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Dipole-Stabilized Carbanions: A Computational Study of *N*-Methylformamide Anion and Methyl *N*-Methylcarbamate Anion

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The relative energies of the rotamers of the carbanions derived from *N*-methylformamide and methyl *N*-methylcarbamate have been studied at the MP2/6-311+G* and B3LYP/6-311+G* theoretical levels. There results are in good agreement but differ substantially from previously reported HF/6-31G* calculations for the *N*-methylformamide anions. Transition states for rotation and inversion of the anions were located. The methoxy group in methyl *N*-methylcarbamate has a large effect on the relative energies of the anions. The results are compared with those previously reported for the *N*-(methoxycarbonyl)piperidine anions, and it is found that the decreased conformational flexibility has an effect on the relative energies of these ions.

A carbanion that is stabilized by an adjacent dipole has been termed a "dipole-stabilized" anion,[1] and such a species is formed when a substituted amide is deprotonated at the position α to the nitrogen atom.[2] Dipole-stabilized anions derived from amides are important in a variety of processes[2,3] including the enantioselective deprotonation of Boc-pyrrolidine[4] and other carbamates[5] by the 1:1 complex of a *sec*-alkyllithium and (−)-sparteine.

The *N*-methylformamide anion, $HCONHCH_2^-$, is the simplest model for such a system and, not surprisingly, it has received considerable study. Houk, Beak, and Schleyer examined the *N*-methylformamide anion at the HF/4-31+G//STO-3G level,[6] Bach, Braden, and Wolber carried out a more detailed study at the HF/4-31G* level,[7] and Bartolotti and Gawley further examined the system, along with the effects of lithium chelation, at the HF/6-31G* level.[8]

In the course of an investigation of the deprotonation of Boc-piperidine by the *i*-PrLi−(−)-sparteine complex[9] we calculated, at the B3P86/6-311+G* level of theory, the acidity of the four diastereotopic α-hydrogens in the piperidine carbamate: the axial hydrogens were found to be the more acidic than the equatorial hydrogens and, for a given type of hydrogen (i.e., axial or equatorial), the hydrogen distal to the carbonyl oxygen was found to be more acidic than that proximal to this group. The results of our investigation of the anions derived from a piperidine carbamate are at odds with conclusions that might be drawn from theoretical studies of the *N*-methylformamide anion, which appear to suggest that the equatorial hydrogens of Boc-piperidine should be more acidic,[6−8] and these discrepancies prompted a reexamination of the calculations for this model anion.

There are several possible explanations for the difference between conclusions drawn from our examination of the anions derived from a piperidine carbamate and previous studies of the *N*-methylformamide anion. First, it is possible that electron correlation plays an important role in both systems and the HF level of theory is not satisfactory for an examination of the *N*-methylformamide anion. Second, the *N*-methylformamide anion may not be a good model for a carbamate. Third, the conformational constraints imposed by the relatively rigid piperidine system may be an important factor in determining the relative hydrogen acidities in Boc-piperidine. As detailed below, each of these factors appears to be important.

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TABLE 1. Relative Energies of *N*-Methylformamide Anions (Figure 1)[a]

	HF/6-31G*	B3LYP/6-311+G*			MP2/6-311+G*		
anion	E_{rel}	E_{rel}	$\Delta\Delta H$	$\Delta\Delta G$	E_{rel}	$\Delta\Delta H$	$\Delta\Delta G$
1	0.0 (0)	0.0 (0)	0.0	0.0	0.0 (0)	0.0	0.0
2	2.3 (0)	1.1 (0)	1.2	1.0	1.0 (0)	1.1	0.5
3	25.4 (2)	10.7 (2)	9.5	10.3	13.1 (2)	11.5	12.1
3a	12.7 (1)	5.4 (1)	4.7	4.5	5.3 (1)	4.5	4.4
3b	7.7 (1)	4.2 (1)	3.7	4.3	5.4 (1)	4.8	5.3
4	28.4 (2)	9.7 (1)	9.0	9.0	11.5 (1)	10.3	9.9
5	8.1 (0)	5.5 (1)	4.8	5.4	5.4 (1)	4.7	5.2
5a	*b*	4.1 (0)	4.3	4.3	5.1 (0)	5.2	4.9
6	12.2 (0)	10.3 (1)	9.1	9.7	11.0 (1)	9.9	10.3
8	22.8 (1)	13.1 (2)	11.3	12.1	14.0 (2)	12.2	12.9

[a] Energies (kcal/mol) have been corrected for both differences in zero point energy and the change in enthalpy on going from 0 K (corresponding to the calculations) to 298 K. The number of imaginary frequencies is given in parentheses. [b] Not calculated since **5** is a minimum at HF/6-31G*.

Results and Discussion

We have reinvestigated the *N*-methylformamide anion at the B3LYP/6-311+G* level,[10] including the calculation of the vibrational frequencies, to properly characterize each species as a ground state, a transition state, or a higher order saddle point. The anion was also investigated at the HF/6-31G* level for a comparison with the previous reports.[6-8] In addition, we have examined the corresponding methyl *N*-methylcarbamate anion, MeOCO-$NHCH_2^-$, to investigate potential differences between carbamate and amide model anions.

A total of 10 geometries of the *N*-methylformamide anion were explored at various theoretical levels. The calculated relative energies, corrected for differences in zero point energies as well as for the change in enthalpy on going from 0 to 298 K (25 °C), along with the number of imaginary frequencies (*N*) found for each species, are summarized in Table 1.[11] The structures of the *N*-methylformamide anions, along with their relative free energies ($\Delta\Delta G$) calculated at the B3LYP level, are shown in Figure 1; structures identified as transition states (one imaginary frequency) are designated by *, second-order saddle points (two imaginary frequencies) are designated by #.

The calculated HF/6-31G* energies of the *N*-methylformamide anions are in good agreement with those previously reported by Bartolotti and Gawley;[8] however, at the B3LYP level, the two planar geometries of the anion, **3** and **8** (Figure 1), are found to be second-order saddle points rather than transition states as found with HF/6-31G* (Table 1). The B3LYP transition states for inversion at N (**3a**), and for rotation about the N−CH_2^- bond (**3b**) in the anti-arrangement of the anion (O−C−N−C torsional angle ≈ 180°), were located by distorting **3** along each of the two imaginary vibrational modes and reoptimizing to transition states. Both transition states (**3a** and **3b**) had significantly lower energies than **3**. It is interesting to note that the CH_2^- group in **3b** remains pyramidal during the rotation process.

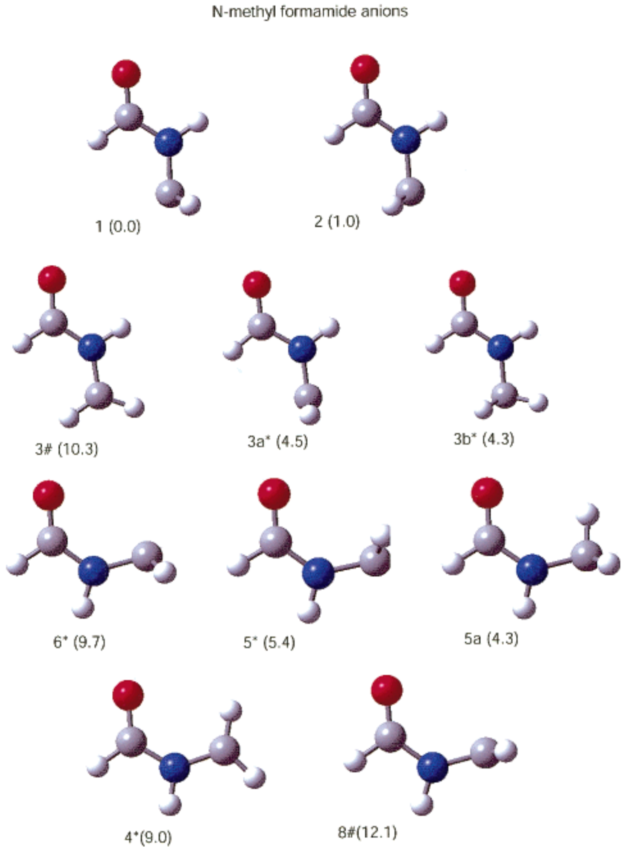

FIGURE 1. Structures of *N*-methylformamide anions along with their relative B3LYP/6-311+G* free energies ($\Delta\Delta G$); structures identified as transition states (one imaginary frequency) are designated by *, second-order saddle points (two imaginary frequencies) are designated by #.

The lowest energy *N*-methylformamide anions, **1** and **2**, have similar energies at the B3LYP/6-311+G* level (Table 1). This result implies that attraction between the anion lone pair and the carbonyl carbon is not a major factor in stabilizing these ions. The B3LYP relative energies of **3**, **3a**, and **3b** have decreased significantly with respect to the HF/6-31G* energies (Table 1). There are several other significant differences between the results of the B3LYP calculations and those found with HF/6-31G* (Table 1): the planar ion, **4**, is a transition state at the B3LYP level rather than a second-order saddle point as found with HF/6-31G*; ions **5** and **6** are also calculated to be transition states at the B3LYP level rather than the ground-state structures identified in the HF/6-31G* calculations. The transition state structures **5** and **6** were distorted slightly and then reoptimized to a local minimum; both led to a lower energy, ground-state structure, **5a**, which had no imaginary frequencies. It is of some interest to note that one of the C−H methylene

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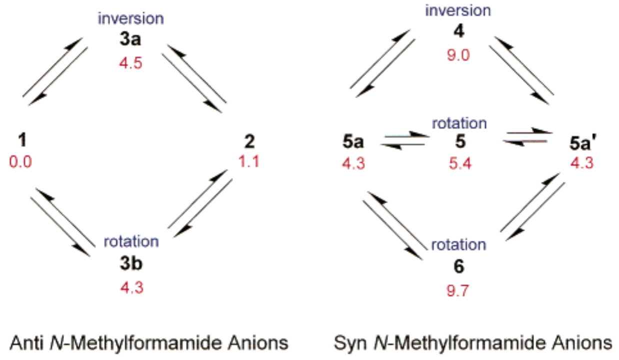
[10] Calculations were performed using Gaussian 99. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Baboul, A. G.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 99*, Development Version (Rev. B.04); Gaussian, Inc., Pittsburgh, PA, 1998.

[11] A summary of the calculations, including calculated absolute energies, zero point energies, and temperature corrections to the calculated enthalpies, are given in Table S1 of the Supporting Information.

SCHEME 1



bonds of **5a** is nearly eclipsed with the carbonyl group (Figure 1), a conformational feature that has been noted in a variety of other carboxylic acid derivatives.[12] Structure **5**, which lies only 1.1 kcal/mol higher in energy than **5a**, is the lower energy transition state for interconversion of **5** with its enantiomer (**5a′**) by rotation about the N−CH_2^- bond, and structure **6** is the higher energy transition state for this process. Structure **4**, which has only one imaginary frequency, is the transition state for interconversion of **5a** and its enantiomer (**5a′**) by inversion at nitrogen. It should be noted that structure **8**, a transition state for inversion at the HF/6-31G* level, is identified as a second-order saddle point at B3LYP/6-311+G*.

The relative B3LYP/6-311+G* free energies ($\Delta\Delta G$) of the various *N*-methylformamide anions, as well as the modes of interconversion of the anions, are summarized diagrammatically in Scheme 1.

In light of the rather large differences between the HF/6-31G* and B3LYP/6-311+G* results, MP2/6-311+G* optimizations were carried out for all of the species discussed above. The results of these calculations,[11] which are summarized in Table 1, demonstrate that there is good agreement between the B3LYP and MP2/6-311+G* relative energies as well as the number of imaginary frequencies calculated for each anion. Therefore, we conclude that HF/6-31G* is not adequate for an examination of *N*-methylformamide anions.

We were interested in examining the difference between the *N*-methylformamide anion and the corresponding methyl *N*-methylcarbamate anion (MeOCONHCH_2^-). The carbamate system was examined at the B3LYP/6-311+G* and MP2/6-311+G* levels, giving the relative energies summarized in Table 2.[11] The structures of the ions, along with their B3LYP energies ($\Delta\Delta G$), are illustrated in Figure 2. It should be noted that the carbamate ions are numbered **11**−**18** (Figure 2) to correspond with structures **1**−**8** (Figure 1) of the formamide anion series. In all cases, the methoxymethyl group of each carbamate anion is staggered with respect to the adjacent C−O bond. As might be expected for the replacement of the formyl hydrogen of the amide with the MeO group of the carbamate, there are some significant changes in relative energies.

TABLE 2. Relative Energies of Methyl *N*-Methylcarbamate Anions (Figure 2)[a]

		B3LYP/6-311+G*			MP2/6-311+G*		
anion	N[b]	E_{rel}	$\Delta\Delta H$	$\Delta\Delta G$	E_{rel}	$\Delta\Delta H$	$\Delta\Delta G$
11	0	3.0	2.7	3.2	3.5	3.2	3.5
12	0	0.2	0.3	0.4	0.0	0.0	0.0
13	2	8.7	7.4	8.7	10.5	8.9	9.5
13a	1	7.5	6.5	6.7	7.9	7.0	7.7
13b	1	3.3	2.5	3.8	4.2	3.4	4.5
14	2	8.5	7.1	8.4	10.6	8.2	10.2
15	1	0.1	−0.6	0.5	0.0	−0.7	0.3
15a	0	0.0	0.0	0.0	0.0	0.0	−0.1
16	0	4.1	3.6	3.5	4.5	4.0	3.6
17	1	4.2	3.1	4.1	5.0	4.0	4.7
18	1	7.9	6.3	7.6	8.3	6.6	7.7

[a] Energies (kcal/mol) have been corrected for both differences in zero point energy and the change in enthalpy on going from 0 K (corresponding to the calculations) to 298 K. [b] Number of imaginary frequencies.

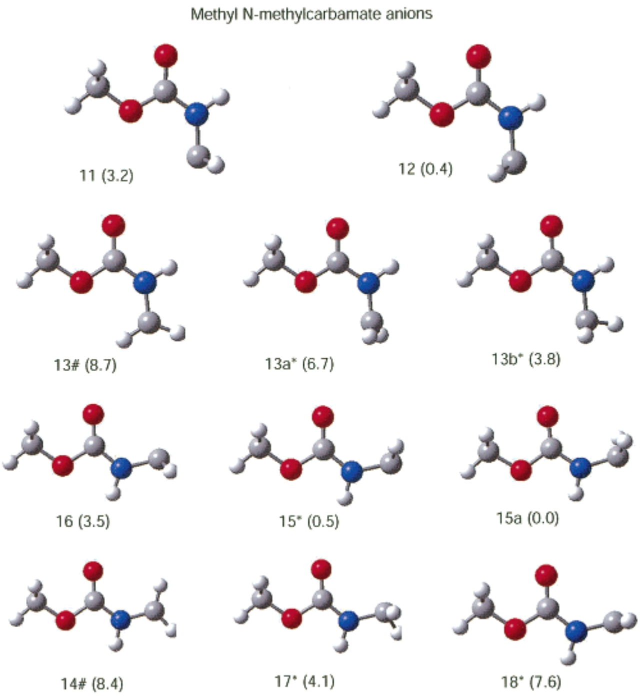


FIGURE 2. Structures of methyl *N*-methylcarbamate anions along with their relative B3LYP/6-311+G* free energies ($\Delta\Delta G$); structures are identified as in Figure 1.

The ground-state carbamate ions with the CH_2^- group anti to the carbonyl oxygen (**11** and **12**) display a much larger difference in energy than found with the corresponding amide ions (**1** and **2**). Moreover, the relative energies of the ions are reversed. The significantly higher energy of **11** probably results from the repulsion between the lone pair electrons and the negatively charged oxygen of the methoxy group.

Ion **13** is a second-order saddle point as found for the corresponding amide structure (**3**). Transition state **13a** is similar in structure to **3a** but **13b** has its CH_2^- group rotated with respect to the conformation of **3b**. The difference in the structures of **13b** and **3b** probably results from the large difference in energy between **11** and **12** since the rotational transition state, **13b**, will necessarily have a geometry close to that of the higher energy ground state (**11**).

The ground-state carbamate ions in the syn series, **15a** and **16**, correspond to structures **5a** and **6** of the amide.

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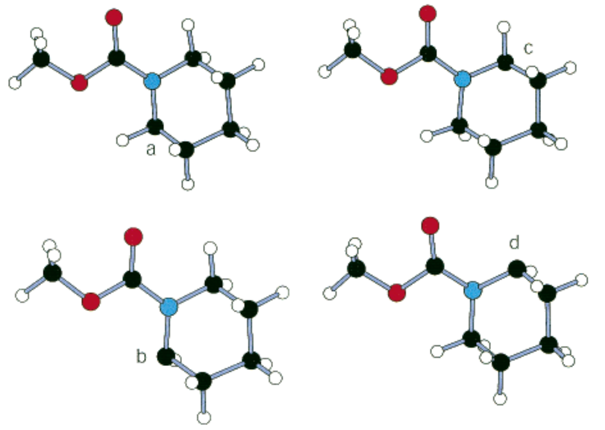
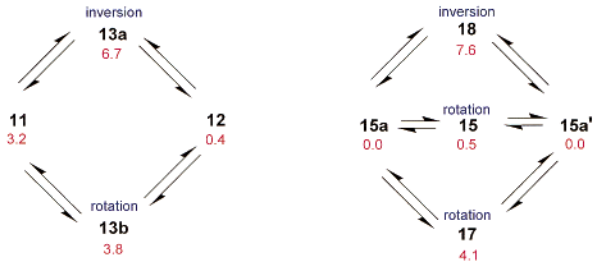


a. axial anion anti to C=O
b. equatorial anion anti to C=O
c. axial anion syn to C=O
d. equatorial anion syn to C-O

FIGURE 3. Structures of *N*-(methoxycarbonyl)piperidine anions (**A**−**D**) (*9*), in an orientation corresponding to those of the analogous methyl *N*-methylcarbamate anions depicted in Figure 2.

SCHEME 2



Anti Methyl *N*-Methylformamide Anions Syn Methyl *N*-Methylformamide Anions

The higher energy of ground state **16** vis-à-vis **15a** is likely a consequence of the fact that the lone pair of the CH_2^- group in **16** is directed toward the negatively charged carbonyl oxygen. Structure **15** is the transition state for interconverting **15a** and its enantiomer (**15a′**), structure **18** is the transition state for interconverting **15a** and **16** via inversion at nitrogen, and **17** is the transition state for interconversion of **15a** and **16** via rotation about the C−N bond. The relative B3LYP/6-311+G* free energies (ΔΔ*G*) of the various methyl *N*-methylcarbamate anions, along with the modes of interconversion among these anions, are diagrammed in Scheme 2.

Finally, we were interested in exploring whether the methyl *N*-methylcarbamate anion is a useful model for the anions derived by deprotonation of Boc-piperidine. The structures of the anions generated by removal of each of the four diastereotopic α-hydrogens of *N*-(methoxycarbonyl)piperidine, which were calculated in our recent investigation of the enantioselective deprotonation of Boc-piperidine,[9] are shown in Figure 3 in an orientation corresponding to those of the analogous methyl *N*-methylcarbamate anions depicted in Figure 2. Structures **B** and **D**, with equatorial lone pairs, have higher energies than anions **A** and **C**, which are derived by removal of axial hydrogens.[9]

TABLE 3. Comparison of the Relative Energies of *N*-(Methoxycarbonyl)piperidine Anions (Figure 3) and Model Methyl *N*-Methylcarbamate Anions[a]

	$MeOCONC_5H_9^-$ anion		$MeOCONHCH_2^-$ anion
	ΔΔ*G*		ΔΔ*G*
A	0.0 (axial anion)	**a**[b]	0.7
B	3.3 (equatorial anion)	**11**	3.0
C	1.5 (axial anion)	**c**[b]	0.2
D	7.0 (equatorial anion)	**16**	4.1

[a] B3LYP/6-311+G* energies (kcal/mol) have been corrected for both differences in zero point energy and the change in enthalpy on going from 0 K (corresponding to the calculations) to 298 K. [b] See text.

The piperidine anions **B** and **D**, generated by removal of equatorial hydrogens, correspond to the anti and syn methyl *N*-methylcarbamate anions **11** and **16**, respectively; the relative free energies of these four species are compared in Table 3. The *N*-(methoxycarbonyl)piperidine anions **A** and **C**, with axial lone pairs, have no direct counterparts among the methyl *N*-methylcarbamate anions. To model these anions, four carbons of the piperidine ring in **A** and **C** were deleted, the hydrogen at the anionic site of each species was fixed at the value found in **A** and **C**, and geometry optimization was carried out to give two new structures, labeled **a** and **c**, respectively. Both model anions, **a** and **c**, had relatively low energies (Table 3). It might be noted that, although the relative energies of **a** and **c** are different than those calculated for the analogous *N*-(methoxycarbonyl)piperidine anions, it is to be expected that **a** and **c** are only approximate models for anions **A** and **C**. On the whole, however, the agreement between the results obtained from the previous study of the anions derived from *N*-(methoxycarbonyl)piperidine[9] and the simple methyl *N*-methylcarbamate models described above is quite reasonable (Table 3).

In summary, it appears that there are several reasons for the difference between the results previously reported for the *N*-methylformamide anion[6−8] and more recent studies of *N*-(methoxycarbonyl)piperidine anions.[9] Electron correlation has an important effect on the relative energies and the number of imaginary frequencies of such species, and the HF level of theory is not satisfactory for such investigations. The methoxy group in methyl *N*-methylcarbamate anions plays an crucial role in establishing the structure and relative energies of the ions; consequently, the *N*-methylformamide system is not a good model for carbamate anions. Finally, the conformational restraints imposed by the ring structure of *N*-(methoxycarbonyl)piperidine anions influences the relative energies of these species.

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Supporting Information Available: A summary of the calculations is available. This material is available free of charge via the Internet at http://pubs.acs.org.

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