dramatically eroded axial selectivities.* Indeed, condensation of **4**-Li with formaldehyde in THF at −78 °C afforded only a 1.7:1 kinetic preference for axial attack. In contrast, methylation of **4**-Li affords >50:1 axial selectivity.[2a] Since hydrazones appear to exhibit highest axial functionalization preferences with sterically less demanding electrophiles and some evidence indicates that the axial selectivity of the Aldol condensation of ketone enolates may actually be slightly *higher* than the corresponding alkylation selectivities,[1h] such a dramatic erosion of axial selectivity seems explicable only if MeI and formaldehyde approach from opposite faces of a π-complexed intermediate.

Summary

From the studies described herein we have been able to demonstrate that hydrazone alkylation stereoselectivities do not derive from anion aggregation effects but rather from stereoselective alkylation of bis-solvated monomeric lithium derivatives. We have proposed a model that hinges upon subtle lithium coordination stereoselectivities and modest stereoelectronic preferences working in concert to afford the observed high alkylation selectivities. However, there still remains a number of unanswered questions. We are currently attempting to elucidate the properties common to all of the metalated Schiff's bases that undergo highly stereoselective alkylation.

Experimental Section

General. All reactions were performed under argon or prepurified nitrogen atmosphere by using a combination of syringe and vacuum line techniques. GLC analyses were performed by using a Varian 3700 series capillary gas chromatograph with flame ionization detection and digital integration. Solvents were distilled and degassed by using standard protocol. The hydrazone alkylations and $CuCl_2$-mediated hydrolyses were effected by using well-documented literature procedures.[2a,b] The resulting 2,5- and 2,3-dimethylcyclohexanones were characterized by comparison with authentic samples prepared by literature procedures.[12]

Kinetics. A typical alkylation kinetic run was effected as follows. To an argon-purged, 25-mL round-bottomed flask fitted with gas adapters and a magnetic stir bar was added 8.50 mL of a stock solution containing diisopropylamine (0.121 mmol/8.50 mL) in 70:30 (by volume) benzene/hexane. After addition of the desired quantity of 2-methyltetrahydrofuran (29–108 mol equiv), enough benzene/hexane (70:30) was added such that, after addition of all reagents (vide infra), the total reaction volume would be 10.0 mL. Following addition of *n*-BuLi/hexane (0.12 mmol, Aldrich; freshly titrated)[24] and stirring for 1.0 h, a 1:1 (by volume) mixure of 4-*tert*-butylcyclohexanone dimethylhydrazone (**4**, 0.10 mmol) and tetradecane (internal GLC standard) was added neat. After allowing the reaction to stir for 15 h at 0 °C for anion formation, the desired quantity of ethyl iodide (12.5–75 mol equiv, chilled to 0 °C with a jacketed gas-tight syringe) was added neat. The temperature of the ice bath was maintained at 0.0 ± 0.2 °C. Aliquots of the reaction were periodically transferred by cannulation under positive argon flow into 0.80 mL of absolute ethanol. The quenches were stirred for 3–9 h prior to gas chromatographic analysis.[25] The course of the alkylation was monitored by loss of the starting hydrazone peak relative to the tetradecane internal standard.[9] All reported errors represent one standard deviation from nonlinear, weighted least-squares analyses.

Condensation of Formaldehyde with 4-Li. To a solution of lithium diisopropylamide (0.70 mmol) in 5 mL of THF under nitrogen at 0 °C was added hydrazone **4** (110 μL, 0.5 mmol) neat. After 3.0 h at 0 °C, excess gaseous formaldehyde (generated from solid paraformaldehyde slurried in mineral oil heated to 140 °C) was passed over the anion solution at −78 °C via a positive nitrogen flow until thin-layer chromatographic analysis showed complete consumption of starting material. The reaction was quenched with water and extracted 3 times with 10 mL of methylene chloride. Drying (Na_2SO_4), concentration, and flash chromatography (5% ethanol/ethyl acetate) afforded, in order of elution, **6a** (34 mg, 30% yield) and **5a** (57 mg, 50% yield). **6a**: ^{1}H NMR (80 MHz, $CDCl_3$) δ 4.25 (br s, 1 H), 3.70–3.45 (m, 2 H), 3.20 (m, 1 H), 2.37 (s, 6 H), 2.20–0.90 (m, 7 H), 0.81 (s, 9 H); ^{13}C {^{1}H} NMR (22.5 MHz, $CDCl_3$) δ 172.2, 64.6, 47.7, 46.9, 45.5, 32.3, 31.1, 28.1, 27.5, 27.3; IR ($CDCl_3$) 3350 (m), 1690 (m), 1620 cm^{-1} (s). Exact mass calcd for $C_{13}H_{26}N_2O$: 226.2045. Found: 226.2043. **5a**: ^{1}H NMR (80 MHz, $CDCl_3$) δ 3.75 (br s, 1 H), 3.55 (d, J = 7 Hz, 2 H), 2.95 (m, 1 H), 2.33 (s, 6 H), 2.20–0.90 (m, 7 H), 0.76 (s, 9 H); ^{13}C {^{1}H} NMR (22.5 MHz, $CDCl_3$) δ 171.5, 63.6, 47.1, 44.0, 42.1, 32.3, 27.2, 27.1, 26.1, 25.1; IR ($CDCl_3$) 3350 (m), 1630 cm^{-1} (m). Exact mass calcd for $C_{13}H_{26}N_2O$: 226.2045. Found: 226.2044.

Hydrazones **5a** and **6a** were each hydrolyzed under nonepimerizing conditions by using the procedure of Corey and Knapp[2b] as follows. To a solution of hydrazone **5a** (166 mg, 0.73 mmol) in THF at 0 °C was added $CuCl_2(H_2O)_2$ (550 mg, 3.20 mmol) in 6 mL of THF/H_2O (4:1). After 0.5 h, the reaction was partitioned between H_2O and CH_2Cl_2. The organic phase was dried (Na_2SO_4), concentrated and flash chromatographed (40% ethyl acetate/hexane), affording 60 mg (45% yield) of **5b**: ^{1}H NMR (80 MHz, $CDCl_3$) δ 3.80–3.50 (m, 2 H), 2.80–1.10 (m, 9 H), 0.86 (s, 9 H); INEPT ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 216.3 (C=O), 62.9 (CH_2OH), 49.6 (CH), 42.4 (CH), 39.2 (CH_2), 32.7 (C), 27.1 (CH_3), 26.6 (CH_2), 24.3 (CH_2); IR ($CDCl_3$) 3520 (m), 1690 cm^{-1} (s); MS (EI), m/z 184 (5%), 57 (100%). Analogous hydrolysis of **6a** afforded **6b** (63% yield): ^{1}H NMR (80 MHz, $CDCl_3$) δ 3.70–3.50 (m, 2 H), 2.60 (s, 1 H), 2.50–1.00 (m, 8 H), 0.88 (s, 9 H); INEPT ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 215.0 (C=O), 62.7 (CH_2OH), 51.3 (CH), 46.5 (CH), 41.5 (CH_2), 32.4 (C), 31.0 (CH_2), 28.2 (CH_2), 27.5 (CH_3); IR ($CDCl_3$) 3600 (m), 1690 cm^{-1} (s); MS (EI), m/z 184 (6%), 57 (98%).

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Registry No. (±)-**3**, 94537-75-4; (+)-**3**, 94537-76-5; **4**, 58911-63-0; *trans*-**5a**, 94537-77-6; *trans*-**5b**, 94537-79-8; *cis*-**6a**, 94537-78-7; *cis*-**6b**, 94537-80-1; HCHO, 50-00-0; $CuCl_2(H_2O)_2$, 13933-17-0.

(24) Within experimental error identical rate constants were obtained using LDA prepared from freshly recrystallized (benzene) and sublimed ethyllithium.

(25) If the anion quenches in ethanol were stirred for less than 3 h, major fluctuations occurred in the GLC integrations. ^{1}H NMR evidence indicated that kinetic N protonation followed by surprisingly slow enamine-to-imine tautomerization could have been the source of the fluctuations.