Amide Coordination Effects in Organolithiums

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Abstract: Organolithiums containing the amide group are examined by ab initio molecular orbital calculations with the 3-21G basis set. Amide coordination with the metal cation results in a large thermodynamic stabilization of the ion pair. Basis set superposition errors at 3-21G are estimated to favor the complex by 10–15 kcal mol^{-1}; nevertheless, qualitative trends at this level are believed to be reliable. The calculated stabilization energy due to the amide drops off depending upon whether lithiation occurs α, β, or γ to the amide—provided the cation is accessible to the amide oxygen. Without correction for basis set superposition error, stabilization energies at 3-21G (in kcal mol^{-1}) are 45 in acetamide, 40 in benzamide, and 38 in *syn*-bicyclo[1.1.1]pentane-2-carboxamide. Amide coordination effects in lithiocubanes are also estimated and found to be large. Thus, thermodynamics plays an important role in amide-assisted metalations. In addition, formation of an acetamide–methyllithium complex is found to be 37.5 kcal mol^{-1} exothermic relative to separated molecules, suggesting that formation of this complex lies along the metalation reaction pathway. This complexation facilitates the reaction kinetically. Analysis of electron density distributions and electrostatic potentials shows that the carbanion–lithium and the amide–lithium interactions are primarily closed-shell ones, being essentially ionic bonds. The lithium cation is stabilized by the negative potential surrounding the oxygen. In addition, inductive effects at the γ position are estimated for several cases and found to be negligible. The amide thus assists metalation predominately through an electrostatic field effect.

1. Introduction

Although metalations of aromatic rings ortho to substituents having lone pairs of electrons are quite familiar,[1,2] similarly assisted metalations in aliphatic systems are proving at least equally useful.[3] For example, Klumpp has shown that lithiation of cyclopropylcarbinols[4] and homocyclopropylcarbinyl ethers[5] is directed by the oxygen atom. Likewise, alkenyl amines are carbolithiated with assistance from the amine group.[6] The amide group, commonly used to activate ortho metalations in aromatic systems because of its ability to form amide–metal ion complexes and its strong anion-stabilizing inductive and resonance effects,[1c,7,8] can also be employed in aliphatic systems to direct and promote metalations.

In interesting and important developments of this technology, Eaton and co-workers used the diisopropylamide amide group to promote the metalation of β carbons on the cubane[9] and cyclopropane[10] nucleus. In the cubane case, they report that treatment with lithium tetramethylpiperidide (LiTMP) in THF at 0 °C followed by quenching with CH_3OD yields deuterium incorporation of <0.5% (none detected) for cubane, nearly 3% for cubane-*N*,*N*-diisopropylcarboxamide, and nearly 80% for cubane-1,4-bis(*N*,*N*-diisopropylcarboxamide). These data show that a single amide group strongly activates metalation and that a second amide group provides additional activation beyond that expected from simply statistical considerations. This additional effect is exerted from a γ position, a rather remote site. Assuming equilibrium is obtained in these systems and that the final deuterium incorporation relates directly to the amount of metalated products formed, an additional stabilization of ~ 1 kcal mol^{-1} can be assigned to the second amide from the Boltzman equation. Eaton and Castaldi[9a] suggest that inductive effects are responsible for the increased activation due to the second amide group, thus implying the remote substituent exerts a primarily thermodynamic effect.

On the other hand, Beak has demonstrated the prominence of metal cation complexation with proximate functional groups in metalation reactions.[11] Furthermore, Beak and Meyers[12] have shown that amide groups complex lithium reagents, giving a stable intermediate. This complex leads to deprotonation faster than in the unsubstituted hydrocarbon analogues, which do not form a complex. Other reactions involving lithium reagents appear to proceed via an initial complexation.[13]

We suggest that the above two viewpoints, rather than being incompatible, refer to two real but separate effects—one thermodynamic, the other kinetic in origin. Thus, there are two distinct coordination complexes involving a lithium cation and the amide group containing substrate. The first type, which we term the lithium reagent complex, is the initially formed alkylithium–substrate encounter complex; its formation preceeds deprotonation. This complex positions the base so that subsequent deprotonation of the substrate is kinetically facilitated.[11-13] The second type of complex, which we term the lithium ion complex, occurs in the metalated substrate; its stability is controlled partly by how well or poorly the lithium counterion is chelated by the amide group.

The importance of both these complexes has been emphasized not only by experiment, but also by theoretical studies. Rondan et al.[14] and later Bach et al.[15] computationally demonstrated the essential role of lithium ion complexation by the carbonyl oxygen in explaining the stereochemical preferences of amides and esters in base-promoted condensations. Thus, the anion resulting from α' deprotonation of *N*-methylformamide prefers the anti geometry,

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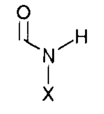
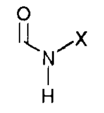
Ia with X = –, while chelation with a lithium cation causes the syn form, Ib with X = Li, to be favored.



Ia: X = –, Li



Ib: X = –, Li

In addition, Houk et al.[16] computationally characterized the alkyllithium–substrate complex in the addition of LiH and CH_3Li to ethylene and acetylene. Similar complexes were also found computationally for the addition of CH_3Li, HLi, and their dimers to formaldehyde.[17]

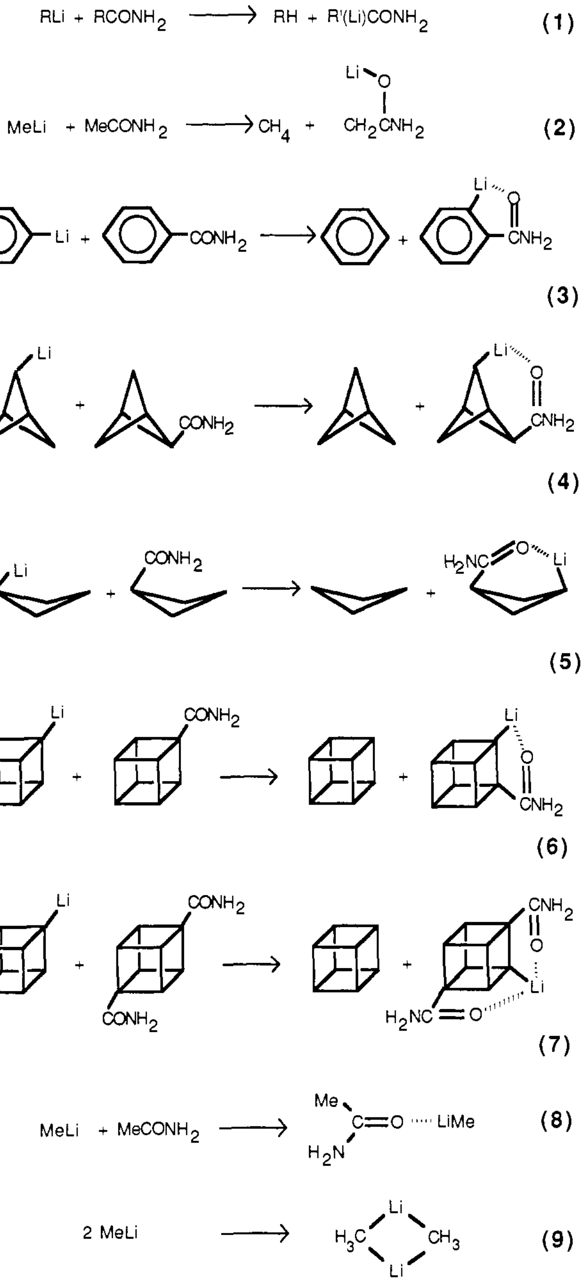
Because of the potential importance of amide group–lithium complexes in preparing highly substituted derivatives of cage compounds, we examined several of these complexes using ab initio molecular orbital theory. Geometries, energies, and electron densities were calculated and analyzed to understand better how the amide group promotes metalations, especially from remote sites, and to characterize the bonds in the amide–metal cation complex. Rondan et al.[14] and Bach et al.[15] pointed out that in *N*-alkylamides the α' anions are dipole stabilized due to the adjacent bond polarities; this effect operates in both the naked anion and in the metalated ion. Additional stabilization, possibly larger than that obtained from dipole stabilization, results when the naked anions are complexed with cations; its magnitude depends upon how effectively the cation is chelated. It is this effect that we wish to investigate. Previously, Pross and Radom[18] found that phenyllithium is strongly stabilized by an OH, F, NO_2, or CN in the ortho position. They suggested this stabilization arises from "direct charge transfer from the substituent into the Li in-plane 2p orbital". A similar effect and explanation might be supposed in aliphatic systems. In unsubstituted systems, anion and ion-pair stabilities are directly related.[19]

Calculations were performed for five systems: acetamide, benzamide, bicyclo[1.1.1]pentane-2-carboxamide, and a series of cyclobutanecarboxamides and cubanecarboxamides. These systems model aromatic and aliphatic systems with α, β, and γ positions of metalation. The importance of the lithium reagent complex was investigated for the methyllithium–acetamide reaction. These calculations were then analyzed in several different ways. The remainder of this paper describes the results of the analyses as follows: After discussing the computational methods employed (Section 2), we present calculations in Section 3 showing the energetic and structural consequences of lithium cation–amide group chelation. In Section 4, results from the topological analysis of the calculated electron densities in the complexes are discussed; these calculations indicate a sizable ionic attraction between lithium and oxygen. The nature of this interaction is further supported by examination of the electrostatic potential of the amide anion in Section 5.

2. Computational Methods

Molecular geometries were optimized at the HF/3-21G[20] level with GAUSSIAN82.[21] In some cases, partial optimizations were required due to time constraints. For all compounds, the amide group was assumed to be planar. Calculations for acetamide verified this assumption. Recent 6-31G** calculations by Wiberg show that although the barrier to out-of-plane bending at nitrogen is small, the amide group is planar.[22]

Chart I. Reactions Used To Evaluate Amide Complexation Effects (See Text for Details)



Additional restrictions were imposed on geometries of cubanecarboxamide, 2-lithiocubane-1-carboxamide, cubane-1,4-bis(carboxamide), and 2-lithiocubane-1,4-bis(carboxamide). For these compounds, the geometry of the cubane nucleus was that found for cubane and the geometry of the amide group was that found in cyclobutanecarboxamide. The position of the lithium and the angle the amide group takes with respect to the cubyl framework were then optimized to obtain our final geometries.

Except for the instances noted above, geometries were completely optimized within the stated symmetry point groups.

Electrostatic potentials were obtained from atom-centered multipole expansions including monopole, dipole, and quadrupole terms determined by the Hirshfeld method[23] as implemented in RHO.[24]

Topological electron density analysis was performed by using EXTREME.[25]

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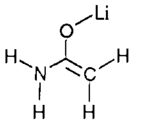
Table I. Energies of Reaction with Various Basis Sets (Reactions Are Shown in Chart I)

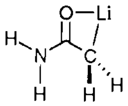
basis sets	ΔH_r, kcal mol^{-1} reactn 5	reactn 8	reactn 9
3-21G//3-21G	−36.98	−37.52	−46.24[a]
6-31G//3-21G		−29.74	−41.76[a]
6-31+G//3-21G	−29.32	−28.68	−40.61
6-31G*//3-21G	−26.84	−25.55	−42.48
6-31+G*//3-21G		−24.34	−41.54

[a] See also: Kaufmann, E.; Raghavachari, K.; Reed, A. E.; Schleyer, P. v. R. *Organometallics* **1988**, *7*, 1597.

3. Energetics and Structures

To evaluate the ability of an amide group to promote metalation, we examined the reactions shown in Chart I. These reactions may be represented generically by reaction 1, where R′ is R without the exchanged hydrogen. This reaction is nearly isodesmic,[26] the discrepancy arising from the different number of bonds to lithium on the left and right sides of the equation. Reactions 2–7 contain an amide interacting with α-, β-, or γ-lithiums. Thus, the exchange of an α-hydrogen in acetamide (reaction 2) and an ortho hydrogen in benzamide (reaction 3) were examined. In lithioacetamide, two possible geometries, shown below, were examined.

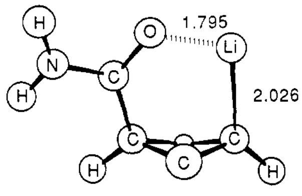

IIa


IIb

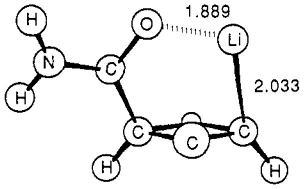
IIa is found to be a true energy minimum, lying 6.1 kcal mol^{-1} below IIb, which is found by calculation of vibrational frequencies to be the transition state for the rotation about the C–C bond. To model remote effects the following positions were exchanged: the hydrogen on the bridge (i.e., the syn 4-position) in bicyclo[1.1.1]pentane-2-carboxamide (reaction 4), in the 3-position in cyclobutane carboxamide (reaction 5), and the hydrogen in the 2-position in cubanecarboxamide (reaction 6) and cubane-1,4-bis(carboxamide) (reaction 7). To examine the importance of the lithium reagent complex, we employed the reaction of methyllithium with acetamide, as given in reaction 8. This complex is analogous to those found by Houk and Schleyer in their studies of metalation of ethylene,[16] acetylene,[16] and formaldehyde.[17] Finally, reaction 9 is used in evaluating basis set superposition errors.

It has been previously pointed out that lithium–heteroatom interactions are too strong at 3-21G because of the basis set superposition error.[27] To determine the magnitude of this preference in the amide–lithium complexes, calculations using larger basis sets were performed for reactions 5, 8, and 9. Reaction 9 shows the dimerization of methyllithium, a system that has only carbanion centers for comparison. Reactions 5 and 8 test the effects of basis set size on systems where lithium bridges a carbanion and the amide oxygen atom. The calculated reaction energies are listed in Table I.

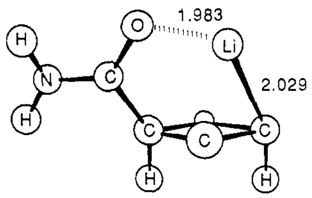
Inspection of reaction energies shows larger superposition errors for lithium–amide complexes than for lithium–carbanion complexes. Reaction energies decrease by 10 and 12 kcal mol^{-1}, respectively, upon going from 3-21G to 6-31G* for reactions 5 and 8, while a decrease of only 3.8 kcal mol^{-1} is found in 9. Apparently, small basis sets do not provide sufficient functional flexibility to describe amides and "borrowing" of lithium basis functions occurs when possible. This results in a spurious destabilization of the reactants, leading to reaction energies upon complexation that are too negative by about 10–15 kcal mol^{-1}.



Model A



Model B



Model C

Figure 1. Structure of 3-lithiocyclobutanecarboxamide for the three model types A, B, and C. All distance in angstroms.

The C–Li and O–Li optimized distances found in the lithioamide salts shown in Chart I are listed in Table II. Total energies at 3-21G for the compounds shown in Chart I and the derived reaction energies are listed in Table III.

The C–Li and O–Li distances listed in Table II are similar to those found in lithiated carbanions[28] and alcoholates,[29] respectively, which are known to be highly ionic.[30] Thus, with the exception of lithioacetamide, geometrical evidence suggests that lithium cations bridge the carbanion and carbonyl oxygen. This result agrees with that obtained by Jayasuriya, Alster, and Politzer[31] and as suggested by Eaton and Castaldi.[9a]

The data in Table III show that suitably situated amide groups in reactions 3–6 chelate a lithium cation, resulting in roughly 35–40 kcal of stabilization. This energy is too exothermic by about 10–15 kcal mol^{-1} due to basis set inadequacies discussed above. Even after subtracting 15 kcal mol^{-1} from the reaction energies, amide complexation is strongly stabilizing. Therefore, amides can increase the thermodynamic ion-pair acidity of neighboring sites. As indicated by reactions 4–7, this stabilization operates only slightly less effectively at the γ site than at the nearer α or β sites (reactions 2 and 3).

In our examples, however, the γ site is readily accessible to the amide group. Also, in the cubanecarboxamides (reactions 6 and 7), one amide group stabilizes the metalated product by nearly 38 kcal mol^{-1}, which is somewhat less than that found for benzamide because of the greater distances involved. A second amide group on cubane, however, makes the exchange reaction 1 kcal mol^{-1} more exothermic than that of the monoamide, in agreement

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Table II. Topological Values in the Lithio–Amide Salts

salt		r_{X-Li}	r_{Li}	ρ_c	$\nabla^2\rho_c$	H_c
lithioacetamide	O–Li	1.580	1.176	0.074	0.615	–0.0017
lithiobenzamide	C–Li	2.049	1.391	0.034	0.205	0.0038
	O–Li	1.783	1.283	0.047	0.369	0.0017
4-lithiobicyclo[1.1.1]pentane-2-carboxamide	C–Li	2.023	1.364	0.039	0.225	0.0021
	O–Li	1.763	1.275	0.048	0.384	0.0017
3-lithiocyclobutanecarboxamide (A)	C–Li	2.026	1.368	0.039	0.221	0.0020
	O–Li	1.795	1.294	0.044	0.356	0.0031
3-lithiocyclobutanecarboxamide (B)	C–Li	2.033	1.391	0.035	0.206	0.0029
	O–Li	1.889	1.348	0.035	0.287	0.0049
3-lithiocyclobutanecarboxamide (C)	C–Li	2.029	1.438	0.026	0.198	0.0066
	O–Li	1.983	1.398	0.027	0.232	0.0062
2-lithiocubane-1-carboxamide	C–Li	2.051	1.395	0.034	0.200	0.0032
	O–Li	1.827	1.309	0.041	0.333	0.0030
2-lithiocubane-1,4-carboxamide	C–Li	2.048	1.392	0.034	0.202	0.0033
	O–Li[a]	1.833	1.313	0.041	0.328	0.0032
	O–Li[b]	5.453				

[a] The bond path between Li and the oxygen in the 1-amide. [b] The distance between Li and the oxygen in the 4-amide.

Table III. Energies (in au) of Compounds in Reactions 2–8 in Chart I

reaction	RH	RLi	$RCONH_2$	$R'(Li)CONH_2$	ΔH_r
2	−78.793 948	−85.562 878	−206.815 802	−213.656 843	−45.24
3	−229.419 445	−236.203 757	−396.266 720	−403.115 919	−40.72
4	−192.825 926	−199.596 183	−359.669 975	−366.501 285	−38.30
4 anti				−366.439 544	0.42
5 A	−155.231 360	−161.999 649	−322.080 620	−328.907 837	−36.98
5 B	−155.230 510	−161.997 288	−322.078 921	−328.889 420	−27.44
5 B anti				−328.846 136	−0.29
5 C	−155.083 923	−161.866 393	−321.926 498	−328.736 741	−17.44
6	−305.695 900	−312.471 104	−472.540 018[a]	−479.375 257[a]	−37.69
7			−639.379 870[a]	−646.216 792[a]	−38.76
8				−253.628 078[b]	−37.52

[a] Incomplete geometry optimization. See text for details. [b] This is the energy of the acetamide–methyllithium complex.

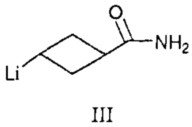
with the previous estimate made from the data of Eaton and Castaldi.[9a]

To determine if any special effects might be operating in the cubanes as a result of its large ring strain, we examined a series of lithium cyclobutanecarboxamides (see Figure 1) with geometrical constraints introduced to increase the O-Li distance. The first model, model A, has no artifical constraints beyond those needed to maintain C_S symmetry and was used to obtain quantities for reaction 5 shown in Tables II and III. The second model, model B, requires the cyclobutyl ring to be planar. The third model, model C, requires the cyclobutyl ring to be planar and the four hydrogens on the anti face to be perpendicular to the ring. Model C essentially mimics a single face of the cubane structure. Other than these constraints, geometries were completely optimized within C_S symmetry and exchange reaction 1 was used to evaluate complexation energies, with all four compounds being of the same model type. The calculated total energies and the derived heats of reaction are given in Table III.

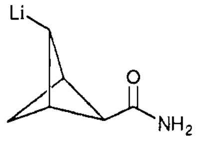
As the O–Li distance increases 1.795 Å in A, 1.889 Å in B, and 1.983 Å in C, the reaction energies decrease due to less effective electrostatic interaction of the lithium cation with the carbonyl oxygen.[32] Also, it is observed that although the O–Li distance lengthens in this series, the C–Li distance remains relatively constant. This indicates that the C–Li interaction energy is significantly stronger than the O–Li interaction.

The stabilization for model C, which models γ metalation on a cubane face, is 17.4 kcal mol^{-1}; yet the calculated stabilization due to the second amide group in cubane-1,4-bis(carboxamide), where the second amide is similarly situated with respect to the carbanion, is but 1 kcal mol^{-1}. This difference is due to the longer distance over which the secondary O–Li interaction operates in the cubane system. As shown in Table II, the calculated primary O–Li and secondary O–Li distances are 1.833 and 5.453 Å, respectively, indicating the different interaction with the lithium. This secondary O–Li distance is far longer than the O–Li distance in the model C 3-lithiocyclobutanecarboxamide of 1.983 Å. Apparently, the lithium cation prefers interacting strongly with one amide and weakly with the other over medium interactions with both.

To separate the inductive and complexation effects, reaction 1 was used to calculate complexation energies for the two structures shown below.



III



IV

In these cases the lithium is anti to the amide group, thus inhibiting complexing of the lithium and the amide group. The strength of the inductive effect, however, should be nearly equal for the syn and anti cases since the bond connectivity is identical. Table III lists the heats of reaction calculated by using reaction 1 for these anti lithio–amide salts. An effect of less than 0.5 kcal mol^{-1} found in both cases—far less than the effect found for the syn cases. Inductive effects are, consequently, quite small at the γ position, being strongly damped by each interceding bond.

Beak and Meyers[12] suggested that the activation of the C–H bond toward metalation of amides is primarily due to kinetic effects. In particular, they suggest that the amide group coordinates the lithium reagent forming a complex that positions the base near the acidic proton, thereby dramatically reducing the activation entropy for the removal of the hydrogen. So far, we have discussed the thermodynamic stability of the product as the driving force for metalation of amides. To investigate the possible formation of a complex, we examined the reaction of methyllithium and acetamide, reaction 8, following the work of Houk and Schleyer.[16,17]

The geometry of this complex was optimized at the 3-21G level invoking C_S symmetry. The structure is shown in Figure 2. In this complex, lithium coordinates to both the carbon of the base

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(32) Associated with the change in the O–Li distance are changes in the geometry of the amide group. As the O–Li distance decreases, the C–O distance increases and the C–N distance decreases.

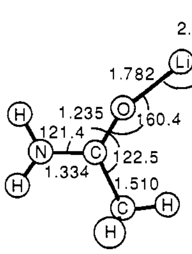

Figure 2. Structure of acetamide–methyllithium complex. All distances in angstroms and angles in degrees.

and the oxygen of the amide. The incoming base ($^-CH_3$) is still quite removed from the acidic proton (4.858 Å). However, the base need only rotate toward the hydrogen from its position in the complex to reach the transition state. This rotation certainly involves less entropic loss than the motion required to move the separated amide and base directly to the transition state, as required for cases where no complexation occurs, i.e., hydrocarbon with base.

Formation of the complex is exothermic by 37.5 kcal mol^{-1} at 3-21G. Deprotonation and departure of methane, leading to lithioacetamide, is only 3.5 kcal mol^{-1} exothermic; the overall reaction is 41.1 kcal mol^{-1} exothermic. Thus, complexation is thermodynamically feasible along the pathway for metalation, a step that may allow for further reaction to occur very rapidly. These results support the idea of an intermediate complex that can promote metalation.

4. Topological Electron Density Analysis

To understand the bonding of the lithium cation–amide complex, we employed the topological electron density analysis developed by Bader.[33] This method analyzes the total electron density in three dimensions and contains no arbitrary constructs or definitions. Of principal interest here is determining which atoms are bonded and the nature of these bonds.

Bonded atom pairs are determined by finding bond paths,[34] which are lines of maximum electron density between atom pairs.[34,35] The interaction between the bonded atom pairs can then be classified according to various calculated quantities associated with the bond critical point that generates the bond path. The quantities of interest at the critical point are ρ_c,[36] the Laplacian of ρ_c, $\nabla^2\rho_c$,[37] and the local energy density, H_c.[38] The Laplacian $\nabla^2\rho$ determines the concentration or depletion of density at a given point relative to neighboring points. For typical covalent bonds, ρ_c is large, indicating significant electron density, $\nabla^2\rho_c$ is negative, indicating a concentration of electron density along the bond path, and H_c is negative, indicating the dominance of potential energy. Conversely, for ionic bonds, ρ_c is small, indicating little electron density, $\nabla^2\rho_c$ is positive, indicating a local depletion of electron density along the bond path resulting from closed-shell overlap, and H_c is positive, indicating the dominant contribution of kinetic energy.

With the exception of lithioacetamide, all lithium cation–amide complexes exhibit bond paths connecting lithium both to the carbanion and to the oxygen of the amide group. These bond path networks are illustrated in Figure 3.[39] The existence of a bond path connecting lithium to oxygen indicates that the topology of the electron density between these two atoms is similar to that found in more common and stronger bonds.

On the other hand, anti-lithio–amide salts do not exhibit lithium–oxygen bond paths, as evidenced by the bond path network of *anti*-4-lithiobicyclo[1.1.1]pentanecarboxamide, also shown in Figure 3. The absence of this O–Li bond path suggests that essentially no complexation between these atoms exists. We also note that there is no bond path connecting lithium to the oxygen of the 4-amide in 1,4-bisamido-2-lithiocubane. This bond path is absent because the interaction between these atoms is quite small; e.g., ~1 kcal mol^{-1}.

Table II also lists values of some topological quantities at the O–Li and C–Li critical points. For both the C–Li and O–Li critical points in all of these compounds (again excepting lithioacetamide), ρ_c is small, $\nabla^2\rho_c$ is positive, and H_c is positive.[40] These values are all in good agreement with previous results for organolithium compounds.[41] Furthermore, the value of r_{Li}, the distance between lithium and the bond critical point, is in the neighborhood of the ionic crystal radius of lithium.[42]

These results clearly indicate that a bridging lithium interacts with both the carbanion and amide oxygen through closed-shell interactions, very much like in an ionic bond. Although the amide oxygen does not carry a formal charge in the most stable resonance structure, we suggest that the oxygen's lone pairs of electrons produce an attractive electrostatic potential for the lithium cation, not unlike that found in formally charged systems. From a topological standpoint, then, the C–Li and O–Li interactions are quite similar in kind and differ in degree only. There is no basis for distinguishing between these interactions by the use of solid lines in the former case and dashed, dotted, or directed lines in the latter. In both instances, the interaction of a positive charge with the negative potential arising from either a carbanion or oxygen lone pair results in ionic bonding.

5. Electrostatic Potentials

To clarify the nature and importance of electrostatic interactions in the cation complexes, we examined some electrostatic potentials. If these complexes are composed of essentially ionic bonds, then the deepest well accessible to the cation in the electrostatic potential of the anion should correspond to the position the cation occupies in the complex. We report this type of analysis for 3-lithiocyclobutanecarboxamide.

We first optimized the structure of cyclobutanecarboxamide anion (the anion being in the 3-position) and calculated its electrostatic potential. Starting from the structure having both the anionic lone pair and the amide group in axial positions (hereinafter called the diaxial structure) to mimic the lithium salt, we obtained upon optimization the structure that has both the anionic lone pair and the amide group in equatorial positions (diequatorial). This anion structure minimizes the repulsion between the anionic lone pair and the negatively charged oxygen atom. These results suggest that cyclobutanecarboxamide anion will have a different conformation in polar solvents than in nonpolar solvents. In polar events, solvent-separated ions will occur and the cyclobutanecarboxamide anion will have the diequatorial form. In nonpolar solvents, the tight ion pair will be present, which has the diaxial form. Nevertheless, the optimized anion structure is unsuitable for the present purposes.

To obtain a meaningful electrostatic map of the cyclobutylamide anion in the conformation of the salt, we determined atom-centered

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(39) Also noted in a few of these bond path networks are some unusual bond paths and critical points. For example 3-lithiocyclobutane-1-carboxamide model A has a bond path connecting the amide oxygen to the 3-carbon and 3-lithiocyclobutane-1-carboxamide model C exhibits a cage point. These features are unusual but are dependent on slight changes in the geometry and basis set. Further analysis is beyond the scope of this paper.

(40) Note that H_c at the O–Li critical point is negative in lithioacetamide. This O–Li interaction is clearly much stronger than in the other lithio–amide salts, as seen in the smaller O–Li distance and great density at the critical point.

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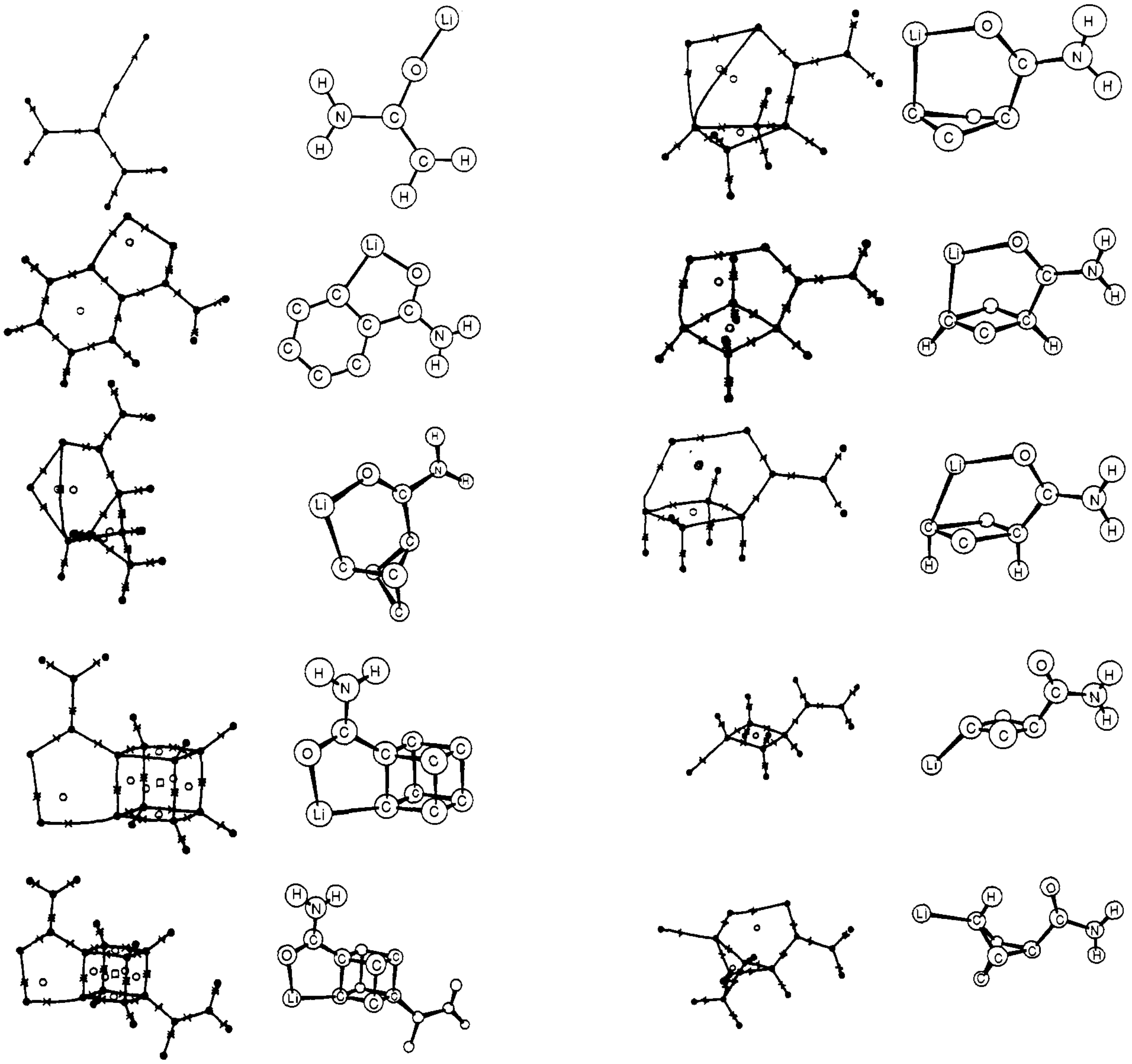

Figure 3. Bond path networks and structures of all lithio–amide salts studied. Bond critical points marked by *, ring critical points marked with ○, and cage critical points marked with □.

multipole expansions, including up to quadrupole terms, of the salt using the Hirshfeld procedure.[23,24] We then deleted values for the lithium atom, retaining just the atomic moments of the anion fragment. Using these moments, we created an electrostatic potential of the anion fragment in the conformation of the salt and in the presence of the counterion, but without any electrostatic contribution from the counterion.

The resulting potential is shown in Figure 4 for cyclobutanecarboxamide model B and indicates that the lithium position is in the center of a deep well between the lone pairs of the carbanion and the oxygen. The position of the lithium is in the deepest well available within the restriction of lithium, being no closer than 2.0 Å to carbon and 1.8 Å to oxygen. A more negative region is found in the direction corresponding to a traditional anionic lone pair on carbon, but it lies within 2.0 Å of carbon and is inaccessible to the lithium. Therefore, the electrostatic prediction for the position of the lithium counterion is confirmed.

6. Conclusions

Amide groups can stabilize lithium salts, thereby increasing the ion-pair acidity of an organic substrate. The primary mode for this stabilization is through complexation of the oxygen with the lithium cation. Complexation can occur effectively from remote sites. In addition to this thermodynamic effect, formation of a complex between the amide and a lithium reagent can be quite energetically favorable and allow for fast metalation to occur.

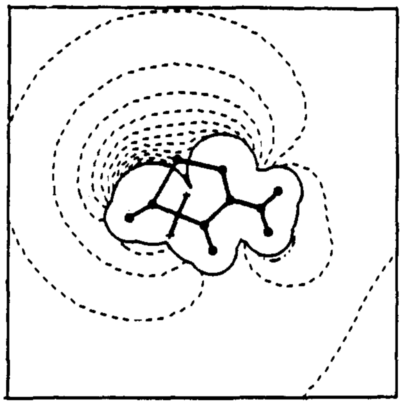

Figure 4. Electrostatic potential of cyclobutanecarboxamide 3-anion, Model B. See text for details on method for determining this potential. Contours from 0.0 to −300.0 kcal e^{-1} by 25.0 kcal e^{-1}.

Analysis of the electron density distribution of the complexes and electrostatic potentialls of the bare anion showed that the amide–lithium cation interaction is a closed-shell one resembling that found in ionic bonds. The lithium cation is stabilized predominately by the field effect exerted by the amide. We find no evidence for the transfer of any significant amount of electron density from the amide to the lithium, such as that which might accompany formation of a less ionic bond. These results emphasize the importance of electrostatic effects in these complexes.

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Supplementary Material Available: Geometries (as Z matrices) and energies for all compounds studied (13 pages). Ordering information is given on any current masthead.

A Study of Nonrigid Aromatic Molecules. Observation and Spectroscopic Analysis of the Stable Conformations of Various Alkylbenzenes by Supersonic Molecular Jet Laser Spectroscopy†

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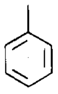
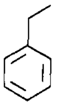
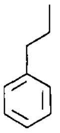
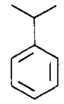
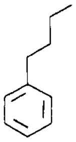
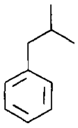
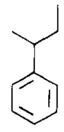
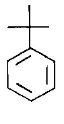
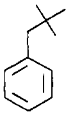
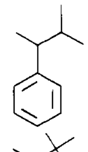
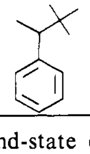
Abstract: The technique of supersonic molecular jet laser spectroscopy was used to determine the stable conformations of a series of alkylbenzenes. This study demonstrates, for the first time, the sensitivity of molecular jet spectroscopy in determining both the number of stable conformations as well as the geometry of various ethyl, propyl, and butyl substituents relative to the aromatic ring. Different rotamers with low barriers to interconversion, <5 kcal/mol, can be isolated in the supersonic jet expansion. Each observed conformation exhibits its own spectroscopic origin ($S_1 \leftarrow S_0$ transition) in a two-color time-of-flight mass spectrum (TOFMS). The number of stable conformations is then used to determine the minimum energy geometries of the substituent group. Previous identification of individual molecular conformations for such low barriers to interconversion has not been attainable with conventional techniques such as variable-temperature NMR.

Molecular conformation and its relationship to the chemical and physical properties of organic molecules have proven to be worthy of the intense effort expended since the pioneering work of D. H. R. Barton in the early 1950's.[2] Nonetheless, the experimental determination of the conformational preferences of many fundamentally important substituents is still lacking.[3] This void is particularly prominent for substituents which have free energy barriers to conformational interconversion of less than ca. 5 kcal mol^{-1} (1750 cm^{-1}), outside the range of variable-temperature NMR spectroscopy. In cases for which the individual conformations have not been "frozen out" and identified using the NMR technique, theoretical calculations have been of considerable value in facilitating conformational analysis and geometry assignments.[4]

Recently, we communicated the results of our initial studies using supersonic molecular jet laser spectroscopy as a novel tool for conformational analysis.[5-8] This technique has allowed us to assign unequivocally the minimum energy geometries of aromatic ethyl and propyl substituents[7,8] and to determine the experimental values for torsional potential barriers in S_0 and S_1 for aromatic methyl groups.[6] The jet spectroscopic technique allows the probing of both ground-state and electronically excited-state features of jet-cooled molecules.

The expansion process results in gas-phase molecules at near absolute zero temperature.[9] Hence, ground-state energy minima can be isolated and studied, even when very low barriers to interconversion are present. Each stable conformation corresponding to a potential energy minimum generates, at least in principle, its own spectroscopic 0_0^0 transition; and conversely, each 0_0^0 transition is associated with a specific stable ground-state conformation. By examining the spectra of specifically substituted alkylbenzenes, one can "count" the number of stable ground-state conformations. Molecular geometry and conformation can be assigned from a knowledge of the number of ground-state energy minima a molecule possesses.

Table I. Substituent Patterns for Substrates Examined in This Work

	aryl-to-alkyl bond type		
no. of atoms in substituents	primary Ar–CH$_2$R	secondary Ar–CHR^{1}R^2	tertiary Ar–CR^{1}R^{2}R^3
C_1			
C_2			
C_3			
C_4	 		
C_5			
C_6			

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† Dedicated to Derek Barton, on the occasion of his 70th birthday and to commemorate his seminal research in conformational analysis.

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