Density functional studies of molecular structures of N-methyl formamide, N,N-dimethyl formamide, and N,N-dimethyl acetamide

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Abstract. Density functional theory was applied to the calculation of molecular structures of N-methyl formamide (NMF), N,N-dimethyl formamide (DMF), and N,N-dimethyl acetamide (DMA). DFT calculations on NMF, DMF, and DMA were performed using a combination of the local functional of Vosko, Wilk, and Nusair (VWN) with the nonlocal exchange functional of Becke and the nonlocal correlational functional of Lee, Yang, and Parr (BLYP). The adiabatic connection method (ACM) of Becke has also been used, for the first time, for the calculation of molecular structures of NMF, DMF, and DMA. The calculated molecular structures are in excellent agreement with the experimental geometries of NMF and DMA derived from gas-phase electron-diffraction studies. Sparse experimental data on the gas-phase geometry of DMF reported in the literature compares well with the DFT results on DMF. DFT emerges as a powerful method to calculate molecular structures.

Keywords. Density functional theory; alkyl amides; molecular structure of alkyl amides; transition state search; peptide models.

1. Introduction

Density functional theory, DFT[1–6], is a first-principle quantum mechanical method originally developed for problems in solid state physics and has recently emerged as a powerful method for molecular structure calculations. DFT includes electron correlation effects[7–9] whose true impact on conformational energetics is yet to be ascertained on a quantitative level. The basic notion in the density functional theory is that the energy of a

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multi-electron system can be expressed in terms of its density. Until recently DFT calculations have been performed[3] with local density functionals (LDF). However, there has been a progressive shift in DFT studies towards utilizing gradient corrected density(nonlocal) functionals (NLF)[3,5], which are considered to be more accurate than LDF for predicting geometries and conformational energetics. NLDFT is computationally efficient and has been demonstrated by previously reported studies in the literature to be of comparable accuracy and in many cases to be much superior to conventional post-Hartree–Fock (HF) methods[7–9].

As a part of our effort in developing fast and dependable force fields for classical molecular mechanics and dynamics studies[10–12] for peptides, polypeptides, and proteins, we have relied on gradient-corrected density functional theory for the prediction of conformation, torsional barriers, NMR chemical shifts (d), vibrational frequencies (u) including isotopic effects of N-alkyl amides and small peptides[13–16]. We have recently reported high-level DFT studies on formamide[13,14], acetamide[15], and N-methyl acetamide[16] and have convincingly demonstrated that DFT can reproduce experimentally derived geometries, conformations, torsional barriers, chemical shifts, and vibrational frequencies. In this report, we present the DFT results on the molecular structures of N-methyl formamide, N,N-dimethyl formamide, and N,N-dimethyl acetamide.

2. Methods

The Fock matrix, F, in Kohn–Sham self-consistent procedure is expressed as

$$F = H + J + K_c^C,$$

where H is the one-electron Hamiltonian matrix, J is the Coulomb matrix, and K_c^C is the DFT exchange-correlation matrix. The calculation of H and J proceeds in the same way as in HF calculations. The DFT exchange-correlation matrix, K_c^C, is calculated by numerical integration using an atom-centered grid[17]. DFT calculations on alkyl amides are performed using two different exchange-correlation functions: (a) A combination of the local functional of Vosko, Wilk, and Nusair (VWN)[18] with the nonlocal exchange functional of Becke[19] and the nonlocal correlation functional of Lee, Yang, and Parr (BLYP)[20]. The exchange functional is combined with the local gradient-corrected correlation functional. The correlation functional used is actually $C \times E_C^{LYP} + (1 - C) \times E_C^{VWN}$, where *LYP* is the correlation functional of Lee, Yang, and Parr[20], which includes both local and nonlocal terms, and *VWN* is the Vosko, Wilk, and Nusair correlation functional[18] fitting the RPA solution to the uniform gas, often referred to as Local Spin Density (LSD) correlation; (b) the adiabatic connection method (ACM) of Becke[21]. For further methodological details, please see references 13, 14 and the original references cited therein. DFT calculations were implemented using an in-house computer program[22] on a workstation without resorting to the use of the CRAY supercomputer. The program is configured to handle a molecular system with more than 100 atoms.

3. Results and discussions

3.1 *N-methyl formamide (NMF)*

The geometry of NMF derived from DFT calculation with BLYP/DZVP and ACM/DZVP basis sets is presented in table 1 and compared with the experimentally observed geometry

Table 1. Comparison of calculated and experimental geometries of N-methyl formamide.

Bond length (Å)/bond angle (°)

	C=O	C–N	N–C	N–H	C–H	C–H(Me)	C–H(Me)	C–H(Me)	N–C=O	N–C–H	H–C=O
BLYP/DZVP	1·239	1·378	1·469	1·019	1·116	1·103	1·097	1·102	125·45	111·53	123·02
ACM/DZVP	1·221	1·359	1·446	1·011	1·108	1·091	1·094	1·094	124·97	112·18	122·85
Expt.[a]	1·219 (5)	1·366 (8)	1·459 (6)				1·114 (25)		124·6 (5)		

	C–N–H	C–N–C(Me)	H–N–C(Me)	N–C(Me)–H	N–C(Me)–H	N–C(Me)–H	H–C(Me)–H	H–C(Me)–H	H–C(Me)–H
BLYP/DZVP	117·46	123·36	119·15	107·50	110·85	111·20	109·07	108·98	109·20
ACM/DZVP	115·73	124·74	119·53	108·86	111·59	111·61	107·95	107·97	108·73
Expt.[a]		121·4 (9)							

[a]Ref. [23]. Values in parentheses are standard deviations

Table 2. Calculated geometries of transition states of N-methyl formamide.

Bond length (Å)/bond angle (°)

	C=O	C–N	N–C	N–H	C–H	N–C=O	N–C–H	O=C–H	C–N–C	C–N–H	H–N–C
Transition state 1											
BLYP/DZVP	1·238	1·377	1·466	1·021	1·117	124·96	111·95	123·09	124·96	115·75	119·29
ACM/DZVP	1·221	1·359	1·446	1·011	1·108	124·97	112·18	123·85	124·74	115·73	119·53
Transition state 2											
BLYP/DZVP	1·239	1·376	1·472	1·020	1·117	124·92	112·17	122·91	124·39	116·05	119·56
ACM/DZVP	1·299	1·358	1·452	1·001	1·108	124·98	112·36	122·66	124·10	116·06	119·84

of NMF from gas-phase electron diffraction studies reported by Kitano and Kushitsu[23]. The ACM/DZVP predicted carbonyl bond length of 1·221 Å is very close to the C⇔O bond length of 1·219 Å from electron diffraction studies[23]. Similarly, the C⇔N bond length of 1·359 Å predicted from ACM/DZVP differs from the experimentally derived value of 1·368 Å within the experimental error margin. In the case of N–C bond length, BLYP/DZVP is in better agreement ($\Delta d = 0.01$ Å) with the experimentally derived value than the ACM/DZVP ($\Delta d = 0.013$ Å). The predicted C–H (Me) bond length of 1·114 Å differs from the experimental C–H (Me) bond length of 1·094 Å by 0·02 Å. Both methods predict N–C⇔O bond angles fairly close to the experimental values from the electron diffraction studies[23]. The predicted C⇔N–C bond angles by the two methods differ from the experimental value by $\Delta q > 4°$. Kitano and Kuchitsu[23] have reported only two experimentally derived bond angles i.e. N–C⇔O and C⇔N–C (Me).

A transition state search for the transition states in NMF was made by looking for the presence of one negative eigenvalue. We were able to locate two transition states for NMF, the geometries of the transition states being presented in table 2. ACM calculations predict a stretching of the C⇔O bond length by 0·078 Å and a stretching of the N–C bond length by 0·006 Å. The BLYP calculations predict a different trend and hence the geometry of the transition state depends on the NLF used in the calculations. The trend observed in the geometries of the transition states of NMF are seen in each NLF class and are similar to the trend previously reported for formamide[13,14], acetamide[14] and NMA[16].

3.2 *N,N-dimethyl formamide (DMF)*

The geometry of DMF was determined using BLYP and ACM NLF with the DZVP basis set. The calculated geometry of DMF is compared with the rather sparse experimental geometry reported in the literature[24–28] in table 3. The ACM NLF predicted C⇔O bond length of 1·219 Å is slightly shorter than the experimental value of 1·20 Å. The BLYP NLF predicted C⇔O bond length of 1·24 Å is much longer than the experimental value. Similarly, the C⇔O bond length of 1.362 Å from ACM NLF calculations is slightly shorter, by $\Delta d = 0.022$ Å, than the corresponding experimental value. The N–C bond length from ACM NLF calculations of 1·449 Å differs from the experimental C–N bond length by $\Delta d = 0.001$ Å. The BYLP NLF consistently predicts longer bond lengths than the ACM NLF calculations for DMF. The C⇔N–C1 bond angles predicted by both NLF's are close to each other ($\Delta q \geq 0.04°$) and differ from the experimental values by $\Delta q > 4°$. The discrepancy between the calculated values from BLYP and ACM are somewhat better with the C⇔N–C2 bond angles, $\Delta q > 3°$. N–C2=O bond angles predicted by both NLF's (BLYP and ACM) are extremely close to each other and differ from the experimental value by $\Delta q < 3°$.

We were able to locate four transition states for DMF (table 4) in which similar divergences in bond lengths and bond angles are observed. Stretching of the C=O bond length and a slight contraction of the C⇔N bond length, between the ground state and transition state geometries, are observed as in the case of NMF.

3.3 *N,N-dimethyl acetamide (DMA)*

The geometry of DMA determined using BLYP and ACM NLF is presented in table 5. The calculated geometry of DMA is compared with the geometry of DMA derived from gas electron diffraction studies of DMA reported by Mack and Oberhammer[29]. The C⇔O

Table 3. Comparison of experimental and calculated geometries for N,N'-dimethyl formamide.

Bond length (Å)/bond angle (°)

	C–O	C̃N	N–C1	N–C2	C1–H	C1–H	C1–H	C2–H	C2–H
BLYP/DZVP	1·240	1·381	1·469	1·465	1·104	1·100	1·104	1·097	1·104
ACM/DZVP	1·223	1·362	1·449	1·446	1·089	1·091	1·096	1·095	1·095
Expt.[a]	1·20	1·34	1·45	1·45					

	C2–H	O=C̃H	C1–N–C2	C̃N–C1	C̃N–C1	CO–N–C2	N–C1–H	N–C1–H	N~C1–H
BLYP/DZVP	1·104	122·73	118·15	121·43	120·43	125·70	111·08	111·08	109·40
ACM/DZVP	1·095	122·52	118·21	121·47	120·31	125·71	111·11	111·11	109·55
Expt.[a]			117·50	117·50	117·50	123·00			

	N–C2–H	N–C2–H	N–C2–H	H–C1–H	H–C1–H	H–C1–H	H–C2–H	H–C2–H	H–C2–H
BLYP/DZVP	110·66	110·66	107·98	108·47	108·27	108·47	108·55	109·48	109·48
ACM/DZVP	110·72	110·72	108·11	108·33	108·33	108·33	108·58	109·35	109·35

[a]Ref. [28]

Table 4. Calculated geometries of transition states of N,N'-dimethyl formamide.

Bond length (Å)/ bond angle (°)	Transition state 1		Transition state 2		Transition state 3		Transition state 4	
	BLYP/DZVP	ACM/DZVP	BLYP/DZVP	ACM/DZVP	BLYP/DZVP	ACM/DZVP	BLYP/DZVP	ACM/DZVP
C'=O	1·240	1·223	1·242	1·224	1·225	1·209	1·290	1·203
C'–N	1·381	1·362	1·378	1·360	1·460	1·438	1·456	1·434
N–C1	1·465	1·449	1·471	1·455	1·490	1·467	1·488	1·465
N–C2	1·469	1·446	1·476	1·451	1·490	1·467	1·488	1·465
O=C'–H	122·73	122·52	122·42	119·24	121·38	121·28	121·20	121·09
C1–N–C2	118·15	118·21	119·56	119·66	111·51	111·76	110·95	111·21
C'–N–C1	121·43	121·47	120·38	120·07	110·49	110·59	108·73	108·95
C'–N–C2	120·31	120·31	120·06	120·27	110·49	110·59	108·73	108·95
N–C'=O	125·70	125·71	125·92	125·94	125·66	125·21	124·44	124·57
N–C'–H	111·58	111·77	111·66	111·83	112·96	121·28	114·36	114·34

Table 5. Geometries of ground state of dimethyl acetamide from BLYP/DZVP and ACM/DZVP calculations.

Bond length (Å)/bond angle (°)

	C=O	C–N	N–C1	N–C2	C–C3	C1–H	C1–H	C2–H
BLYP/DZVP	1·247	1·392	1·472	1·468	1·538	1·104	1·104	1·105
ACM/DZVP	1·231	1·373	1·451	1·448	1·518	1·096	1·096	1·096

	C2–H	C2–H	C3–H	C3–H	C3–H	C3–H	C1–H	C2–H
BLYP/DZVP	1·053	1·095	1·102	1·102	1·096	1·096	1·096	1·105
ACM/DZVP	1·096	1·087	1·093	1·093	1·088	1·088	1·088	1·096

	C–N–C2	C1–N–C2	N–C=O	N–C–C3	O=C–C3	C–N–C1	C–N–C1
BLYP/DZVP	125·29	115·52	121·79	117·70	120·52	119·19	119·19
ACM/DZVP	125·23	116·62	121·84	117·68	120·48	119·16	119·16

	C1–N–C2	C–C3–H	C–C3–H	C–C3–H	C–C3–H	H–C3–H	H–C3–H	N–C1–H	N–C1–H
BLYP/DZVP	125·29	107·11	111·97	111·97	108·84	108·03	108·84	108·33	110·46
ACM/DZVP	125·23	107·15	111·85	111·85	108·89	108·89	108·15	108·44	110·54

	N–C1–H	H–C1–H	H–C1–H	H–C3–H	N–C2–H	N–C2–H	H–C2–H	H–C2–H	H–C2–H
BLYP/DZVP	109·58	108·42	109·58	107·85	110·59	111·22	107·85	108·24	108·24
ACM/DZVP	109·44	108·44	109·44	107·90	110·63	111·33	107·90	108·12	108·12

[a]Ref. [29]

bond length calculated using ACM NLF of 1·231 Å differs from the experimental value by $\Delta d = 0.005$ Å, the C⇐N bond length by $\Delta d = 0.005$ Å, the C–C bond length by $\Delta d = 0.009$ Å, and the N–C bond length by $\Delta d = 0.005$ Å. The BLYP NLF differs much less from the experimental bond length than the ACM NLF calculation. The N–C⇐O bond length by both NLF are in good agreement with the experimental value. Similar trends can be observed for other bond angles, e.g. N–C⇐C3, C⇐N–C1, C⇐N–C2 as well.

Three transition states of DMA were derived from the transition state search, but their geometries are not reported here.

4. Conclusion

DFT is seen to predict geometries of the methyl and dimethyl derivatives of formamide and acetamide accurately in agreement with experimentally derived geometries. DFT is promising as a powerful tool in the elucidation of gas-phase geometries and we are exploiting its full potential to explore di and tri-peptides with the ultimate goal of deriving DFT configured force fields for better description of protein structures and their dynamical fluctuations.

Acknowledgements

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