solution of the acid **17** (250 mg, 0.79 mmol) in THF (15 mL) followed by trimethylsilyl chloride (0.5 mL) and the reaction was left stirring at 0 °C for 1 h. The reaction mixture was then concentrated in vacuo, the residue dissolved in dry dichloromethane and filtered, and the filtrate evaporated to dryness. The crude product was pyrolyzed and the pyrolyzate purified by PLC (silica gel, ethyl acetate as eluant) to obtain the acid **24** (67 mg, 61%) as colorless crystals: mp 168–169 °C (dichloromethane–hexane); IR (Nujol) 2800–2600 (br), 1715, 1665, 1215, 910, 720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.10 (t, J = 2 Hz, 3 H), 2.45–2.60 (m, 2 H), 2.73–2.91 (m, 2 H), 9.29 (br s, 1 H, removed with D_2O); mass spectrum, m/e (relative intensity) 140 (100), 112 (40). Anal. Calcd for $C_7H_8O_3$: C, 60.00; H, 5.71. Found: C, 59.88; H, 5.95.

Conclusion

It should be emphasized that the tandem Michael addition–Dieckmann condensation method shown above is extremely attractive for the construction of such a cyclopentenoid nucleus, and it makes large quantities of sarkomycin easily obtainable. Consequently, we were able to obtain good-quality NMR spectra for both sarkomycin and its ester. In addition, the method is not limited and should extend readily to other antibiotics in this series.

Acknowledgment. We thank The National Research Council (Thailand) for support of this work.

Registry No. (±)-**2** ($R^1 = R^2$ = H), 90913-14-7; (±)-**6**, 72581-31-8; (±)-**7**, 72525-99-6; (±)-**12**, 90913-15-8; **13**, 39915-66-7; (±)-**14**, 90913-16-9; (±)-**15**, 90913-17-0; (±)-**16**, 90913-18-1; (±)-**17**, 90913-19-2; (±)-**18**, 90913-20-5; (±)-**20**, 90913-21-6; (±)-**23**, 90941-10-9; **24**, 1909-79-1; dimethyl itaconate, 617-52-7; anthracene, 120-12-7; methyl acrylate, 96-33-3.

Supplementary Material Available: ^1H NMR spectra of **12**, **14–18**, **20**, **10**, **7**, **7** + EuFOD, **6**, **24**, and **24** methyl ester (13 pages). Ordering information is given on any current masthead page.

Substituent Effects on the Stereochemistry of Substituted Cyclohexanone Dimethylhydrazone Alkylations. An X-ray Crystal Structure of Lithiated Cyclohexanone Dimethylhydrazone

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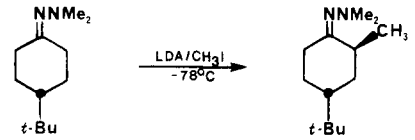
Abstract: Substituent effects on the alkylations of the dimethylhydrazones of 2,4- and 2,6-disubstituted cyclohexanones are reported. High axial selectivities are observed in the alkylations of cyano-substituted metalated hydrazones, but not with alkoxycarbonyl-substituted cases. Hydrazones of 2-substituted cyclohexanones appear to alkylate axially out of a conformer with the 2-substituent pseudoaxially disposed. The possible origins of the stereoselectivities are addressed in light of an X-ray crystal structure of lithiated cyclohexanone dimethylhydrazone.

During the course of a total synthesis effort in our laboratory, we required a geminal difunctionalization of a 2-substituted ketone as depicted in eq 1. The major portion of any relative stereo-

(1)

selectivity would have to arise via a stereoelectronically controlled axial entry of an electrophile to the corresponding ketone enolate or its equivalent. Although ketone enolates exhibit mediocre selectivities toward axial alkylation,[1,2] the corresponding dimethylhydrazones and related Schiff's base derivatives show remarkable preferences for axial alkylation (eq 2).[3,4]



98% axial

(2)

We report herein substituent effects on the stereochemistry of the alkylations of metalated cyclohexanone dimethylhydrazones. Dramatic substituent-dependent stereoselectivities are observed in the alkylations of highly stabilized 4-*tert*-butylcyclohexanone-derived hydrazone anions, as well as unanticipated stereochemical reversals in the alkylations of 2-substituted and 2,6-disubstituted cyclohexanone hydrazones. The stereoselectivities are discussed in relation to an X-ray crystal structure of lithiated cyclohexanone dimethylhydrazone.

Results

Product Characterization. Hydrazones **3a–6a** could not be rigorously characterized by simple spectroscopic methods. Ac-

(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) Trans decalones can alkylate axially with high stereoselectivity when axial entry is sterically accessible: Agami, C.; Levisalles, J.; Lo Cicero, B. *Tetrahedron* **1979**, *35*, 961. Stork, G.; McMurry, J. E. *J. Am. Chem. Soc.* **1967**, *89*, 5464. However, these selectivities can be attributed to allylic strain unique to fused-ring systems: Lansbury, P. T.; Dubois, G. E. *Tetrahedron Lett.* **1972**, 3305. Although high axial selectivities are observed in the condensation of tetrabutylammonium enolates with aldehydes, the corresponding alkylations are poorly selective.[1h]

(3) (a) Corey, E. J.; Enders, D. *Chem. Ber.* **1978**, *111*, 1337. (b) Corey, E. J.; Knapp, S. *Tetrahedron Lett.* **1976**, 4687.

(4) Review: Hickmott, P. W. *Tetrahedron* **1982**, *38*, 1975.

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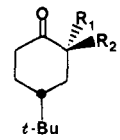
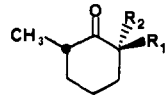
cordingly, known ketones **3b–6b** were prepared by the method of



3b, R_1 = COOEt; R_2 = CH_3
4b, R_1 = CH_3; R_2 = COOEt
5b, R_1 = CN; R_2 = CH_3
6b, R_1 = CH_3; R_2 = CN
7b, R_1 = CN; R_2 = Et
8b, R_1 = Et; R_2 = CN
9b, R_1 = CN; R_2 = CH_2Ph
10b, R_1 = CH_2Ph; R_2 = CN
11b, R_1 = CN; R_2 = *i*-Pr
12b, R_1 = *i*-Pr; R_2 = CN

Kuehne[1g] and converted to their corresponding hydrazones for correlation using infrared (IR), carbon-13 nuclear magnetic resonance (^{13}C NMR), and proton nuclear magnetic resonance (^1H NMR) spectroscopy. The stereochemical assignments for hydrazones **7a–12a** were based on analogy to the above cases. To rule out the possibility of misassigning a syn–anti isomer or an N-alkylation product as the minor stereoisomer, **7a–12a** were separated, characterized, and then hydrolyzed ($CuCl_2/H_2O$/THF;[3b] 70–100% yield after flash chromatography) to their respective ketones **7b–12b**. The 2-methylcyclohexanone-derived hydrazones **17a–24a** were independently hydrolyzed to their respective ketones **17b–24b** in a manner similar to that described



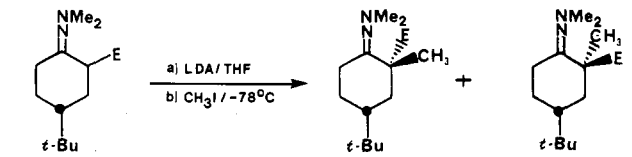
17b, R_1 = CH_3; R_2 = H
18b, R_1 = H; R_2 = CH_3
19b, R_1 = CH_3; R_2 = CN
20b, R_1 = CN; R_2 = CH_3
21b, R_1 = CH_3; R_2 = SCH_3
22b, R_1 = SCH_3; R_2 = CH_3
23b, R_1 = CH_3; R_2 = $COOCH_3$
24b, R_1 = $COOCH_3$; R_2 = CH_3

above. Ketones **17b–24b** were easily characterized by the well-documented downfield shifts of the methyl proton resonances in the ^1H NMR of axially disposed 2-methylcyclohexanone derivatives relative to the equatorial counterparts.[5]

Alkylation of 4-*tert*-Butylcyclohexanone Dimethylhydrazone Derivatives. We initiated our investigations with β-keto ester hydrazone **1** prepared from the corresponding known ketone[1g] (*uns*-dimethylhydrazine/50 °C;[6] 69% yield). This material existed predominantly in the enamino tautomeric form[7] as shown by ^{13}C NMR and IR spectroscopy. The lithiated hydrazone was formed upon treatment of **1** with lithium diisopropylamide (LDA) in tetrahydrofuran (THF) with stirring for 15 min at 0 °C. Addition of methyl iodide to the lithiated hydrazone at −78 °C immediately provided a 7:1 mixture of **3a** and **4a** (84% yield after chromatography).

Schiff's base derivatives exhibit exceptional stereoelectronic preferences not only in the alkylation of their anions[4] but may also do so in their deprotonation.[8] The existence of the enamine tautomeric form of **1a** indicates that abstraction of both axially and equatorially disposed protons readily occurred during hydrazone formation. However, in removing stereoelectronic constraints in the deprotonation, the stereoselectivity of the alkylation was also lost and the metalated hydrazone derived from **1** alkylated with mediocre stereocontrol very similar to that found for the corresponding keto ester.[1g]

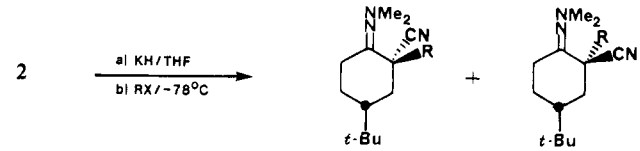
β-Keto nitrile hydrazone **2**, prepared from the corresponding known ketone[1g] (*uns*-dimethylhydrazine/50 °C/1.0 h; 90% yield), existed exclusively in the enamine tautomeric form. In contrast to the ester substituted hydrazone **1**, hydrazo nitrile **2** alkylated under analogous conditions with an exceptional (26:1) preference for axial alkylation (eq 3). Curiously, the alkylation stereoselectivity was relatively insensitive to changes in the solvent and metal counterion; alkylations of **2** at −78 °C via the corresponding lithium, sodium, or potassium anions in THF containing up to 40% hexamethylphosphoramide afforded axial selectivities falling in the range of 20–27:1. The selectivities were moderately sensitive to the structure of the alkyl halide electrophile (eq 4). The poor



1, E = COOEt
2, E = CN

3a, E = COOEt (7:1) 4a, E = COOEt
5a, E = CN (26:1) 6a, E = CN

(3)



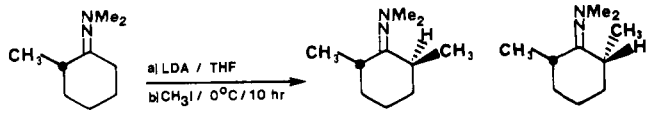
CH_3CH_2I (R = CH_2CH_3; 70%)	7a	(20:1)	8a
$PhCH_2I$ (R = CH_2Ph; 80%)	9a	(14:1)	10a
i-PrI (R = *i*-Pr; 76%)	11a	(6:1 at −20 °C)	12a

(4)

selectivity for the alkylation of **2** with 2-iodopropane presumably arose from the higher temperature (−20 °C) required to effect the alkylation. Methylation of the lithium salt of **2** in THF afforded the following temperature-dependent ratios of **5a**/**6a**: 0 (7:1); −78 (26:1); −110 °C (35:1).

Some of the enhanced stereoselectivity shown in the alkylation of β-hydrazo nitrile amines compared to the corresponding anions of β-keto nitriles could be attributed to the lower reaction temperatures. However, the stereoselectivities resulting from the nitrile- vs. ester-stabilized hydrazone anions were inescapably different. The independence of the stereoselectivity to the nature of the solvent and the metal counterion provided interesting constraints on the origin of the axial selectivity (see Discussion).

Alkylation of 2-Methylcyclohexanone Dimethylhydrazone Derivatives. For stereoselective introduction of the quaternary center (eq 1), we turned to the dimethylhydrazones of 2-methylcyclohexanones. Corey and Enders[3a] reported that alkylation of **13** afforded **17a** and **18a** as indicated in eq 5. We found cyano-

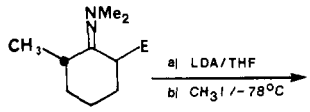


13 17a (90:10) 18a

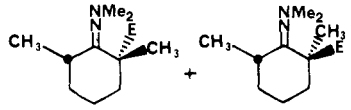
(5)

substituted hydrazone **14**, prepared from the corresponding cyano ketone,[9] alkylated (LDA/THF followed by CH_3I at −78 °C) to afford a 1:17 mixture of hydrazones **19a** and **20a** (68% combined yield after chromatography). Thus, *the alkylation of **13** proceeded in the opposite sense to the alkylation of **13** reported by Corey and Enders.* Alkylation of the thiomethyl-substituted hydrazone **15** with CH_3I (eq 6) occurred with an even higher (1:44) stereoselectivity.[10] Ester hydrazone **16** also alkylated with stereochemistry opposite to that reported by Corey and Enders, albeit with reduced (1:5.3) stereoselectivity.

(5) See: Branca, S. J.; Smith, A. B., III. *J. Org. Chem.* **1977**, *42*, 1026 and references cited therein.
(6) Newkome, G. R.; Fishel, D. L. *J. Org. Chem.* **1966**, *31*, 677.
(7) Ahlbrecht, H. *Tetrahedron Lett.* **1971**, 545.
(8) (a) Fraser, R. R.; Dhawan, K. L. *J. Chem. Soc., Chem. Commun.* **1976**, 674. (b) Lyle, G. G.; Fribush, H. M.; Marshall, J. L.; Lijinsky, W.; Singer, G. M.; Lyle, R. E. *Tetrahedron Lett.* **1976**, 4431.
(9) Kahne, D.; Collum, D. B. *Tetrahedron Lett.* **1981**, *22*, 5011.
(10) Exceptional axial selectivity in the alkylation of the dimethylhydrazone of 4-*tert*-butyl-2-(thiomethyl)cyclohexanone has been observed.[3]



14, E = CN
15, E = SCH_3
16, E = $COOCH_3$
13, E = H



19a, E = CN (1:17, 64%) 20a, E = CN
21a, E = SCH_3 (1:44, 63%) 22a, E = SCH_3
23a, E = $COOCH_3$ (1:5, 35%) 24a, E = $COOCH_3$
17a, E = H (1:11, 54%) 18a, E = H

(6)

The following experiments were effected to demonstrate the origin of the odd stereoselectivities. Hydrolyses of **19a–24a** using anhydrous $CuCl_2$, anhydrous THF, and D_2O afforded the respective ketone products with neither epimer cross contamination nor deuterium incorporation, indicating that the hydrolyses preceding stereochemical analyses left the stereocenters intact. Alkylation of hydrazone **13** *at −78 °C followed by warming to −20 °C* provided a 10:1 mixture of two alkylated products. These were not simply syn–anti isomers since *a chair–chair interconversion achieves the equivalent of syn–anti isomerization.* Hydrolysis of the crude product with $CuCl_2/THF/H_2O$ and correlation of the resulting ketones with a commercially available mixture of ketones **17b** and **18b**[11] demonstrated that the alkylation of hydrazone **13** provided a 1:11 mixture of **17a** and **18a**, respectively. Thus, *alkylation with opposite stereoselectivity to that previously reported* was confirmed. When **17a** and **18a** were separated (flash chromatography) and independently hydrolyzed by anhydrous $CuCl_2$/anhydrous THF/D_2O, we obtained ketones **17b** and **18b**, respectively, without significant[12] epimerization or deuterium incorporation.

The source of the discrepancy proved to be a subtle one. Upon standing neat at 25 °C for several hours, a *pure* sample of hydrazone **18a** epimerized almost completely (>95%) to **17a**. Upon repetition of the Corey and Enders alkylation procedure (0 °C, 10 h) the course of the epimerization could be followed by TLC, providing a thermodynamically derived 10:1 mixture of **17a** and **18a**.[13-15]

The source of the exceptional preferences for conformationally biased cyclohexanone hydrazones, oximes, oximino ethers, and related Schiff's base derivatives to alkylate axially has remained obscure. Chair vs. twist-boat transition-state arguments frequently have been invoked to explain the modest axial selectivities in ketone enolate alkylations.[1] However, these arguments would appear to be inadequate to explain the often >98% axial selectivities observed in the alkylations of hydrazones and related Schiff's bases.[4]

In order to address putative steric biases favoring axial entry of electrophiles to metalated hydrazones, we required hitherto unknown anion structural information including the rotameric distribution of the dimethylamino group around the nitrogen–nitrogen bond and the structure and location of the metal counterion and its coordination sphere.[17] We have obtained preliminary information on these points from a molecular structure determination of lithiated cyclohexanone dimethylhydrazone described below.

Table I. Selected Bond Distances for Hydrazone Anion **25** (Å)

C1–C2	1.360(7)	C1A–C2A	1.364(6)
C1–N7	1.355(6)	C1A–N7A	1.382(6)
C1–N8	2.358(5)	C1A–N8A	2.379(6)
C1–L1	2.196(9)	C1A–L1A	2.255(9)
C2–L1	2.298(9)	C2A–L1A	2.298(10)
N7–N8	1.507(5)	N7A–N8A	1.470(6)
N7–L1	2.156(9)	N7A–L1A	2.176(9)
N7–L1A	1.934(9)	N8A–L1A	1.995(9)
N8–L1	2.062(9)		

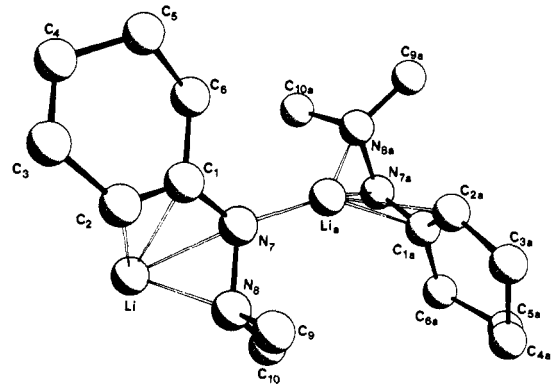


Figure 1. Molecular structure of the asymmetric unit of lithiated cyclohexanone dimethylhydrazone polymer. Hydrogen positions have been calculated but left off for clarity.

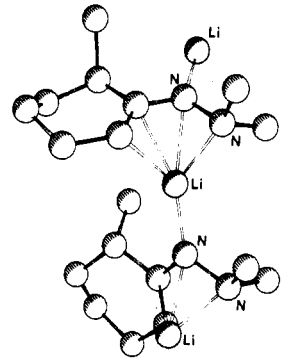


Figure 2. Low-resolution molecular structure determination of the asymmetric unit of lithiated 2-methylcyclohexanone dimethylhydrazone polymer.

Molecular Structure of Lithiated Cyclohexanone Dimethylhydrazone (25). A computer-generated perspective drawing of the final X-ray model of **25**, less hydrogens, is given in Figure 1. Selected bond distances are listed in Table I. There are two crystallographically independent molecules in the asymmetric unit. The structure is not dimeric in the sense that the lithiums and anions form an extended array. In each molecule the cyclohexene ring adopts a half-chair conformation with C1, C2, C3, and C6 being planar and C4 and C5 being above and below the plane. In one of the cyclohexenes there is evidence of disorder in the C4 and C5 positions; the displacements from the plane are reduced and the apparent bond distance is reduced to 1.48 Å. The lithium

(11) Sodium borohydride reduction of the minor ketone (**17b**) affords an alcohol exhibiting eight resonances in the ^{13}C NMR: ($CDCl_3$) δ 77.7, 33.7, 33.2, 31.4, 30.6, 19.9, 17.9, 13.7.

(12) The facile epimerization precludes isolation of **18a** totally pure; hydrolysis of **18a** affords **18b** contaminated by 10% **17b**.

(13) Professor R. R. Fraser has also observed these stereochemical anomalies in the alkylation of **13**. We thank both Dr. Fraser and Dr. Enders for very helpful discussions.

(14) Meyers, A. I.; Williams, D. R.; Erickson, G. W.; White, S.; Druelinger, M. *J. Am. Chem. Soc.* **1981**, *103*, 3081.

(15) For studies on facile imine–enamine tautomerizations, see: Kalinowski, H.-O.; Kessler, H.; Leibfritz, D.; Pfeffer, A. *Chem. Ber.* **1973**, *10b*, 1023 and references cited therein.

(16) Alkylations of 2-methylcyclohexanone imines clearly provide trans disubstituted cyclohexanones.[14] The subtle, yet seemingly important, differences between metalated imines and hydrazones remain incompletely resolved.

(17) See ref 4. For some representative spectroscopic studies of metalated Schiff's base derivatives, see: (a) Lee, J. Y.; Lynch, J. L.; Mao, D. T.; Bergbreiter, D. E.; Newcomb, M. *J. Am. Chem. Soc.* **1981**, *103*, 6215. (b) Fraser, R. R.; Chuaqui-Offermanns, N. *Can. J. Chem.* **1981**, *59*, 3007. (c) Fraser, R. R.; Chuaqui-Offermanns, N.; Houk, K. N.; Rondan, N. G. *J. Organomet. Chem.* **1981**, *206*, 131. (d) Davenport, K. G.; Newcomb, M.; Bergbreiter, D. E. *J. Org. Chem.* **1981**, *46*, 3143. (e) Ludwig, J. W.; Newcomb, M.; Bergbreiter, D. E. *J. Org. Chem.* **1980**, *45*, 4666. (f) Bergbreiter, D. E.; Newcomb, M. *Tetrahedron Lett.* **1979**, 4145. (g) Albrecht, H.; Duber, E. O.; Enders D.; Eichenauer, H.; Weuster, P. *Tetrahedron Lett.* **1978**, 3691.

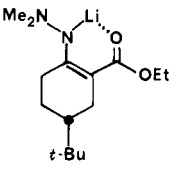
is coordinated to one anion in an η^4 fashion and to the other in an η^1 fashion. The Li–NMe_2 contacts are short relative to values reported for Li–TMEDA complexes.[18] The four atoms C1, C2, N7, and N8 are planar with a mean deviation of 0.01 Å, but the terminal dimethylamino group is twisted out of this plane. The η^4 coordinated Li is 1.64 Å from this plane, and the η^1 coordinated Li is 0.5 Å from the plane. Each Li connects two of these planes, one in an η^1 fashion and one in an η^4 fashion. The angle between these two planes is 111°.

Discussion

Elegant spectroscopic studies by Bergbreiter, Fraser, Newcomb, Enders, and others have elucidated some of the structural features of the metalated Schiff's base derivatives.[4,17] Early hypotheses supported chelation and orbital symmetry effects to explain the strong preference (up to 4.5 kcal) for the substituent on the imine nitrogen atom to orient syn to the carbanionic carbon. However, in 1980 Fraser, Houk, and co-workers demonstrated theoretically that most if not all of the observed thermodynamic preference for syn orientation in metalated Schiff's base derivatives could be explained by electron-repulsion considerations.[19] Consistent with several early postulates and more recent predictions by Enders,[20] anion **25** exhibits a carbon–lithium interaction, although the primary (shortest) lithium contact appears to be an η^1-interaction at nitrogen. We might begin to speculate that at least some of the preference for syn orientation arises from the ensuing superior η^4 (6 electron) interaction with the lithium atom of a neighboring molecule. It is interesting to note that syn orientation selectivities in lithiated aldehyde dimethylhydrazones are dramatically eroded in highly polar media.[21]

The anions derived from 2,6-disubstituted cyclohexanone hydrazones appear to alkylate axially with the residing methyl groups at the α' carbons pseudoaxially disposed. The origin of the allylic ($A_{1,3}$) strain forcing these conformational biases is attributed to the disposition of the η^1 nitrogen-bound lithium and its coordination sphere. Preliminary X-ray crystallographic data was obtained for lithiated 2-methylcyclohexanone dimethylhydrazone i. Although significant disorder and partial occupancy of lattice-bound THF precluded acceptable refinement, we were able to show that the atomic coordinates were as depicted in Figure 2. Anion i proves to be an extended array with alternating η^1 and η^4 lithium interactions in analogy to **25**. However, it exists in the opposite half-chair conformation. We tentatively note that the oberved cis alkylations of anion i may proceed axially on the face *opposite* to the η^4 bound lithium.

By comparison of the structure of **25** to the tetrameric enolate crystal structures elucidated by Seebach and Dunitz,[22] the most dramatic difference appears to be that the two faces of the π system of **25** are sterically differentiated by virtue of the η^4 coordination of lithium not found in the enolate structures. Accordingly, the origins of the axial alkylation selectivities might be related to coordination-face selectivity (and in turn to the syn selectivity[23]). The substitution of a cyano or thiomethyl moiety at the carbanionic carbon presumably would exert only moderate steric inhibitions on the syn orientation of the dimethylamino group. However, a carbomethoxy group in the 2-position might force the dimethylamino group anti by virtue of stabilized chelate ii. Loss of face differentiation of the dissociated oligomer could eliminate the high axial alkylation selectivity.



ii

We were provided some authority to compare solution and solid-state structures of lithiated hydrazones from an osmometric molecular weight determination at room temperature that showed **25** to be oligomeric in tetrahydrofuran with an average molecular weight of 515 amu (3.5 subunits). Although solubility problems precluded a study of a dependence of the molecular weight on temperature, *the alkylation stereoselectivities were essentially invariant over a 100-fold change in concentration.* Combining this result with the almost *complete* independence of stereoselectivity on the nature of the metal counterion and solvent (an independence that initially seemed attractive in light of the solvent-free oligomeric solid-state structure of **25**), we conclude that the monomer–oligomer distributions play insignificant roles in determining alkylation stereochemistries.

The molecular weight determination of **25** and alkylation solvent independencies underscore the possibility that the major structures in solution may be solvent-free tetramers. Inspection of molecular models indicates that cyclic tetramers with alternating η^1–η^4 lithium contacts analogous to **25** are quite plausible and would have one of the two faces in each of the subunits sterically inaccessible to incoming electrophiles. If we tentatively postulate that tetrameric intermediates are determinant of the high axial alkylation selectivities, there are still a number of pressing unanswered questions to be addressed: (1) What factors control tetramerization stereoselectivity? (The most appealing molecular model of a cyclic tetramer of **25** has subunits with alternating absolute configurations resulting in an S_4 rotational axis; however, three other diastereoisomers are plausible.) More specifically, what factors contribute to the implicit high lithium coordination face selectivities relative to stereocenters at the 4-position of the cyclohexane ring? (2) Why do metalated isopropylimines of substituted cyclohexanones exhibit high axial alkylation and syn orientation selectivities[23] despite the fact that an η^4 interaction with lithium is not possible? (3) Do Schiff's base derivatives really exhibit exceptional preferences for axial *deprotonation*[8] and if so why?

Experimental Section[24]

Single-Crystal X-ray Analysis of Lithium Anion 25. Suitable crystals of lithiated hydrazone **25** were grown at 40 °C in a sealed ampule containing 1.60 mmol of lithium diisopropylamide, 1.60 mmol of cyclohexanone dimethylhydrazone, and 1.60 mL of 55% THF in hexane. Anal. Calcd for $C_8H_{15}LiN_2$: C, 66.20; H, 10.20; Li, 4.69; N, 18.91. Found: C, 65.53; H, 10.15; Li, 4.90; N, 19.03. Osmometric molecular weight determination of **25** in THF at 25 °C: 515 amu (calcd for $C_8H_{15}LiN_2$, 146 amu).[24] A large crystal with approximate dimensions 0.8 × 0.5 × 0.3 mm was mounted in a Lindemann capillary. Preliminary X-ray photographs displayed orthorhombic symmetry and accurate lattice constants of a = 8.503 (1) Å, b = 11.247 (1) Å, and c = 19.244 (2) Å. Systematic extinctions were consistent with space group $P2_12_12_1$ and an estimated density indicated that two molecules of composition $C_8H_{15}N_2Li$ formed the asymmetric unit. All unique diffraction maxima with $2\theta \leq 114°$ were collected by using a variable-speed 1° ω-scan and graphite monochromated Cu Kα radiation (1.541 78 Å). Of the 1369 reflections measured in this way, 1136 (83%) were judged observed ($|F_o| \geq 3\sigma(F_o)$) and used in subsequent calculations. A phasing model was

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(24) Hydrazone alkylations, hydrolyses, and analyses were performed using detailed literature procedures with modifications as described in the text. Full experimental details are found in the supplementary material. Microanalyses were performed by Galbraith Laboratories, Knoxville, TN. Microanalysis and molecular weight determination of **25** were performed by Alfred Bernhardt Analytisches Laboratorien, Elbach, West Germany. ^1H NMR spectra were recorded on a Varian EM-390 90-MHz instrument or a Varian CFT-20 80-MHz instrument. ^{13}C NMR spectra were recorded on a JEOL FX-90Q spectrometer operating at 22.7 MHz. Gas chromatography was performed on a Varian 3700 chromatograph with digital integration. Solvents and reagents were dried and purified using standard protocol.

achieved uneventfully by a multisolution weighted tangent formula approach.[25] Hydrogen atoms were located on a ΔF synthesis following partial refinement of the heavy atoms. Block-diagonal least-squares refinements with anisotropic heavy atoms and isotropic hydrogens have converged to a conventional crystallographic residual of 0.043 for the observed reflections. Additional crystallographic details are available and are described in the supplementary material.

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Registry No. 1(enamine), 90941-38-1; **1**·Li, 90941-39-2; **2**(enamine), 90941-40-5; **2**·Li, 90941-41-6; **2**·Na, 90941-42-7; **2**·K, 90941-43-8; **3a**, 90941-44-9; **3b**, 15839-54-0; **4a**, 90941-45-0; **4b**, 15839-55-1; **5a**, 90941-46-1; **5b**, 22249-31-6; **6a**, 90941-47-2; **6b**, 22249-30-5; **7a**, 90941-48-3; **7b**, 90941-49-4; **8a**, 90941-50-7; **8b**, 90941-51-8; **9a**, 90941-52-9; **9b**, 90941-53-0; **10a**, 90941-54-1; **10b**, 90941-55-2; **11a**, 90941-56-3; **11b**, 90941-57-4; **12a**, 90941-58-5; **12b**, 90941-59-6; **13**, 5758-08-7; **14**, 90941-60-9; **15**, 90941-61-0; **16**, 90941-62-1; **17a**, 58911-79-8; **17b**, 766-43-8; **18a**, 66930-26-5; **18b**, 766-42-7; **19a**, 90941-63-2; **19b**, 90941-64-3; **20a**, 90941-65-4; **20b**, 90941-66-5; **21a**, 90941-67-6; **21b**, 60774-42-7; **22a**, 90941-68-7; **22b**, 60774-43-8; **23a**, 90941-69-8; **23b**, 73751-60-7; **24a**, 90941-70-1; **24b**, 73751-61-8; **25**, 66930-59-4.

Supplementary Material Available: Procedures for the characterization, alkylation, and stereochemical analysis of substituted cyclohexanone dimethylhydrazones and tables of fractional coordinates, bond distances, bond angles, and observed and calculated structure factors for lithiated hydrazone **25** (24 pages). Ordering information is given on any current masthead page.

(25) All crystallographic calculations were done on a PRIME 850 computer operated by the Cornell Chemistry Computing Facility. Principal programs employed were: REDUCE and UNIQUE, data reduction programs by M. E. Leonowicz, Cornell University, 1978; MULTAN78 and -80, a system of computer programs for the automatic solution of crystal structures from X-ray diffraction data (locally modified to perform all Fourier calculations including Patterson syntheses) written by P. Main, S. E. Hull, L. Lessinger, G. Germain, J. P. DeClercq, and M. M. Woolfson, University of York, England, 1978; BLS78A, an anisotropic block-diagonal least-squares refinement written by K. Hirotsu and E. Arnold, Cornell University, 1980; PLUTO78, a crystallographic illustration program by W. D. S. Motherwell, Cambridge, Crystallographic Data Centre, 1978; and BOND, a program to calculate molecular parameters and prepare tables written by K. Hirotsu, Cornell University.

Nucleophilic Reactivity toward Acetyl Chloride in Water[1]

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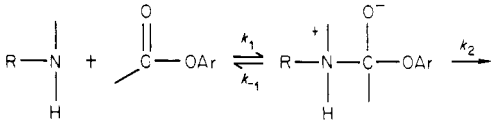
Contribution No. 1485 from the Graduate Department of Biochemistry, Brandeis University, Waltham, Massachusetts 02254. *Received February 6, 1984. Revised Manuscript Received March 26, 1984*

Abstract: Rate constant ratios for the reactions of acetyl chloride with nucleophilic reagents in water containing 2.5% (v/v) dioxane were determined by product analysis. The rate constants show a small dependence on the basicity of primary amines, with $\beta_{nuc} = 0.25$, and are assigned to rate-limiting attack of the nucleophile. Pyridines with $pK_a > 5$ behave similarly, with $\beta_{nuc} = 0.24$, but less basic pyridines react more slowly. Several "α-effect" amines and anionic oxygen nucleophiles show small rate enhancements that are attributed to increases in the rate of nucleophilic attack. The rate constants do not fit the N_+ correlation equation, and it is concluded that the reactions of nucleophilic reagents with acyl compounds are not satisfactorily correlated by simple modifications of this equation.

Rate constants for the uncatalyzed reactions of amines with acetate esters follow a biphasic dependence on amine basicity, with a slope of $\beta_{nuc} = 0.9 \pm 0.1$ that levels off sharply to a much smaller slope in plots of log k against pK_a for the aminolysis of a series of substituted phenyl acetates.[2] The change in slope occurs when the attacking amine is ~5 pK units more basic than the leaving phenolate anion. After an initial incorrect assignment, because it was not appreciated that proton-transfer steps could control the direction of breakdown of the tetrahedral addition intermediate,[2] the reactions with $\beta_{nuc} = 0.9$ were assigned to rate-limiting breakdown of the addition intermediate (k_2, eq 1), and the smaller slope was assigned to rate-limiting attack of the amine (k_1).[3]



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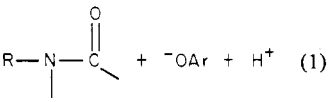

(1)

The experiments reported here were carried out to determine the value of β_{nuc} for rate-limiting attack of amines on acetate derivatives. The value of $\beta_{nuc} = 0.9 \pm 0.1$ for rate-limiting breakdown of the intermediate is well established and is consistent with the expected amount of charge development on the nitrogen atom in the transition state for cleavage of the tetrahedral addition intermediate, **1**, but the range in which amine attack is rate limiting is too small to establish a reliable value of β_{nuc} for the attack of amines on acetate esters.[2] A value of $\beta_{nuc} = 0.2$–0.4 was estimated from the data for phenyl acetates,[3] and values in this range have been reported for reactions of basic amines with acetic anhydride,[4,5] methyl chloroformate,[6] diphenyl carbonates,[7] and penicillins.[8]

However, a computer-assisted analysis of rate constants for the aminolysis of phenyl acetates, based on the N_+ scale of nucleophilic reactivity for reactions with carbocations, led to the conclusion that the attack of amines on esters follows N_+ and has a larger

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