^{6}Li and ^{23}Na NMR Spectroscopic Studies of Metalated Hydrazone Cryptates. Effects of Ion Triplet Formation on the Stereochemistry of Alkylation

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Abstract: Effects of cryptand complexing agents on the structure and reactivity of metalated *N,N*-dimethylhydrazones is described. Cyano-stabilized lithiated hydrazones are shown by ^{6}Li NMR spectroscopy to form 1:1 complexes with C[2.1.1] (C[2.1.1] = 4,7,13,18-tetraoxa-1,10-diazabicyclo[8.5.5]eicosane). Carbomethoxy-stabilized and unstabilized lithiated hydrazones form structures in which only 50% of the lithium ions become complexed by C[2.1.1]. The ^{6}Li NMR spectral data are ascribed to the formation of anionic ion triplets of general structure $(R_2Li)^-/Li^+$C[2.1.1]. Temperature- and gegenion-dependent chemical shifts of all of the Li^+C[2.1.1] complexes indicate incomplete shielding of the encapsulated lithium ion from the surrounding medium and implicate equilibria between inclusive and exclusive cryptate structural forms. The structures of cyano- and carbomethoxy-stabilized natriated hydrazones in the absence and presence of C[2.2.2] (C[2.2.2] = 4,7,13,16,21,24-hexaoxa-1,10-diazabicylo[8.8.8]hexacosane) were investigated by ^{23}Na NMR spectroscopy. Incomplete complexation and ion triplet formation was evidenced by the appearance of two resonances in approximate 1:1 ratios and further supported by preliminary ^{13}C NMR spectroscopic analysis showing that solutions of the metalated hydrazones containing 0.9 equiv of cryptand complexing agent displayed substantial concentrations of uncomplexed cryptand. The effects of the cryptands on the hydrazone alkylation stereoselectivities are discussed in the context of the spectroscopic data and proposed stereochemical models.

Metalated hydrazones, oximes, oximino ethers, and imines have become increasingly prominent in organic synthesis due to their relatively high reactivity, resistance to proton transfers and self-condensation, and propensity to alkylate exclusively on carbon.[1] They frequently exhibit substantially improved alkylation stereoselectivities and, unlike their ketone enolate counterparts, are readily adapted to asymmetric alkylations. To explain the often dramatic alkylation stereoselectivities, a number of groups have proposed working hypotheses in which the proximity of the lithium counterion relative to the azallylic fragment is pivotal in determining the stereochemical result.[2,3] To further understand the role of the metal counterions we have explored the effects of cryptands[4] on the structures and reactivities of metalated hydrazones and have uncovered a number of unexpected results.

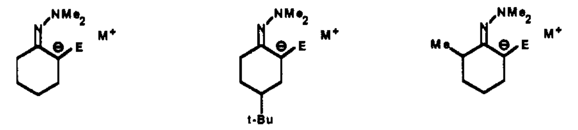
Described herein are ^{6}Li, ^{23}Na, and ^{13}C NMR spectroscopic studies of Li^+C[2.1.1] and Na^+C[2.2.2] cryptates derived from metalated hydrazones.[5] We will demonstrate that such reactive ambident anions show a strong propensity to form ion triplets of general formula i.[6-8] The Li^+C[2.1.1] counterions display temperature-dependent chemical shifts consistent with an equilibrium between inclusive (fully encapsulated) and exclusive (partially encapsulated) forms. Rate studies of lithiated hydrazone alkylations previously interpreted as supporting tetramer-to-monomer preequilibria will be discussed in light of an alternative, mathematically indistinguishable model based on tetramer-to-ion-triplet preequilibria. Overall, the results described herein illustrate the first application of ^{6}Li NMR spectroscopy to the study of lithium cryptates and highlight some of the complexities and limitations of cryptands as qualitative mechanistic probes.

$$\left[(\text{Hydrazone}^-)_2\text{M}^+\right]^{\ominus}\ \text{M}^{\oplus}\text{Cryptand}$$

i

Results

Preparation of Metalated Hydrazones. Lithium salts **1-Li–9-Li** were prepared as 0.12–0.14 M solutions in THF from the corresponding hydrazones[9] and analytically pure ethyllithium-^{6}*Li*.[10] The sodium salts **1-Na–6-Na** and potassium salts **2-K**, **3-K**, and **6-K** were prepared analogously from recrystallized sodium hexamethyldisilazide[11] and KH (respectively).



1-Li; E = CN, M = Li
1-Na; E = CN, M = Na

4-Li; E = COOMe, M = Li
4-Na; E = COOMe, M = Na

7-Li; E = H, M = Li

2-Li; E = CN, M = Li
2-Na; E = CN, M = Na
2-K; E = CN, M = K

5-Li; E = COOMe, M = Li
5-Na; E = COOMe, M = Na
5-K; E = COOMe, M = K

8-Li; E = H, M = Li

3-Li; E = CN, M = Li
3-Na; E = CN, M = Na
3-K; E = CN, M = K

6-Li; E = COOMe, M = Li
6-Na; E = COOMe, M = Na
6-K; E = COOMe, M = K

9-Li; E = H, M = Li

^{6}Li and ^{23}Na NMR Spectroscopy. Due to the absence of reports of ^{6}Li NMR spectroscopic studies of ^{6}Li cryptates[12-14] and the

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(5) C[2.1.1] = 4,7,13,18-tetraoxa-1,10-diazabicyclo[8.5.5]eicosane: C[2.2.2] = 4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo[8.8.8]hexacosane.

(6) The terms "ion triplet", "ion triple", "triple ion", and "triplet ion" have been used interchangeably to describe clusters of three ions. The clusters can be either anionic (e.g. $[R^-M^+R^-]^-$), neutral (e.g. $[R^-M^{2+}R^-]$; ref 7). or cationic (e.g. $[M^+R^-M^+]^+$; ref 8). Throughout this manuscript we will refer only to the anionic forms and use only the "ion triplet" nomenclature. Such anionic ion triplets bear some similarity to a variety of high valent "ate" complexes of groups 2 and 12–14.

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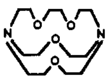
Table I. ^{6}Li NMR Spectroscopic Data[a]

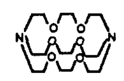
				chemical shifts ($\nu_{1/2}$, Hz)		
compd	entry	equiv. of C[2.1.1]	temp, °C	hyd-Li	Li$^+$C[2.1.1]	other
^{6}LiBPh$_4$	1	0	21	0.41 (1)		
	2	0	−77	0.42 (1)		
	3	0.5	22	0.44 (2)	0.37 (1)	
	4	3.4	22		0.38 (1)	
	5	3.0	−77		0.34 (1)	
1-Li	6	0	22	1.70 (1)		
	7	0.56	25	1.86 (2)	0.57 (2)	
	8	0.56	−93	1.35 (7)	0.31 (1)	
	9	2.0	20		0.54 (1)	
2-Li	10	0	25	1.59 (16)		
	11	0.56	25	1.85 (4)	0.57 (1)	
	12	1.1	26		0.57 (2)	
	13	2.0	−77		0.35 (1)	
3-Li	14	0	21	1.72 (4)		
	15	0.6	21	1.65 (4)	0.66 (1)	
	16	1.8	21		0.55 (1)	
	17	1.8	−77		0.32 (1)	
4-Li	18	0	19	1.98 (1)		
	19	0.6	21		0.48 (1)	2.44 (19)
	20	2.0	19		0.54 (2)	2.72 (24)
	21	1.8	−78		0.30 (1)	2.94 (1)
5-Li	22	0	26	2.09 (5)		
	23	0	−50	2.06 (3)		
	24	0.6	24		0.54 (1)	2.00 (63)
	25	1.2	24		0.53 (2)	2.90 (10) 1.50 (5)
	26	1.8	−78		0.29 (1)	2.95 (1) 2.93 (1)
6-Li	27	0	21	2.08 (9)		
	28	0.6	−78	2.13 (5)	0.54 (4)	2.99 (8)
	29	2.0	21		0.52 (6)	3.00 (10) 1.53 (20)
	30	1.8	−78		0.31 (2)	3.05 (2) 2.96 (2)
7-Li	31	0	−77	1.32 (37)		
	32	0.38	−78		0.29 (1)	2.34 (56)
	33	2.0	25		0.57 (1)	1.45 (3)
	34	1.8	−77		0.33 (1)	2.63 (1)
8-Li	35	0	−77	1.36 (27)		
	36	0.48	27		0.58 (2)	1.32 (8)
	37	2.6	26		0.55 (1)	1.50 (35)
	38	1.8	−77		0.33 (1)	2.68 (2)
9-Li	39	0	−78	0.93 (31)		
	40	1.8	25		0.54 (6)	1.39 (6)
	41	1.9	−78		0.34 (1)	1.12 (1) 1.53 (6)

[a] Spectra were recorded on 0.14–0.19 M solutions of lithiated hydrazones in tetrahydrofuran. Chemical shifts are reported relative to 0.30 M ^{6}LiCl/MeOH set at 0.0 ppm.

lack of a universally accepted chemical shift scale for alkali-metal NMR spectra,[15] we established a ^{6}Li chemical shift scale by arbitrarily setting the resonance of 0.30 M ^{6}LiCl in methanol at 20 °C[16] to 0.0 ppm with a secondary 0.35 M LiI/MeOH reference at 0.86 ppm as described previously.[17–19] On this scale, a spectrum of 0.026 M ^{6}LiBPh$_4$ in THF at 20 °C showed a sharp singlet at 0.41 ppm. In the presence of 0.5 equiv of C[2.1.1] cryptand,[5] ^{6}LiBPh$_4$ displayed the original singlet along with a new resonance at 0.37 ppm (Table I). In the presence of >1.0 equiv of C[2.1.1], only the latter resonance could be observed. The chemical shift of the complexed form underwent a minor (0.04 ppm) upfield shift upon cooling the probe to −77.5 °C.[16,19] On the basis of previous ^{7}Li NMR spectroscopic studies of ^{7}Li$^+$C[2.1.1] cryptates showing temperature, counterion, and solvent-independent chemical shifts,[12] the resonance at 0.37 ppm is assigned to the inclusive (totally encapsulated) complex of the Li$^+$ ion.



C[2.1.1]



C[2.2.2]

^{23}Na NMR spectra were calibrated to 0.25 M NaCl/D$_2$O reference set at 0.0 ppm according to the protocol of Popov et al.[20] On this scale, a 0.15 M solution of NaBPh$_4$ at 20 °C resonates at −7.13 ppm ($\nu_{1/2}$ = 28 Hz). The Na$^+$C[2.2.2] cryptate derived by treatment of NaBPh$_4$ with 1.3 equiv of C[2.2.2][5] displayed a temperature-independent resonance at −11.33 ppm (Table II). The narrow peak width ($\nu_{1/2}$ = 41 Hz), the temperature independence, and the shielding were consistent with an inclusive complex.[20,21]

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(12) ^{7}Li NMR spectroscopic studies of X$^-$/Li$^+$C[2.1.1] salts by Popov and co-workers (ref 13) have uncovered solvent-, temperature-, and counterion-independent chemical shifts. However, Hubert and co-workers recently reported that a variety of Li$^+$C[2.1.1] salts in THF display variable ^{7}Li chemical shifts, which they ascribed to ion pairing and the anisotropic effects of the aromatic gegenions (ref 14).

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Table II. ^{23}Na NMR Spectroscopic Data Recorded at 20 ± 0.3 °C^a

compd	entry	equiv of C[2.2.2]	chemical shifts ($\nu_{1/2}$) Hyd-Na	chemical shifts ($\nu_{1/2}$) Na$^+$C[2.2.2]
^{23}NaBPh$_4$	1	0.5	−7.13 (28)^c	−11.34 (42)
	2	1.3		−11.33 (41)
1-Na	3	0	6.83 (890)	
	4	0.5		−11.13 (120)^b
	5	1.5		−10.91 (130)^b
2-Na	6	0	7.90 (1210)	
	7	2.0		−10.73 (170)^b
3-Na	8	0	7.27 (750)	
	9	1.6		−10.77 (170)^b
4-Na	10	0	6.55 (830)	
	11	0.5		−11.16 (120)^b
	12	2.0		−11.14 (940)^b
5-Na	13	0	6.82 (1530)	
	14	0.5		−11.13 (177)^b
	15	2.0		−11.34 (940)^b
6-Na	16	0	6.30 (920)	
	17	0.5		−11.00 (1070)^b
	18	1.6		−10.70 (1100)^b

^{a}Spectra were recorded on 0.12–0.14 M solutions of natriated hydrazones in tetrahydrofuran. Chemical shifts are relative to a 0.25 M NaCl/D$_2$O external reference set at 0.0 ppm. ^{b}Chemical shifts and peak widths ($\Delta\nu_{1/2}$) refer to the sharp Na$^+$C[2.2.2] resonance. In each case, a resonance at approximately the same chemical shift and greater than 2000 Hz peak width was superimposed (cf. Figure 2B). ^{c}Shift corresponds to uncomplexed NaBPh$_4$.

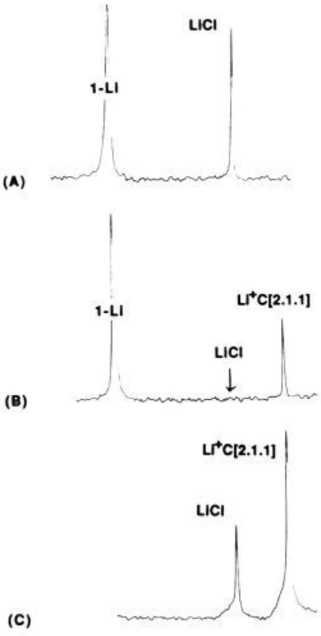


Figure 1. ^{6}Li NMR spectra of cyano-substituted lithiated hydrazone **1-Li**. Detailed chemical shift and peak width data are listed in Table I. Spectra were recorded in THF under the following conditions: (A) 0.19 M, 22 °C; (B) 0.19 M, 0.56 equiv of C[2.1.1], 25 °C; (C) 0.19 M, 2.0 equiv of C[2.1.1], 20 °C.

Cyano-Substituted Metalated Hydrazones. We first investigated the ^{6}Li NMR spectroscopic behavior of the cyano-stabilized lithium salts **1-Li–3-Li** (Table I). In the absence of C[2.1.1], **1-Li–3-Li** each displayed a relatively broad resonance in the downfield region of the spectra (cf. Figure 1A). Upon cooling the probe, severe additional broadening occurred with no evidence of a coalescence. The broadening proved to be characteristic of certain classes of metalated hydrazones and is reflected by the scarcity of ^{6}Li or ^{7}Li NMR spectroscopic studies of lithiated hydrazones.[17,18] Although we do not understand its origins, we suspect that the broadening may derive from strong Li–π interactions[22] and a propensity to form polymeric structures evident in the solid-state structures.[9,23]

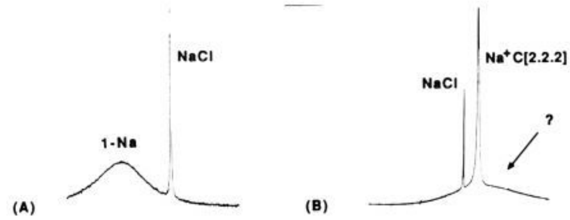
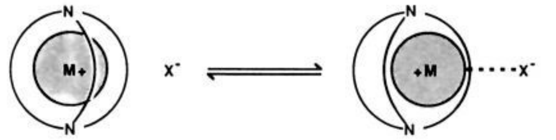


Figure 2. ^{23}Na NMR spectra of natriated hydrazone **1-Na**. Detailed chemical shift and peak width data are listed in Table II. Spectra were recorded in THF under the following conditions: (A) 0.14 M, 21 °C; (B) 0.14 M, 2.0 equiv of C[2.2.2], 21 °C.

Partial and complete complexation of **1-Li–3-Li** was observed upon addition of 0.6 and ≥1.0 equiv of C[2.1.1], respectively (Figure 1B,C). However, a distinct variation in the ^{6}Li resonances relative to the BPh$_4^-$/^{6}Li$^+$C[2.1.1] cryptate indicated that the complexed Li$^+$ ions were not fully shielded from the influence of the medium and anionic fragment. Upon cooling the NMR probe to −77.5 °C, the cryptate ^{6}Li resonances shifted upfield to a common chemical shift (0.32 ppm) that corresponded to the temperature-independent chemical shift of the BPh$_4^-$/^{6}Li$^+$C[2.1.1] cryptate.

Several groups have reported equilibria between inclusive and exclusive complexed metal cryptates (eq 1) when poorly matched cavity dimensions of the cryptand and the cation radius lead to a nonoptimized fit.[24-33] The exclusive structural forms have been



(1)

observed crystallographically for Mg^{2+}C[2.1.1],[24] Na$^+$C[2.1.1],[25] and K$^+$C[2.2.1][26] cryptates[27] and implicated as solution species for cryptates such as Li$^+$C[2.2.2],[28] Pb^{2+}C[2.1.1],[29] K$^+$C[2.2.1],[30] Cs$^+$C[2.2.2],[31] among others.[32,33] The inclusive-exclusive cryptate equilibria are characterized by temperature-dependent alkali-metal chemical shifts, which converge to common values at reduced temperatures. Preferences for the inclusive form at low temperatures have been ascribed to the large negative entropy of encapsulation.[4]

Thus, the spectroscopic properties of C[2.1.1] cryptates derived from **1-Li-3-Li** are fully consistent with a delicately balanced

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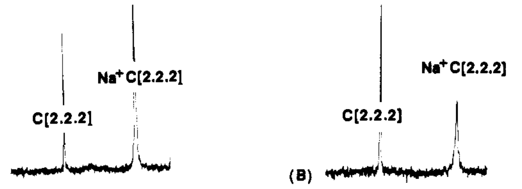


Figure 3. Partial ^{13}C NMR spectra of natriated hydrazones. Spectra were recorded in THF under the following conditions: (A) 0.12 M in **1-Na**, 0.9 equiv. of C[2.2.2], -77 °C; (B) 0.12 M in **4-Na**, 0.9 equiv of C[2.2.2], -79 °C.

equilibrium between inclusive and exclusive complexation. To the best of our knowledge, however, this is unprecedented for $Li^+C[2.1.1]$ cryptates, which have been shown to be among the most tightly bound cryptates reported to date. Such counterion and temperature-dependent shifts were observed for all of the lithiated hydrazone cryptates investigated (vide infra).[12]

The corresponding sodium derivatives **1-Na**–**3-Na** provided distinctly different results (Figure 2A; Table II). At room temperature in THF each displayed a single broad resonance in their ^{23}Na NMR spectra (Figure 2A). Addition of 0.5 equiv of C[2.2.2] afforded spectra containing a single, extremely broad resonance and a sharp resonance superimposed. The sharp resonances appeared within a narrow chemical shift range showing reasonable correspondence to the observed shift of the $BPh_4^-/Na^+C[2.2.2]$ cryptate. Most importantly, the spectra remained unchanged upon addition of up to 3.0 equiv of C[2.2.2] (Figure 2B). Integration by triangulation showed the peak ratios to be approximately 1:1. Cooling the probe caused further broadening of both resonances.

Similar phenomena observed in many of the earliest ^{23}Na NMR spectroscopic studies were attributed to ^{23}Na nuclei in two distinct environments.[21] However, it was subsequently shown that, in many instances, the broad resonance was due instead to the spin 3/2 transition deriving from the quadrupolar interaction at the ^{23}Na center. To determine which of the two models accurately describes the sodium hydrazone cyptates, we carried out ^{13}C NMR spectroscopic studies. Because of the significant temperature-dependent broadening of the hydrazone, cryptand, and cryptate resonances, detailed ^{13}C NMR studies were not practical. However, a clearly resolved set of methylene resonances corresponding to uncomplexed C[2.2.2] provided an excellent probe of the extent of complexation. A mixture of **1-Na** and 0.9 equiv of C[2.2.2] exhibited approximately equimolar concentrations of C[2.2.2] and $Na^+C[2.2.2]$ (Figures 3A). Thus, only 50% of the Na^+ ions of **1-Na**–**3-Na** become complexed by the C[2.2.2]. The 1:1 stoichiometries of complexed and uncomplexed Na^+ ions are indicative of ion triplets of general structure i. The $Na^+C[2.2.2]$ cryptate ^{23}Na chemical shifts show some dependence on the anionic counterion. Contact between the ion triplet fragment and the cryptate was further evidenced by the broadening of the $Na^+C[2.2.2]$ resonance, which could be ascribed to a nonspherically symmetric coordination shell of an exclusive form.[21,22] Further speculation on the structural details of the triplet fragment will be deferred until the Discussion.

Carbomethoxy-Substituted Metalated Hydrazones. We next turned to the carbomethoxy-substituted metalated hydrazones **4**–**6** (Table I). In contrast to the corresponding cyano-substituted and unsubstituted analogues (vide infra), **4-Li**–**6-Li** displayed sharp resonances over the temperature range between -90 and 20 °C. In the presence of C[2.1.1] we observed evidence of ion triplet structures in which the cryptate counterion did not appear to be fully encapsulated. For example, addition of 0.6 equiv of C[2.1.1] to a THF solution of **4-Li** provided a ^6Li NMR spectrum (-77 °C) that displayed a pair of resonances in a 1:1 ratio corresponding to complexed and uncomplexed lithium ions. The spectra remained unchanged upon addition of up to 3 equiv of C[2.1.1] (Figure 4A). The resonance assigned to the $Li^+C[2.1.1]$ fragment displayed a temperature-dependent chemical shift consistent with an exclusive–inclusive equilibrium as described above. The uncomplexed lithium ion resonated substantially downfield at 2.72 ppm and sharpened considerably at reduced probe temperatures (cf. Table I; entries 20, 21).

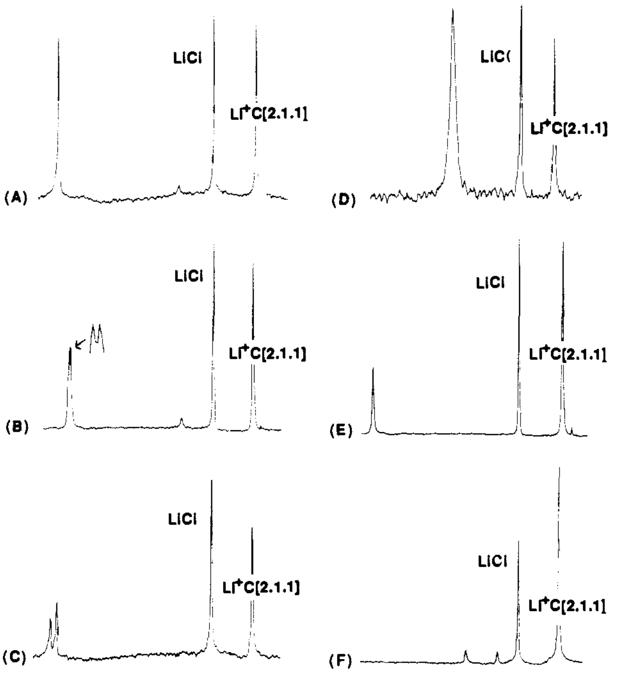


Figure 4. ^6Li NMR spectra of lithiated hydrazones. Detailed chemical shift and peak width data are listed in Table I. Spectra were recorded in THF under the following conditions: (A) 0.14 M in **4-Li**, 1.8 equiv of C[2.1.1], -78 °C; (B) 0.14 M in **5-Li**, 1.8 equiv of C[2.1.1], -78 °C; (C) 0.14 M in **6-Li**, 1.8 equiv of C[2.1.1], -77 °C; (D) 0.17 M in **7-Li**, 2.0 equiv of C[2.1.1], 21 °C; (E) 0.13 M in **7-Li**, 1.8 equiv of C[2.1.1], -77 °C; (F) 0.14 M in **9-Li**, 1.9 equiv of C[2.1.1], -78 °C.

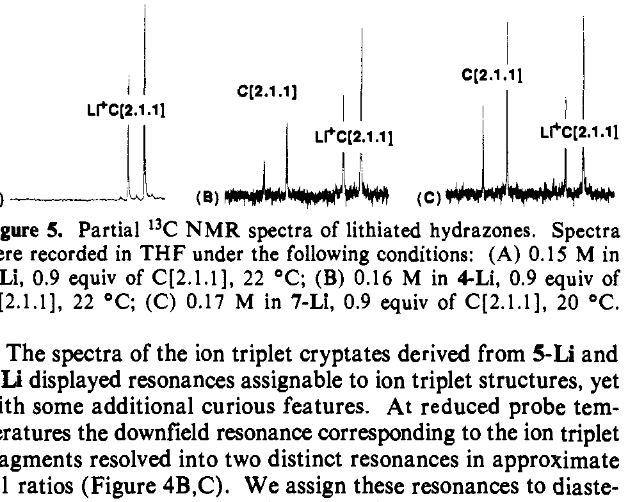


Figure 5. Partial ^{13}C NMR spectra of lithiated hydrazones. Spectra were recorded in THF under the following conditions: (A) 0.15 M in **1-Li**, 0.9 equiv of C[2.1.1], 22 °C; (B) 0.16 M in **4-Li**, 0.9 equiv of C[2.1.1], 22 °C; (C) 0.17 M in **7-Li**, 0.9 equiv of C[2.1.1], 20 °C.

The spectra of the ion triplet cryptates derived from **5-Li** and **6-Li** displayed resonances assignable to ion triplet structures, yet with some additional curious features. At reduced probe temperatures the downfield resonance corresponding to the ion triplet fragments resolved into two distinct resonances in approximate 1:1 ratios (Figure 4B,C). We assign these resonances to diastereomeric fragments resulting from the chiral centers on the carbon frameworks. Further structural details will be described in the Discussion.

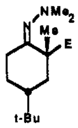
^{13}C NMR spectroscopic analyses on the lithiated hydrazones again proved problematic because of the solvent resonances and the temperature-dependent peak broadenings of the cryptate and hydrazone resonances. However, by focusing on the well resolved C1 and C7 methylene resonances of the uncomplexed C[2.1.1] and $Li^+C[2.1.1]$, the ion triplet assignment gained additional support. Thus, a mixture of **4-Li** and 0.9 equiv of C[2.1.1] showed approximately equimolar concentrations of C[2.1.1] and $Li^+C[2.1.1]$ (Figure 5B). As a comparison, a mixture of the cyano derivative **1-Li** and 0.9 equiv of C[2.1.1] showed no evidence of free cryptand (Figure 5A).

The spectral properties of **4-Na**–**6-Na** were similar to those of the analogous lithium salts (Table II). In the absence of C[2.2.2], the ^{23}Na NMR spectra (20 °C) each showed a single resonance that line broadened at reduced temperatures. In the presence of 0.5 equiv of C[2.2.2], sharp resonances assigned to the $Na^+C[2.2.2]$ ions were superimposed upon severely broadened resonances barely observable above the base line. Addition of up to 2.0 equiv of C[2.2.2] caused no further change in the crudely approximated 1:1 peak ratio previously observed for **1-Na** shown in Figure 2B. Once again, ^{13}C NMR analysis of **4-Na** in the presence of 0.9 equiv of C[2.2.2] showed substantial concentrations of free C[2.2.2] (Figure 3B), confirming the incomplete complexation.

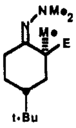
Unsubstituted Lithiated Hydrazones. The last class of metalated hydrazone to be studied included the nonstabilized unsubstituted cases. Since the sodium and potassium derivatives have received very little attention in the synthesis literature to date, we restricted our focus to lithiated hydrazones **7-Li–9-Li** (Table I; Figure 4). In the absence of cryptands, each displayed a single broad resonance in the ^{6}Li NMR spectrum at ambient temperatures that broadened severely upon cooling. Again, the ^{6}Li NMR spectra of **7-Li–9-Li** at ambient temperature were quite similar. In the presence of 0.5–3.0 equiv of C[2.1.1], each showed the general properties consistent with ion triplet structures as typified by spectrum D in Figure 4, yet with relatively large and upfield shifted triplet fragment resonances.[34] At reduced probe temperatures, the spectra of **7-Li** and **9-Li** showed substantial downfield shifting of the triplet resonance to approximately the same chemical shift as seen for the carbomethoxy deriviatives (Figure 4E). The origin of the strong temperature dependence is not clear at this time. The ion triplet structures were supported by a ^{13}C NMR spectroscopic analysis showing free cryptand in samples of **7-Li** containing 0.9 equiv of added C[2.1.1] (Figure 5C).

The spectral properties of **9-Li** in the presence of excess C[2.1.1] showed odd features, which we do not yet understand. At ambient temperature the general spectral features of the ion triplet formulation were observed (Table I). However, at low temperatures relatively minor resonances at 1.53 and 1.12 ppm appeared, which cannot be assigned at present, along with the $Li^{+}C[2.1.1]$ resonance (Figure 4F). We suspect that differences in the spectroscopic properties of **9-Li** reside in the severe steric hindrance imparted by the methyl substituent.

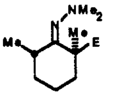
Stereochemistry of Alkylation. The effects of the cryptand-mediated structural changes on the alkylation stereochemistries of the metalated hydrazones are listed in Table III. The alkylations were effected at −78 °C with NMR samples immediately following the spectroscopic analysis to insure a maximum correlation between structure and reactivity. The methylated hydrazones **10–21** have been fully characterized.[9] The previously reported selectivities in the absence of cryptands were reproduced during the course of this study with minor corrections noted.[35] Although the structures of cryptates derived from potassium salts **2-K**, **3-K**, **5-K**, and **6-K** were not studied spectroscopically, the effects of the C[2.2.2] on their alkylation selectivities have been included.



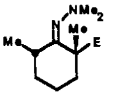
10; E = CN
14; E = COOMe
18; E = H



11; E = CN
15; E = COOMe
19; E = H



12; E = CN
16; E = COOMe
20; E = H



13; E = CN
17; E = COOMe
21; E = H

Overall, the cyano-substituted and unsubstituted metalated hydrazones in the presence of the cryptands showed distinct losses in alkylation stereochemistry, with the 2-methyl-substituted substrates exhibiting the most substantial changes. In contrast, the carbomethoxy-substituted cases exhibited virtually no cryptand-dependent selectivity changes. In the case of the cryptates of **5-Li** and **6-Li**, the participation of the cryptand was readily apparent due to approximately 30- and 2-fold alkylation rate increases, respectively. Alkylation rates of the cyano-substituted and unsubstituted metalated hydrazone were too high to conveniently monitor. The alkylation selectivities of **3-Li** proved to be highly variable and thus are not listed.[35] The variability appeared to arise from changes in the kinetic selectivity rather than from equilibration pathways, but remained poorly understood even after systematic studies of the effects of anion aging,[36] lithium halide[37] and secondary amine impurities,[38] and changes in the percent conversion.[39] Oddly enough, the corresponding sodium and potassium salts **3-Na** and **3-K** provided highly reproducible results. A facile thermal epimerization of *cis*-2,5-dimethylcyclohexanone *N*,*N*-dimethylhydrazone (**20**) described in the earlier studies[9] renders the reported selectivities for **9-Li** to be only crudely approximated lower limits.

Table III. Effects of Cryptands on the Stereochemistry of Metalated Hydrazone Alkylation

compd	entry	equiv of C[2.1.1]	equiv of C[2.2.2]	products	selectivity[a]
2-Li	1	0		**10/11**	30:1
	2	1.8		**10/11**	25:1
2-Na	3		0	**10/11**	30:1
	4		1.5	**10/11**	25:1
2-K	5		0	**10/11**	30:1
	6		1.5	**10/11**	24:1
3-Li	7	0		**12/13**	[b]
	8	2.8		**12/13**	1:2
3-Na	9		0	**12/13**	8:1
	10		1.3	**12/13**	1:2
3-K	11		0	**12/13**	9:1
	12		1.3	**12/13**	1:1
5-Li	13	0		**14/15**	9:1[c]
	14	2.0		**14/15**	9:1
5-Na	15		0	**14/15**	7:1[c]
	16		1.5	**14/15**	7:1
5-K	17		0	**14/15**	9:1[c]
	18		1.5	**14/15**	8:1[c]
6-Li	19	0		**16/17**	6:1[c]
	20	2.5		**16/17**	5:1[c]
6-Na	21		0	**16/17**	5:1
	22		0.5	**16/17**	5:1
6-K	23		0	**16/17**	4:1
	24		1.5	**16/17**	4:1
8-Li	25	0		**18/19**	11:1
	26	2.4		**18/19**	6:1
9-Li	27	0		**20/21**	10:1
	28	1.1		**20/21**	3:1

[a] All alkylations proceeded to greater than 86% conversion unless otherwise stated. Selectivities and product structures were determined as described previously (ref 9). [b] Alkylation selectivities proved uncontrollable. [c] Some alkylations were very slow at −78 °C. Percent conversions were as follows: entry 13, 40% in 4 h; entry 15, 40% in 1 h; entry 17, 76% in 4 h; entry 18, 10% in 3 h; entry 19, 30% in 6.5 h; entry 20, 73% in 6.5 h; entry 23, 40% in 4.5 h; entry 24, 67% in 4.5 h.

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(34) The origin of this phenomena is not clear at this time. However, it could derive from a temperature-dependent equilibrium between the ion triplet cryptate and another species. Time averaging of the additional species and the triplet fragment (but not the $Li^{+}C[2.1.1]$ portion) could produce such an effect.

(35) We had previously determined the alkylation selectivity of **3-K**, yet inadvertantly reported it as **3-Li**. Adjustments of the alkylation selectivities of **8-Li** and **9-Li** appeared previously (ref 3 and 9).

(36) Dramatic aging effects on the stereochemistry of lithiated imine alkylation have been observed. Meyers, A. I.; Williams, D. R.; Erickson, G. W.; White, S.; Druelinger, M. *J. Am. Chem. Soc.* **1981**, *103*, 3081.

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(38) Evidence of secondary amine participation in reactions of N-lithiated species: (a) Strazewski, P.; Tamm, C. *Helv. Chim. Acta* **1986**, *69*, 1041. (b) Seebach, D.; Aebi, J. D. *Helv. Chim. Acta* **1985**, *68*, 1507. (c) Seebach, D.; Miller, D. D.; Müller, S.; Weber, T. *Helv. Chim. Acta* **1985**, *68*, 949. (d) Seebach, D.; Laube, T.; Dunitz, J. D. *Helv. Chim. Acta* **1985**, *68*, 1373. (e) Duhamel, L.; Fouquay, S.; Plaquevent, J.-C. *Tetrahedron Lett.* **1986**, *27*, 4975. (f) Narita, T.; Imai, N.: Tsurata, T. *Bull. Soc. Chem. Jpn.* **1973**, *46*, 1242. (g) Creger, P. L. *J. Am. Chem. Soc.* **1970**, *92*, 1396. (h) Pfeffer, P. E.; Silbert, L. S.; Chirinko, J. M., Jr. *J. Org. Chem.* **1972**, *37*, 451. (i) Regan, A. C.; Staunton. J. *J. Chem. Soc., Chem. Commun.* **1983**, 764.

(39) The intervention of mixed aggregates generated during the course of a reaction can have dramatic influences on the reaction selectivity as a function of percent conversion. See, for example: Jackman, L. M.; Dunne, T. S. *J. Am. Chem. Soc.* **1985**, *107*, 2805. Seebach, D. In *Proceedings of the Robert A. Welch Foundation Conferences on Chemistry and Biochemistry*; Wiley: New York, 1984; p 93.

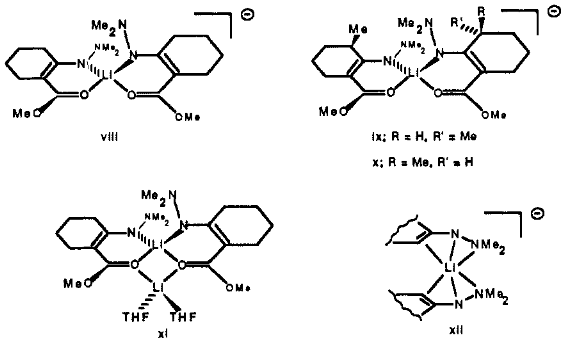
Discussion

Of the 18 different metalated hydrazones described herein only the cyano-substituted lithiated hydrazones **1-Li–3-Li** forfeited all of the metal counterion to the cryptand. All others exhibited spectral properties consistent with ion triplets bearing cryptate counterions of general structure i. Furthermore, we infer from the temperature- and substrate-dependent ^{6}Li chemical shifts of the $Li^+C[2.1.1]$ ions that none of the encapsulated Li^+ ions were fully shielded from the influence of the medium and anionic counterion. Additional studies will be required to delineate the details of the cation–anion interaction. Nonetheless, to the best of our knowledge, this represents important additional evidence of medium influences on the tightly bound $Li^+[2.1.1]$ cryptates.[12] The apparent increased resolution provided by observing the ^{6}Li rather than the ^{7}Li nucleus may prove advantageous in future studies of lithium cryptates.[40,41]

Without exception, the hydrazone sodium salts appeared to be converted to ion triplets upon treatment with C[2.2.2]. The apparent resistance of even the cyano-substituted cases to forfeit the sodium cation from the triplet fragment could simply be the result of a lower binding constant for the $Na^+C[2.2.2]$ cryptates relative to $Li^+C[2.1.1]$ cryptates.[4] In addition, calculations by Streitweiser have demonstrated that the azallylic fragment of oxime-stabilized carbanions should interact more strongly with Na^+ than Li^+.[42] The observed anion-dependent peak broadenings of the ^{23}Na cryptate resonances implicate distortion of the spherically symmetric Na^+ coordination spheres by metal–counterion contact.[21,22]

To understand the effects of ion triplet formation on the stereochemistry of alkylation we must first consider the possible structural variants of the triplet fragment. Despite the well-documented role of ion triplets in electrochemistry[43] originating from the seminal work of Fuoss in the 1930s,[44] as well as their importance in anionic polymerizations,[45] the vast literature detailing applications of organolithium reagents to organic synthesis contains little mention of them.

The most well characterized examples of organolithium-derived anionic ion triplets are the metalated β-dicarbonyls of general structure ii reported by Arnett,[46] Cambillau,[47] Raban,[48] Bordwell,[49] and Casabo.[50] Triplet ii bearing an alkali-metal cryptate counterion has been characterized in both the solution and solid state.[47,51] Other examples include peralkylated cyclohexadienyl salt iii characterized spectroscopically by Fraenkel and co-workers,[15] metalated methacrylonitrile dimer of ill-defined structure iv implicated by conductometric studies of Tsvetanov et al.[52] and the especially interesting mixed anionic and cationic ion triplet v characterized crystallographically by Eaborn and co-workers.[53] Most recently, Jackman and co-workers detected ion triplets vi and vii (eq 2 and 3) through ^{6}Li–^{15}N double-labeling spectroscopic studies and noted the potential importance of such species in polar (ionizing) media.[54]


viii

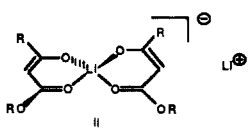
ix; R = H, R' = Me

x; R = Me, R' = H

xi

xii

Figure 6. Molecular structure of **4-Li**.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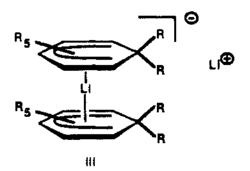
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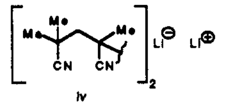
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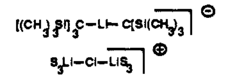
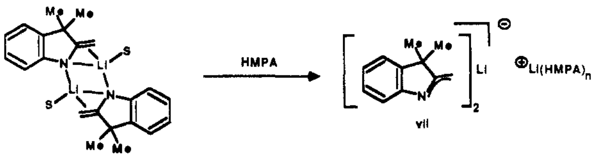

v

$$(\mathrm{Ph(i\text{-}Pr)N\text{-}Li\cdot THF})_2 \xrightarrow{\mathrm{HMPA}} (\mathrm{Ph(i\text{-}Pr)N\text{-}Li\text{-}N(i\text{-}Pr)Ph})^{\ominus}\ {}^{\oplus}\mathrm{Li(HMPA)}_n \qquad (2)$$

vi


(3)

vii

From the structures of metalated β-dicarbonyl compounds we assign the ion triplets of the carbomethoxy-substituted hydrazone salts as depicted by viii. The stereoisomers observed for **6-Li** would correspond to homo- and heterochiral ion triplets ix and x. Stereoisomers were also observed for **5-Li**. Of further note, the X-ray crystal structure of **4-Li** displayed structural form xi (Figure 6) in which one of the two chemically inequivalent lithium ions appeared to be precariously bound between the two carbonyl oxygens.[18,32] Colligative measurements on hydrocarbon solutions of **4-Li** showed evidence of further solvation in the presence of added THF. This phenomenon is consistent with a THF-concentration-dependent equilibrium between the neutral dimer xi and ion triplet viii.

The structural details of the triplets derived from the cyano-substituted sodium salts (**1-Na–3-Na**) and the unsubstituted lithium salts (**7-Li–9-Li**) are far less apparent. However, a common feature to many anionic ion triplets appears to be the capacity to form either chelate or π complexed (sandwich) structures. Some support for a sandwich structure such as xii comes from analogy with the solid-state structures of η^3-azallyllithium dimers.[55] Nonetheless, direct evidence on the structures

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(40) The quadrupole moment of ^{7}Li is approximately 100 times that of ^{6}Li. *The Multinuclear Approach to NMR Spectroscopy*; Lambert, J. B., Riddel, F. G., Ed.; Riedel: Holland, 1983. Wehrli, F. W. *J. Magn. Reson.* **1978**, *30*, 193.

(41) As an example of the increased resolution provided by ^{6}Li NMR spectroscopy, we found that the stereoisomeric ion triplets derived from **8-Li** did not resolve by ^{7}Li NMR spectroscopy on the same spectrometer.

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(54) Jackman, L. M.; Scarmoutzos, L. M.; Porter, W. *J. Am. Chem. Soc.* **1987**, *109*, 6524. Jackman, L. M.; Scarmoutzos, L. M.; Smith, B. D.; Williard, P. G. *J. Am. Chem. Soc.*, in press.

of the triplet fragments of metalated hydrazone cryptates is still lacking.

The evidence is strong that metalated hydrazones can be forced to form ion triplets through the addition of cryptand complexing agents. That is not to say, however, that ion triplets are the key reactive intermediates under normal alkylation conditions. In fact, it proves to be very difficult to distinguish organolithium reaction mechanisms involving dissociations to monomers versus those involving ion triplets. For example, rate studies of the ethylation of **8-Li** afforded the empirically derived rate expression in eq 4.[3] In conjunction with a number of stereochemical studies we had previously argued that unstabilized lithiated hydrazones alkylated via spectroscopically invisible tetramer-to-monomer dissociative preequilibria (eq 5 and 6). In light of the results described herein, a plausible alternative mechanism would involve tetramer-to-ion triplet preequilibria as depicted in equations 7–10. Direct alkylation of ion triplet xiii—corresponding to an ion paired structure wherein the $^+Li(THF)_4$ and triplet fragment remain electrostatically associated–would afford a $^1/_2$ order rate dependence on **8-Li** concentration rather than the observed $^1/_4$ order. If, on the other hand, the $^+Li(THF)_4$ counterion undergoes complete (spectroscopically invisible) dissociation prior to alkylation (eq 8), then the rate would be described by eq 4, and the ion triplet and monomer mechanisms would be methematically indistinguishable. Thus, it is important to keep in mind that *although rate studies of organolithium reactions can detect aggregate dissociations, they often do not reveal the nature of the dissociative process or the structures of the reactive intermediates.*[56]

$$\text{rate} = k_{obs}[(\text{Hyd-Li})_4]^{1/4}[\text{THF}]^2[\text{MeI}] \qquad (4)$$

Mechanism I

$$(\text{Hyd-Li})_4 \xrightleftharpoons{\text{THF}} 4\ \text{Hyd-Li(THF)}_2 \qquad (5)$$

$$\text{Hyd-Li(THF)}_2 \xrightarrow{\text{MeI}} \text{Hyd-Me} \qquad (6)$$

Mechanism II

$$(\text{Hyd-Li})_4 \xrightleftharpoons{\text{THF}} 2\Big[\underset{\text{xiii}}{[(\text{Hyd})_2\text{Li}]^{\ominus}\,{}^{\oplus}\text{Li(THF)}_4}\Big] \qquad (7)$$

$$\Big[[(\text{Hyd})_2\text{Li}]^{\ominus}\,{}^{\oplus}\text{Li(THF)}_4\Big] \rightleftharpoons [(\text{Hyd})_2\text{Li}]^{\ominus} + {}^{\oplus}\text{Li(THF)}_4 \qquad (8)$$

$$[(\text{Hyd})_2\text{Li}]^{\ominus} \xrightarrow{\text{MeI}} \text{Hyd-Me} + \text{Hyd-Li} \qquad (9)$$

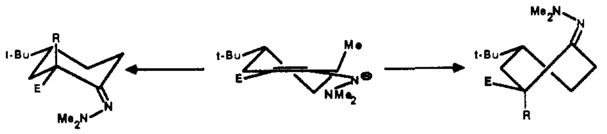
$$\text{Hyd-Li} \rightleftharpoons (\text{Hyd-Li})_4 \qquad (10)$$

A complete understanding of the hydrazone alkylation mechanisms and the role of ion triplets is far from resolved. Although we have not rigorously demonstrated that the observed ion triplet cryptates undergo the alkylation prior to some further structural change, tentative conclusions and observations can still be made as follows.

(1) The alkylations of carbomethoxy-substituted metalated hydrazones may very well proceed through ion triplets. The cryptand-derived alkylation rate increases that occur without detectable changes in the stereoselectivities are *consistent* with common (ion triplet) intermediates.

(2) The losses in stereochemistry upon addition of cryptands to the natriated cyano-substituted and lithiated unsubstituted hydrazones indicate that the spectroscopically observed ion triplets show distinctly different selectivity than the reactive intermediates generated in the absence of cryptands. We interpret this as tacit evidence against ion triplets as intermediates under standard alkylation conditions. Furthermore, to the extent that the ion triplet structure is a form of aggregate, stereochemical probes of aggregation effects, which had provided strong evidence against direct aggregate alkylation, are also inconsistent with ion triplet intermediates.[3]

(3) Since C[2.1.1] complexed all of the Li^+ ions of the cyano-substituted lithiated hydrazones, we can tentatively ascribe the observed alkylation stereoselectivities to the inherent alkylation selectivity of solvent-separated ion pairs or free ions. (Caution must be exercised, however, since ^6Li NMR spectroscopic studies indicated that the anions and cations were not fully shielded from each other). Although this neither supports nor refutes any of the published stereochemical models,[2,3] it does indicate that the inherent axial alkylation selectivities of conformationally anchored substituted 4-*tert*-butylcyclohexanone hydrazone derivatives *can be* quite high (eq 11) and that the metal counterions are only minor stereochemical determinants in some instances.



(11)

(4) Stereochemical changes caused by added complexing agents are substantial for the 2-methyl-substituted hydrazones, wherein the stereocenter and metal counterion are in close proximity. The high propensity to alkylate from the more hindered face cis to the methyl substituent under normal alkylation conditions could be explained either by invoking alkylation away from the lithium ion in η^4–π complex xiv[3,57] or axially from η^1–σ complex xv (X = NMe_2). In either case, the metal counterions appear to be important.

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(55) Colgan, D.; Papasergio, R. I.; Raston, C. L.; White, A. H. *J. Chem. Soc., Chem. Commun.* **1984**, 1708. Papasergio, R. I.; Raston, C. L.; White, A. H. *J. Chem. Soc., Chem. Commun.* **1983**, 1419. Schleyer, P. v. R.; Hacker, R.; Dietrich, H.; Mahdi, W. *J. Chem. Soc., Chem. Commun.* **1985**, 622. Dietrich, H.; Mahdi, W.; Knorr, R. *J. Am. Chem. Soc.* **1986**, *108*, 2462. See also ref 54.

(56) As a referee pointed out, mechanism I and II could be distinguished by a detailed study of common ion rate inhibitions (barring any additional complexities caused by the added lithium salt). Clearly, at the time the kinetics of lithiated hydrazone alkylations were carried out, many mechanistic subtleties were not fully appreciated.

(57) See also, Meyers, A. I.; Dickman, D. A. *J. Am. Chem. Soc.* **1987**, *109*, 1263.

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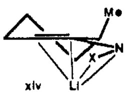
(60) For examples in which cryptate reactivities have been correlated with spectral and physical properties, see Bottin-Strzalko, T.; Etemad-Moghadam, G.; Seyden-Penne, J. *Nouv. J. Chim.* **1983**, *7*, 155. Collman, J. P.; Finke, R. G.; Cawse, J. N.; Brauman, J. I. *J. Am. Chem. Soc.* **1977**, *99*, 2515. Chang, C. J.; Kiesel, R. F.; Hogen-Esch, T. L. *J. Am. Chem. Soc.* **1973**, *95*, 8446. Viguier, M.; Abadie, M.; Schue', F. *Eur. Polym. J.* **1977**, *13*, 213. Richey, H. G., Jr.; Farkas, J., Jr. *Tetrahedron Lett.* **1985**, *26*, 275.

(61) Decompositions of the cryptate by the highly basic counterions produces an additional complication. Many of the cryptates described herein exhibited thermal lability. Also, treatment of lithium diisopropylamide with C[2.1.1] at −78 °C results in complete destruction of the cryptand within seconds as evidence by very complex resonances in the ^6Li NMR spectrum. One can only surmise the effects of such decomposition pathways on observed product distributions. For related decompositions, see: Squiller, E. P.; Whittle, R. R.; Richey, H. G., Jr. *Organometallics* **1985**, *4*, 1154. Thompson, T. B.; Ford, W. T. *J. Am. Chem. Soc.* **1979**, *101*, 5459. Pierre, J.-L.; Le Goaller, R.; Handel, H. *J. Am. Chem. Soc.* **1978**, *100*, 8021. Pierre, J.-L.; Le Goaller, R.; Handel, H.; Ripert, A. *Tetrahedron Lett.* **1978**, 3259.



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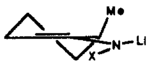

xv

(5) The common practice of using cryptands as mechanistic tools in the absence of the proper structural probes has several latent dangers.[54-57] The often implicit assumption that organoalkali species will quantitatively form fully encapsulated cryptates irrespective of the anion structure is simply not valid. The solution structures and reactivities of many organolithium/cryptand mixtures remain poorly understood.

Summary

Cyano-stabilized lithiated hydrazones cleanly form cryptates upon treatment with C[2.1.1]. The high resolution afforded by ^{6}Li NMR spectroscopy was clearly demonstrated by the detection of anion and temperature-dependent chemical shifts of the encapsulated Li$^+$C]2.1.1] cryptate ion. All other metalated hydrazones including the sodium and lithium salts of stabilized and unstabilized hydrazones were shown by ^{6}Li (or ^{23}Na) and ^{13}C NMR to be converted to ion triplets upon treatment with cryptand complexing agents. The structure of the triplet fragments derived from carbomethoxy-substituted hydrazones could be assigned by analogy to a number of literature results. In two instances, stereoisomeric ion triplet fragments were detected. The structural details of the ion triplets derived from unsubstituted lithiated hydrazones and sodium salts of cyano-substituted hydrazones could not be ascertained; π-complexed sandwich structures were suggested. Formation of the ion triplet cryptates from the carbomethoxy-substituted anions had no effect on the alkylation stereochemistries, implicating ion triplet intermediates under normal alkylation conditions. Alkylation selectivity changes observed from the other ion triplets provided tacit evidence against ion triplets as reactive intermediates in the absence of cryptands.

Experimental Section

Instrumentation. ^{6}Li and ^{23}Na NMR spectra were recorded on a Varian XL 400 spectrometer operating at 58.84 and 105.76 MHz (respectively). The ^{6}Li chemical shifts are reported in ppm downfield of an external 0.30 M LiCl/methanol standard with a 0.35 M LiI/MeOH secondary reference at 0.86 ppm. The ^{23}Na chemical shifts are reported in ppm relative to an external 0.25 M NaCl/D$_2$O standard set at 0.0 ppm.[18] ^{6}Li and ^{23}Na NMR spectroscopic data are summarized in Tables I and II. ^{13}C NMR spectra were recorded on a Varian XL 400 spectrometer operating at 100.55 MHz.

Solvents and Materials. All solvents were distilled from sodium benzophenone ketyl. The hydrocarbon solvents contained 1% tetraglyme to dissolve the ketyl. ^{6}Li metal (95.5%) was obtained from Oak Ridge National Laboratory. Ethyllithium and [^{6}Li]ethyllithium prepared by the standard literature procedure were recrystallized from benzene and doubly sublimed to remove lithium halide impurities.[10] Sodium hexamethyldisilazide was prepared and purified by a literature procedure.[11] The hydrazones were prepared and purified as described previously.[9] Air- and moisture-sensitive materials were manipulated by standard glove box and vacuum line techniques with the aid of gas-tight syringes.

Nuclear Magnetic Resonance Studies. The following is a representative procedure for preparing samples for spectroscopic analysis. Ethyllithium was weighed in a glove box and carefully transferred to an oven-dried 5-mm NMR tube. After addition of a sealed acetone-d_6 capillary for spectrometer locking and a sealed capillary containing a 0.35 M LiI/MeOH internal standard, the tube was capped with a septum and removed from the glove box. The tube was cooled to −78 °C under positive argon pressure and charged with a solution of the hydrazone (0.09 mmol) in anhydrous THF (300 μL) via a gas-tight syringe. The tube was placed under an internal vacuum, sealed with a flame, and stored briefly at −30 °C until NMR spectroscopic analysis.

The samples for ^{23}Na NMR spectroscopic analysis were prepared similarly by replacing ethyllithium-^{6}*Li* with sodium hexamethyldisilazide.

Alkylation Studies. Upon completion of the spectroscopic analysis (as described above), the tube was opened, quickly placed under positive nitrogen pressure, cooled to −78 °C, and treated with methyl iodide (3–5 equiv) by a gas-tight syringe. After the specified alkylation time (Table III), the reaction was quenched, warmed to ambient temperature, and extracted with ether. The gas chromatographic analyses were performed on a Varian 3700 gas chromatograph with digital integration as described previously.[9]

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