C, H. **10**: IR (neat) 3090, 3000, 1630, 1015, 810 cm^{-1}; ^1H NMR (CCl_4) δ 0.1–0.8 (m, 16 H), 0.9–1.2 (m, 2 H), 1.4–1.7 (m, 2 H), 2.46 (s, 4 H); UV (hexane) λ_{max} 278 nm (log ϵ 4.14). Anal. ($C_{18}H_{24}$) C, H. **11**: IR (neat) 3080, 3000, 2930, 2850, 1660, 1015, 880 cm^{-1}; ^1H NMR (CCl_4) δ 0.2–0.55 (m, 8 H), 0.55–1.2 (m, 6 H), 1.2–1.4 (m, 1 H), 1.60 (d, 1 H, J = 12 Hz), 2.12 (d, 1 H, J = 12 Hz), 2.12 (br s, 4 H), 4.63 (s, 1 H), 4.70 (s, 1 H). Anal. ($C_{18}H_{24}$) C, H.

On heating at 200 °C in benzene, **9** rearranged cleanly to **11** (56% rearrangement being observed after 32 h). In contrast, **10** isomerized gradually to **9** (13.6% after 32 h at 200 °C).

In a similar manner, **1b** (1.06 g, 13.2 mmol) gave a fraction [bp 90–180 °C (bath temperature); 434 mg, 41%] which was found to be a mixture of more than 20 components. GC purification permited us to isolate one of the components in a small amount, and it was characterized as a head-to-head dimer:[19] IR (neat) 3100, 3010, 1660, 1430, 1045, 1015, 950 cm^{-1}; ^1H NMR (CCl_4) δ 0.25–0.5 (m, 4 H), 0.5–0.9 (m, 4 H), 1.77 (m, 2 H), 2.40 (s, 4 H), 4.32 (s, 1 H), 4.41 (s, 1 H); UV (hexane) λ_{max} 267 nm (log ϵ 4.14). Anal. ($C_{12}H_{16}$) C, H.

Reactions of 9 and 10 with PTAD. Into a solution of PTAD (42 mg, 0.24 mmol) in dichloromethane (2 mL) was added a solution of **9** (58 mg, 0.24 mmol) in dichloromethane dropwise at room temperature. The evaporation of dichloromethane gave a solid residue, which was recrystallized from benzene to give **12**: 76 mg (76%); mp 122.5–124.5 °C; IR (KBr) 3080, 3000, 2945, 2920, 1765, 1705, 1600, 1500, 1420, 1010 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.0–0.8 (m, 16 H), 0.8–1.2 (m, 2 H), 1.4–1.8 (m, 2 H), 2.18 (t, 2 H, J = 3 Hz), 3.97 (t, 2 H, J = 3 Hz), 7.20–7.90 (m, 5 H). Anal. ($C_{26}H_{29}O_2N_3$) C, H, N.

In a similar manner, **10** (79 mg, 0.33 mmol) and PTAD (57 mg, 0.33 mmol) produced a solid residue, which was purified by means of column chromatography followed by recrystallization from ethyl acetate to give **13**: 87 mg (64%); mp 106–109 °C; IR (KBr) 3110, 3030, 2940, 1770, 1705, 1610, 1510, 1410, 1025 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.3–1.0 (m, 16 H), 1.4–1.8 (m, 4 H), 2.62 (s, 4 H), 7.20–7.70 (m, 5 H). Anal. ($C_{26}H_{29}O_2N_3$) C, H, N.

The reactions of both **9** and **10** with PTAD proceeded fairly rapidly since a red color of the PTAD solution faded almost instantly on the addition of the solution of **9** or **10**. In contrast, the reaction of **9** with **2b** required heating and gave a complex mixture, from which **5** could not be isolated.

Registry No. **1a**, 60166-70-3; **1b**, 22975-43-5; **1c**, 598-25-4; **2a**, 96-33-3; **2b**, 624-49-7; **2c**, 624-48-6; **2d**, 3377-20-6; **2e**, 108-31-6; **2f**, 107-13-1; **2g**, 764-42-1; **2h**, 928-53-0; **2i**, 922-64-5; **2j**, 670-54-2; **3a**, 82742-61-8; **3b**, 82736-60-5; **3c**, 82736-61-6; **3d**, 85084-70-4; **3e**, 85084-71-5; **3f**, 85084-72-6; **3g**, 85084-73-7; **3h**, 85084-74-8; **3i**, 85084-75-9; **3j**, 85084-76-0; **3k**, 85084-77-1; **3m**, 85084-78-2; **4a**, 82736-55-8; **4b**, 82736-56-9; **4c**, 82736-57-0; **4d**, 85084-79-3; **4f**, 85084-80-6; **4g**, 85084-81-7; **4h**, 85084-82-8; **4i**, 85084-83-9; **4k**, 85084-84-0; **4l**, 85084-85-1; **4m**, 85084-86-2; **4n**, 85084-87-3; **5**, 85084-88-4; **6**, 85084-89-5; **7**, 85084-90-8; **8**, 85084-91-9; **9**, 85084-92-0; **10**, 85084-93-1; **11**, 85084-94-2; **12**, 85084-95-3; **13**, 85084-96-4; PTAD, 4233-33-4; $AlCl_3$, 7446-70-0.

Stereochemistry of Lithiation of *N*-Methylformamide: A Theoretical Study

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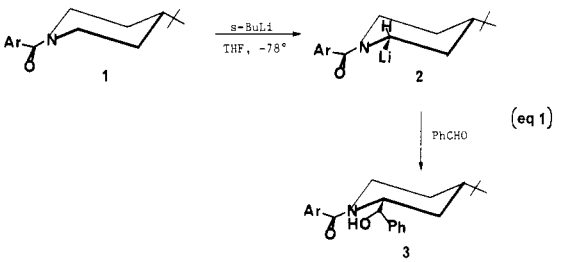
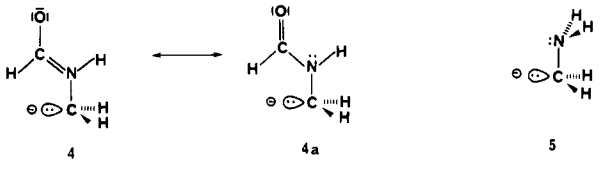
A theoretical examination of the destabilizing effects of a carbanion adjacent to the nitrogen of an amide is presented. When the methyl anion of *N*-methylformamide is placed in conjugation with the amide π system, the molecule is calculated to be 22.3 kcal/mol higher in energy than the ground-state "dipole-stabilized" conformer when a 4-31G basis set is employed. A perturbational molecular orbital (PMO) treatment suggests that the destabilization arises from the increase in energy of the molecular orbital that is largely comprised of the carbanionic center. A similar PMO treatment of formamide provides a rationale for the origin of the barrier to rotation in amides where the energy minimum involves the planar delocalized conformer. The significance of four-electron HOMO–HOMO interactions in both rotational barriers is discussed. A stereoelectronic argument is offered to explain the syn equatorial alkylation of cyclic α-amido anions.

Dipole-stabilized carbanions adjacent to an ester oxygen or the nitrogen of an amide group have recently been shown to be of synthetic utility.[1] For example, Beak[1a] has found that lithiation of the 2,4,6-triisopropylbenzamide **1** followed by reaction with benzaldehyde gave exclusively syn equatorial substitution affording **3**, the thermodynamically *less stable* stereoisomer (eq 1). A sufficient number of related examples[2] of the specificity of metalation have appeared that support the suggestion[1a,3] that syn metalation and substitution of amides is general.



A recent ab initio SCF study[3] presented convincing arguments that the stabilization of such "dipole-stabilized" anions[1a] is relatively high. When the internal dipoles are oriented for maximum stability, as depicted in anion **4**,



extended basis set (4-31+G//STO-3G)[4a] calculations

(1) (a) Beak, P.; Reitz, D. B. *Chem. Rev.* **1978**, *78*, 275. (b) Lubosch, W.; Seebach, D. *Helv. Chim. Acta* **1980**, *63*, 102. (c) Macdonald, T. L. *J. Org. Chem.* **1980**, *45*, 193.

(2) (a) Beak, P.; Brubaker, G. R.; Farney, R. F. *J. Am. Chem. Soc.* **1976**, *98*, 3621. (b) Schlecker, R.; Seebach, D.; Lubosch, W. *Helv. Chim. Acta* **1978**, *61*, 512.

(3) Rondan, N. G.; Houk, K. N.; Beak, P.; Zajdel, W. J.; Chandrasekhar, J.; Schleyer, P. v. R. *J. Org. Chem.* **1981**, *46*, 4108.

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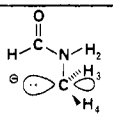
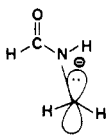
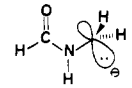
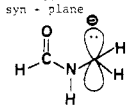
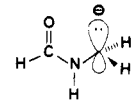
Table I. Calculated Energies (hartrees) of Conformers for Anions 4 and 6

anions	basis set	energy, au	E_{rel}, kcal/mol
 4a anti - in plane	STO-3G	−204.440 61	0.0
	4-31G	−206.968 85	0.0
 4b anti - perpendicular	STO-3G	−204.388 26	32.85
	4-31G	−206.940 08	18.05
 6a syn - plane	STO-3G	−204.433 52	4.45
	4-31G	−206.958 23	6.66
 6b syn - perpendicular	STO-3G	−204.380 90	37.47
	4-31G	−206.933 33	22.29
 6c syn - in plane eclipsed	STO-3G	−204.430 51	6.34
	4-31G	−206.949 89	11.90

suggest that the formyl group provides a net stabilization of 28 kcal/mol relative to anion **5** when their relative proton affinities are compared. The syn α-amido anion **6a**, where the attractive interaction between the partially positive carbonyl carbon and the carbanionic center is diminished, was calculated (4-31G//STO-3G) to be 9 kcal/mol higher in energy than the ground-state anti α-amido anion **4a**.[3] The geometric preference for the anti conformation of the "naked anion" in such model compounds is not consistent with the experimental observations in eq 1, where a syn metalated intermediate is probable. This discrepancy was attributed to lithium ion complexation of the carbonyl oxygen in a syn chelated structure that domainated the rotational barrier about the N–CO bond, thwarting the natural conformational preference for the anti "naked anion" **4a**. We now provide additional theoretical data that specifically address the relative stability of the "axial" vs. "equatorial" anion in **2**. We attribute the preference for syn equatorial metalation to the kinetic acidity of the equatorial hydrogen as a consequence of the destabilizing effect of the delocalized carbanion required in the "axial" organolithium corresponding to **2**.

With anions of acyclic N-substituted amides (e.g., **4a** and **6a**), conformational equilibration may be achieved by N–CO bond rotation or by inversion at carbon, which is normally a low activation process (Table I). While the energy differences resulting from dipole stabilization influence the position of equilibrium, the magnitudes of the rotational barriers determine the rate of interchange. However, interconversion of diastereomeric anions in a cyclic structure like **2** can be a relatively high-energy process requiring ring reversal or carbanion inversion in the absence of hydrogen exchange. At low temperature (−78 °C) it is highly unlikely that the carbanionic center will invert. If the carbanionic center attains planarity, a destabilizing electronic interaction of the filled p orbital with the amide π system can occur in the transition state (vide infra). Therefore, the product distribution upon metalation of **1** should be a reflection of the relative kinetic acidities of the axial and equatorial hydrogens. This assumes that lithium complexation does not influence the stability of the transition state for formation of the syn anion until the proton is essentially removed. This raises the question whether it is energetically more favorable to have a developing carbanion that is isolated and perpendicular to the amide π system (equatorial attack) or to have the anion in extended conjugation with the delocalized amide system (axial attack).

We chose selected conformers of anions **4** and **6** as model substrates. As noted previously,[3] syn **6a** and anti **4a** represent pyramidal carbanions in which the lone-pair orbital is coplanar with the amide σ-bond skeleton and orthogonal to the π system of the resonance-stabilized amide group. With geometry optimization[4b] (Table II), the latter anion **4a** is 6.66 kcal/mol (4-31G, Table I) lower in energy. The energetic contribution of a maximized dipole–dipole orientation of the negatively charged carbon is further noted in the increase (5.24 kcal/mol) in energy that accompanies inversion of configuration at carbon (**6a** → **6c**). Thus, the in-plane eclipsed anion **6c** is 11.90 kcal/mol (4-31G) above the ground state in the absence of the chelating stabilization of a lithium cation. In contrast, syn **6b** and anti **4b** anions are perpendicular to the plane of the amide skeleton and have a planar sp^2 geometry at the carbanionic carbon. The calculated (4-31G) N–CH_2 rotational barriers of 18.1 (**4a** → **4b**) and 15.6 (**6a** → **6b**) kcal/mol suggest that placing the planar carbanion in extended conjunction with the amide group results in appreciable destabilization. It is worthy of note that delocalized anions (**6b** and **4b**) are isoelectronic with the dianion of butadiene.

The inherent energy differences between the dipole-stabilized anions (**4a** and **6a**), and anions (**4b** and **6b**) where the π orbitals are coplanar, strongly suggest that the equatorial hydrogen in **1** would be the more acidic one, affording anion **2** upon treatment with strong base. In order to address the origin of these significant energy differences, we elected to dissect the anions into fragment orbitals and examine the relative energies of orbital "recombination." An isolated carbonyl functional group has two π electrons in two atomic p orbitals; an amide has four π electrons delocalized in three orbitals, while **6b** has six π electrons in four atomic p orbitals. Anion **6b** has a HOMO containing two nodes that has similar symmetry properties (Figure 3) to ψ_3 in the butadiene π-molecular orbitals.

We first applied perturbation molecular orbital (PMO) theory to the simplest amide, formamide (**7**), to see if we could identify those molecular orbitals largely responsible for its rotational barrier. The maximum in its rotational barrier as measured experimentally (19 kcal/mol)[5] is

(4) (a) The geometry was optimized with the minimal STO-3G basis set, and a single point calculation on that geometry employing the extended split-valence 4-31G basis, or the 4-31+G basis (the 4-31G basis set augmented by a set of diffuse s and p functions on all nonhydrogen atoms), was used to provide a more reliable total energy difference. (b) This study used the Gaussian 80 series of programs. The geometries of anions **4** and **6** were optimized with both STO-3G and 4-31G basis sets. In the conjugated structure C_s symmetry was maintained and the two hydrogens of the CH_2 group were treated as identical. The energies are given in Table I and the geometries in Table II. (c) Binkley, J. F.; Whiteside, R. A.; Krishnan, R.; Seeger, R.; DeFrees, D. J.; Schlegel, H. B.; Topiol, S.; Kahn, L. R.; Pople, J. A. *QCPE* **1981**, *13*, 46.

(5) Drakenberg, T.; Fŏrsen, S. *J. Phys. Chem.* **1970**, *74*, 1.

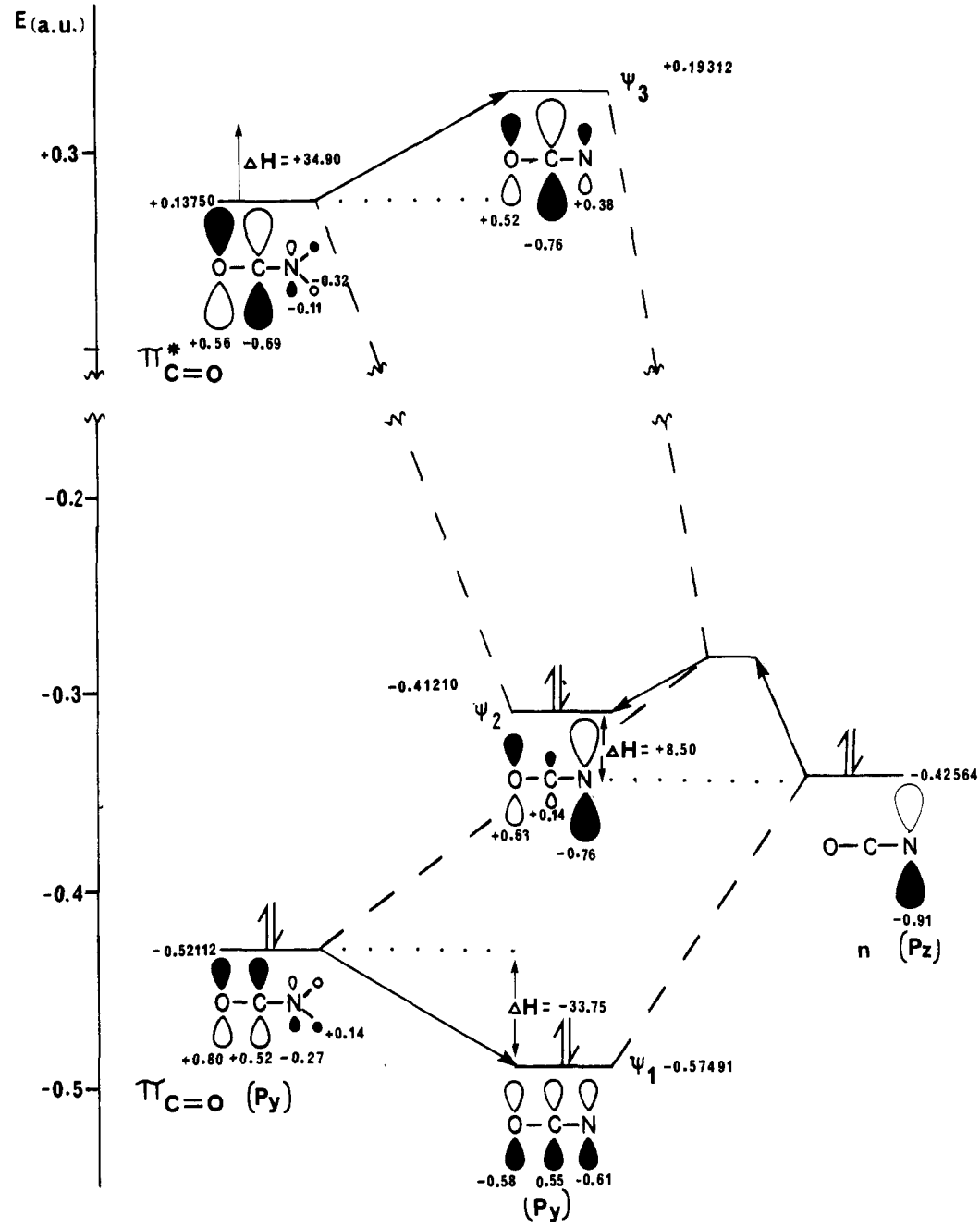
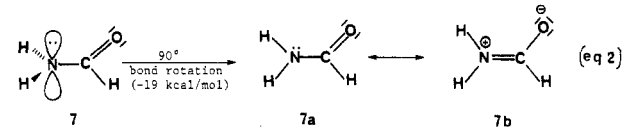


Figure 1. Interaction of a filled nitrogen p orbital with the carbonyl system (4-31G).

achieved when the nitrogen lone pair is perpendicular to the carbonyl π bond. The stabilizing influence of a nitrogen lone pair in conjunction with $\pi_{C=O}$ has been calculated to be 21.7 kcal/mol (including d atomic functions)[6a] and 24.7 kcal/mol with a 4-31G basis set.[6b] The parent amide has been shown to be essentially planar at nitrogen at its energy minimum.[7] We therefore chose as our basis orbitals the orthogonal nitrogen lone pair[8] and the π and π^* orbitals of the carbonyl group in formamide (7), where interaction of the nitrogen lone pair and the π-orbitals is precluded by symmetry. A 90° bond rotation in conformer 7 (eq 2) allows mixing of the doubly occupied nitrogen p



7 7a 7b

orbital with the carbonyl π orbitals affording formamide (**7a**) at its energy minimum. The calculated (4-31G) energy levels and coefficients for the three "isolated" basis orbitals and the resultant three delocalized molecular orbitals are given in Figure 1. It should be noted that the basis π orbitals contain a small contribution from a π-type NH_2 fragment orbital[9] that lies in the same plane as the car-

(6) (a) Radom, L.; Lathan, W. A.; Hehre, W. J.; Pople, J. A. *Aust. J. Chem.* **1972**, *25*, 1601. (b) Carlsen, N. R.; Radom, L.; Riggs, N. V.; Rodwell, W. R. *J. Am. Chem. Soc.* **1979**, *101*, 2233. (c) Christensen, D. H.; Kortzeborn, R. N.; Bak, B.; Led, J. J. *J. Chem. Phys.* **1970**, *53*, 3912.

(7) Hirota, E.; Sugisaki, R.; Nielsen, C. J.; Sørensen, G. O. *J. Mol. Spectrosc.* **1974**, *49*, 251.

(8) The CNH bond angle was calculated to be 115.95° at its energy maximum with an HN–CO dihedral angle of 67.95°. We calculated a 4-31G rotational barrier of 19.96 kcal/mol with full geometry optimization of the nondelocalized 90° conformer with a pyramidal nitrogen.

(9) A π-type NH_2 fragment is comprised of an atomic 2p orbital on nitrogen and the 1s orbitals of hydrogen. For a discussion, see: Jorgensen, W. L.; Salem, L. "The Organic Chemist's Book of Orbitals"; Academic Press: New York, 1973; p 6. Fleming, I. "Frontier Orbitals and Organic Chemical Reactions"; Wiley: New York, 1967; p 7.

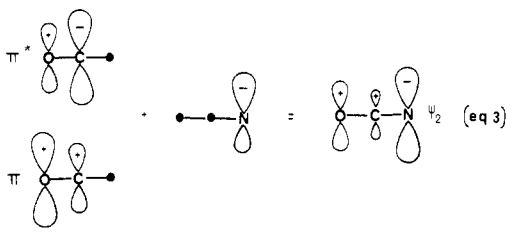
Table II. Geometry Optimization (4-31G) of *N*-Methylformamide Anions[a]

	4a	4b	6a	6b	6c
$r_{C=O}$	1.2462	1.2703	1.2367	1.2600	1.2304
r_{N-CO}	1.3156	1.3021	1.3191	1.3083	1.3259
r_{C-N}	1.5155	1.4526	1.5190	1.4350	1.5033
r_{C-H_1}	1.0864	1.0855	1.0984	1.0936	1.1002
r_{N-H}	0.9945	0.9958	0.9929	0.9930	1.0020
r_{C-H_3}	1.1035	1.0668	1.1030	1.0656	1.1064
r_{C-H_4}	1.1035	1.0668	1.1030	1.0656	1.1064
∠NCO	127.70	126.56	129.26	127.92	131.34
∠CNC	128.37	130.57	130.48	129.97	126.74
$\angle H_1CN$	112.37	113.47	112.67	112.68	111.12
$\angle H_2NC(O)$	115.41	114.07	115.23	115.54	112.45
$\angle H_3CN$	106.29	117.29	105.31	117.23	105.39
$\angle H_4CN$	106.29	117.29	105.31	117.23	105.39
∠CNCO	180.00	180.00	0.00	0.00	0.00
$\angle H_1CNC$	0.00	0.00	180.00	180.00	180.00
$\angle H_2NCO$	0.00	0.00	180.00	180.00	180.00
$\angle H_3CNH_1$	123.37	0.00	124.58	0.00	55.92
$\angle H_4CNH_1$	−123.37	180.00	−124.58	180.00	−55.92

[a] Bond lengths are in angstroms; bond angles are in degrees.

bonyl π system. These π-type NH_2 fragments are perpendicular to the π orbitals in conformer **7a**.

We can attain a better understanding of the relative energy changes attending the interaction of the three basis orbitals by assuming that the resulting molecular orbitals are the consequence of both two- and four-electron interactions. The four-electron interaction[10] of the nitrogen lone pair (n) and the filled $\pi_{C=O}$ orbital upon 90° bond rotation (eq 2) gives rise to a low-lying bonding combination ψ_1 (Figure 1) and an occupied antibonding ($\pi_{C=O}$ − n) orbital where the π bond and the lone pair are mixed in an out-of-phase manner. The orbital splitting resulting from the two-electron interaction of the nitrogen lone pair with the empty $\pi^*_{C=O}$ affords the LUMO ψ_3 and a filled ($\pi^*_{C=O}$ + n) combination. The central orbital, ψ_2, may be derived from a linear combination of the two central fragment orbitals where ($\pi^*_{C=O}$ − n) + ($\pi^*_{C=O}$ + n) = ψ_2. Alternately, ψ_2 may be constructed by combining the basis orbitals given in eq 3, where the nitrogen lone pair is el-



evated in energy by mixing with the $\pi_{C=O}$ orbital below it and decreased in energy by combination with the higher lying $\pi^*_{C=O}$ orbital. Following perturbation rules the ultimate position of the node in ψ_2 will depend upon the amount of cancellation at the central carbon atom in ψ_2 by the coefficients of different sign and magnitude in the π and π^* orbitals. Since the nitrogen lone pair at −0.42 au (4-31G) is closer in energy to the occupied $\pi_{C=O}$ level at −0.52 au (Figure 1), this orbital interaction dominates; and the central carbon of ψ_2 has a positive coefficient despite the fact that the negative coefficient at carbon in $\pi^*_{C=O}$ is larger. Consequently, the phasing in the resulting central orbital ψ_2 more closely resembles the ($\pi_{C=O}$ − n) basis orbital. By analogy, the interaction of three degenerate p orbitals gives exact cancellation as noted for the classical allyl anion where ψ_2 has a node at the central carbon.[11]

The above PMO analysis is in accord with the observed calculated changes in the energy levels of the resulting molecular orbitals (Figure 1). The interaction between two basis orbitals in Figure 1 is indicated by dotted lines, while the relative changes in energies of the resultant molecular orbitals are shown by the heavy arrows. Thus, the $\pi_{C=O}$ orbital is calculated (4-31G) to decrease in energy by 33.75 kcal/mol as the result of the four-electron interaction. Theoretically,[10] the nitrogen p level should increase in energy by slightly more than that *in the absence of a higher lying molecular orbital* of proper symmetry. However, the accompanying decrease in the *n* level as a result of the two-electron interaction of the occupied ($\pi_{C=O}$ − n) orbital with the $\pi^*_{C=O}$ component (or as in eq 3) affords ψ_2 that is only 8.50 kcal/mol above the energy of the unperturbed nitrogen lone pair. Thus, the resonance energy of the amide group, or the decrease in the overall ground state of planar delocalized formamide (**7a** → **7b**), is a manifestation of the fact that the energy liberated (33.8 kcal/mol) in forming ψ_1 is greater than that expended (8.5 kcal/mol) upon formation of ψ_2. These energy differences in the frontier molecular orbitals provide a reasonable account of the calculated barrier (19.96 kcal/mol) to C–N bond rotation in **7** and identifies ψ_1 as the orbital most responsible for this barrier as a consequence of its sharp increase in energy when conjugation is lost. It is also important to note that the HOMO–HOMO (four-electron) interaction played a significant role in determining both the relative energy and the position of the node in the central orbital ψ_2 (HOMO) in formamide. We feel that it is important to stress this point since these interactions are typically ignored in PMO treatments involving two reactants. For example, if one tried to explain amide resonance employing the argument that the lone pair on nitrogen (HOMO) interacts solely with the $\pi^*_{C=O}$ orbital (LUMO), the conclusion would be reached that the nitrogen lone pair would *decrease* in energy and the phase of the resultant occupied orbital (ψ_2) would be ($\pi^*_{C=O}$ + n). Obviously, both two- and four-electron interactions must be included in any PMO treatment of electron delocalization such as that occurring in amides, esters, etc.

It now remains to extend the above exercise on an amide, where the rotational barrier was known, to the syn per-

(10) For a discussion of the destabilizing influence of a four-electron interaction see: Epiotis, N. D.; Cherry, W. R.; Shaik, S.; Yates, R. L.; Bernardi, F. "Topics in Current Chemistry"; Springer-Verlag: New York, 1977; p 7.

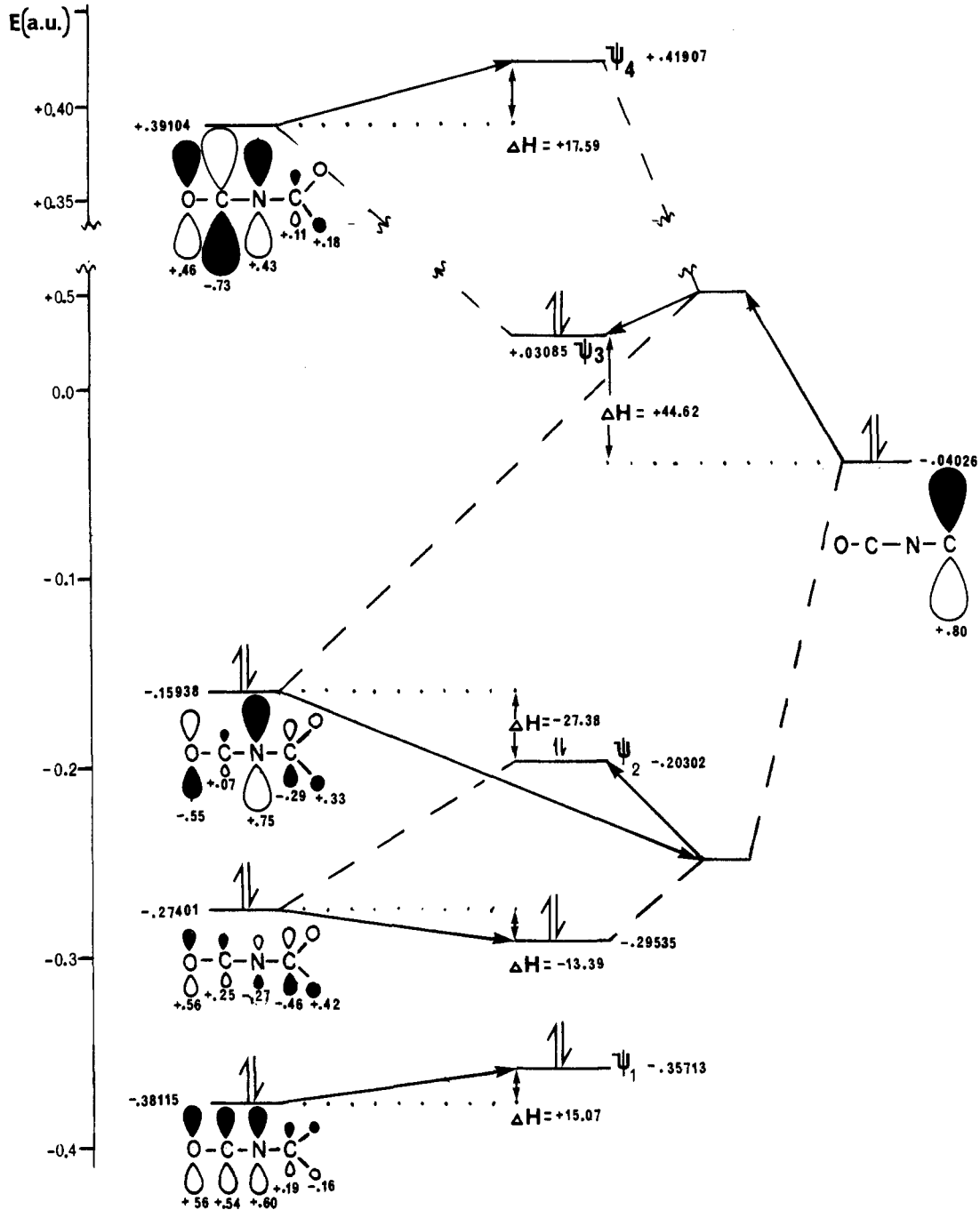


Figure 2. Interaction of a filled carbon p orbital with planar formamide (4-31G).

pendicular carbanion **6b** in order to assess the energetic effects of placing a carbanion in conjugation with the amide moiety. In similar fashion, we chose the three π-molecular orbitals of the amide portion of the anion and the nonconjugated orthogonal carbanionic center in the syn in-plane dipole-stabilized anion **6a** as our basis orbitals. A 90° H_2C–N bond rotation in **6a** affords delocalized anion **6b**. The calculated (4-31G) energy levels for the noninteracting anion and the conjugated anion are shown in Figure 2. The delocalized molecular orbitals for **6b** that result upon bond rotation are given in Figure 3. The lowest lying amide fragment π orbital (ψ_1) is split into two orbitals, each containing a contribution from a π_{CH_2}-type orbital (Figure 2). Thus, we have utilized an additional occupied basis orbital. The additional π_{CH_2} orbital is omitted from the molecular orbitals in **6b** (Figure 3) for clarity. We emphasize the fact that these π_{CH_2}-type orbitals[9] are in the plane of the π system in **6a** and perpendicular to the π system after bond rotation affording **6b**.

It is immediately obvious that the π-molecular orbitals of **6b** have the same nodal properties as the linear combination of π orbitals, ψ_1, ψ_2, ψ_3, and ψ_4 in butadiene. The significant concentration of negative charge (coefficient = –0.85) on the carbanionic center in the occupied ψ_3 is also evident. The relatively high energy of this HOMO is a reflection of the strong antibonding interactions as a result of the two nodes.

Our PMO treatment of **6a** and the calculated changes in energy levels of the frontier orbitals of **6b** upon 90° bond rotation again provides a very reasonable approximation to the C–N torsional barrier. The two lower lying molecular orbitals can exert only a modest effect upon the barrier since they essentially cancel each other with one level increasing by 15.1 kcal/mol and the other decreasing in energy by 13.4 kcal/mol. The most important orbital

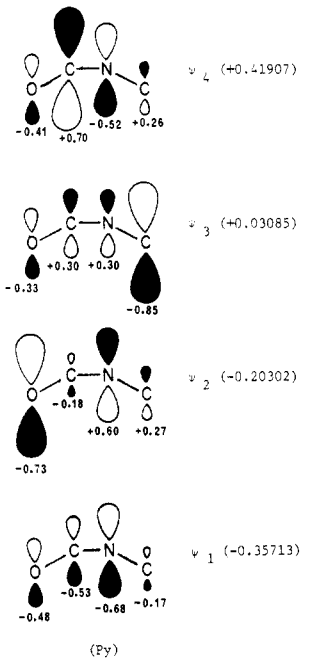
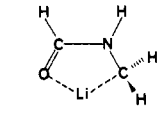


Figure 3. Molecular orbitals of the syn-perpendicular conjugated anion **6b** (4-31G).

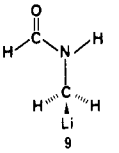
mixing encountered in the conjugated anion is the four-electron interaction between the doubly occupied carbon p orbital and the highest occupied level of the amide fragment (Figure 2). This orbital splitting affords a lower lying combination (ψ_2) containing one node that will obviously be elevated in energy by a secondary interaction with occupied orbitals below it (i.e., four-electron interactions). The upper antibonding combination containing one additional node (ψ_3) is lowered in energy by mixing with the empty orbital above it as indicated by the arrows in Figure 2. One estimate of the magnitude of this two-electron interaction comes from noting the 17.59 kcal/mol increase in the highest amide basis orbital to give ψ_4 in **6b**. The incipient ψ_3 orbital should be lowered by approximately that amount as the linear combination of fragment orbitals is achieved. The final result of the four-electron "HOMO–HOMO" interaction is that ψ_3 is elevated 44.62 kcal/mol above the isolated (carbanionic) p orbital. This significant increase in orbital energy is accompanied by a decrease of only 27.38 kcal/mol in the highest occupied basis "amide" orbital as it is transformed into ψ_2. Consequently, anion **6b** exhibits an energy maximum in its planar delocalized geometry in direct contrast to formamide.

The net difference in the relative energy changes of 17.2 kcal/mol for the two frontier orbitals is in excellent agreement with the calculated rotational barrier (15.6 kcal/mol) for interconversion of **6a** to **6b** and the calculated energy difference of 18.1 kcal/mol for the ground-state **4a** and anion conformer **4b** (Table I). This PMO analysis clearly identifies ψ_3 as the "culprit orbital" responsible for these rotational barriers. Thus, the destabilization realized upon extending amide conjugation by a repulsive anionic interaction is largely attributable to different energetic effects on ψ_2 and ψ_3. The increase in energy of ψ_3, due to the primary four-electron orbital splitting, is greater than the energy lowering of ψ_2 and the overall ground-state energy of the "butadienyl" anion system is increased.

We suggest that the electronic effects of extended amide conjugation should be felt relatively early along the reaction coordinate for proton removal forming an α-amido anion. This assumption should be valid even if the lithium ion is bonding to the carbon in concert with proton removal (i.e., a four-center attack) by the alkyl anion. Since the C–Li bond is highly ionic, there will still be extensive accumulation of negative charge at the developing carbanionic carbon. This should strongly affect the kinetic acidity of axial vs. equatorial hydrogens in cyclic compounds such as **1**. Once lithiation of the amide has been achieved, the solvated anion should obviously be more stable in a chelated structure such as **8**. Although our



8



9

$r_{C\text{-}Li}$ = 2.00 Å
$r_{O\text{-}Li}$ = 1.73 Å
∠OCN = 125.35°
∠NCLi = 90.47°
∠CNC = 120.82°

calculations suggest that in the absence of a lithium cation, equatorial metalation should be anticipated, we feel that it is reasonable to assume that initial complexation of the RLi with the carbonyl oxygen under the reaction conditions (eq 1) would favor a syn metalation. Partial geometry minimization (STO-3G) of **8** shows that the oxygen–lithium bond is shorter than the carbon–lithium bond and that this structure is considerably more stable than **9**, where a lithium cation has also been placed at carbon with a C–Li bond distance of 2.0 Å.[12]

We conclude that proton removal adjacent to an amide nitrogen will be best achieved when the resulting anion attains a conformation where it is not conjugated with the amide π system. We have provided an example where extending conjugation has a net destabilizing effect. In both the amide and the α-amido anion system the energy levels of the resulting molecular orbitals were shown to be a consequence of *both* two-electron and four-electron interactions. In the conjugated amide **7** the stabilizing influence of the two-electron interaction is dominating, while the conformational preference for the nonconjugated anions is a result of a net destabilizing four-electron interaction.

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Registry No. Methylformamide anion, 78715-78-3; formamide, 75-12-7.

(11) For a discussion of the allyl system, see: Lowry, T. H.; Richardson, K. S. "Mechanism and Theory in Organic Chemistry"; Harper and Row: New York, 1981; p 73.

(12) The skeletal geometry of **9** was taken from **6b** without further geometry optimization. As a result, the calculated energy difference of 67 kcal/mol (STO-3G) serves as a crude estimate.