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Assessment of Density Functionals, Semiempirical Methods, and SCC-DFTB for Protonated Creatinine Geometries

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Abstract

Creatinine concentrations in blood and urine can be used to detect renal insufficiencies and muscle diseases, but current chemical sensors cannot measure creatinine with sufficient selectivity and robustness because they lack a receptor that binds protonated creatinine (creatininium) selectively enough. As a first step toward identifying potential receptors for creatininium, we examine the accuracy of density functional theory (DFT) and wave function theory (WFT) calculations for creatininium cation geometries, evaluated against reference parameters from experiment. We tested twenty-one local and nonlocal density functionals, Hartree-Fock theory, four semiempirical molecular orbital (SEMO) methods of the neglect of differential overlap (NDO) type, and one self-consistent-field nonorthogonal tight-binding method (SCC-DFTB) as implemented in two closely related software packages. DFT and HF calculations were carried out with the MG3S augmented polarized triple-zeta basis set. We find that DFT significantly outperforms SEMO methods for our dataset, and both SCC-DFTB releases we tested (which gave almost identical results) were less accurate than 81% of the density functionals evaluated. The top five functionals for the creatininium structures we examined were MPW1B95, PBEh, mPW1PW, SVWN5, and B97-2, with MMUEs in bond length of 0.0126 Å, 0.0129 Å, 0.0133 Å, 0.0142 Å, and 0.0144 Å respectively, which indicates that all five functionals are similarly suitable for creatininium. The popular B3LYP functional has a MMUE of 0.0178 Å, which ranks it 16th overall. B3LYP also performs less favorably than the best local functional (SVWN5), which is less expensive.

Keywords

creatininium; biosensors; DFT

1. Introduction

Creatine phosphate (also known as phosphocreatine) is a high-energy compound used in human skeletal muscle tissue to convert adenosine diphosphate to adenosine triphosphate, in a

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Supplementary Information. Geometric parameters at the MPW1B95 and PBEh theory levels, and mean signed errors in bond length for all methods studied, using both sets of experimental benchmark data.

reversible reaction catalyzed by creatine kinase. [1] In a side reaction, creatine phosphate also nonenzymatically converts to creatinine, which cannot be metabolized by human enzymes and is almost exclusively eliminated through the kidney into the urine as a waste product. As renal tubular reabsorption of creatinine is minimal, blood creatinine levels will rise if renal filtering is deficient. Creatinine concentrations in blood and urine can therefore be used as indicators of renal dysfunction, muscle pathologies, and for the early detection of myocardial infarction. [1,2]

Our ultimate goal is to fabricate a receptor-based ion-selective electrode (ISE) [3] to accurately measure system creatinine levels; this requires a receptor that specifically and selectively binds protonated creatinine (creatininium, Fig. 1). Computational methods have proven valuable for the rational design of synthetic receptors [4], but systematic validation studies are necessary to establish the suitability of specific *in silico* techniques for creatininium. As the primary mode of ligand binding to the creatininium receptor will be hydrogen bonding, an appropriate computational method must accurately model creatininium geometries, charge distributions, proton affinities and dipole moments. As a first step in this systematic validation strategy, we evaluate both fundamental types of practical electronic structure methods, DFT (density functional theory) and WFT (wave function theory), for creatininium ion geometric parameters. The methods are tested here against reference values obtained from two published experimental X-ray structures of creatininium. [5,6] DFT methods we examine include the three most accurate functionals [7-11] for the prediction of bond lengths in an extensive evaluation [7] of DFT methods for a variety of systems incorporating H, C, N, and O. We also include four recently developed functionals [12-14] and fourteen other density functionals with varying percentages of Hartree-Fock exchange. [15-33] The semiempirical molecular orbital (SEMO) methods we test are all based on neglect of diatomic differential overlap (NDO), and include AM1 [34-37], MNDO [38,39], PM3 [40] and the newer PM6 method. [41] We also test an iterative extended Hückel theory (IEHT) method: self-consistent-charge density-functional tight-binding (SCC-DFTB) theory as implemented in two software packages, DFTB/DYLAX [42-44] and the more recent DFTB+ release. [44]

2. Theoretical Approach

2.1 Basis sets

DFT and HF calculations in this work incorporate the valence-optimized, augmented and polarized MG3S triple-zeta basis set [45], which is 6-311+G(2df,2p) for H, C, N, and O. [46-49] MG3S is the same as G3Large [50] without core polarization functions, and the same as MG3 [45] without diffuse functions on hydrogen.

2.2 Density Functionals

Table 1 gives the properties of the density functionals examined in this study. The three most accurate functionals for bond lengths from Ref. 7 are M06-L [7], VSXC [8], and B3LYP [9-11]; all of these are included here. In addition to M06-L, we examined the following recently developed functionals: M05 [12], M05-2X [13], M06 [14], and M06-2X. [14] (M05-2X has demonstrated superior performance for the prediction of geometries and charge distributions in peptidomimetic compounds comprising H, C, N, O and S [51], as well as for geometries, dipole moments and bond dissociation energies in transition-metal centers.) [52] We also include a variety of popular and representative density functionals, for an overall total of 21 DFT methods. The complete set consists of one local spin density approximation (LSDA), three generalized-gradient exchange (GGE), one GGE with scaled correlation (GGSC), six hybrid generalized gradient approximation (HGGA), three meta GGA (MGGA), and seven hybrid meta GGA (HMGGA) methods (see Table 1). LSDA functionals depend on the spin densities; GGA functionals depend on the gradient of the spin densities as well as the spin

densities themselves; HGGA functionals depend on percentage of Hartree-Fock (HF) exchange, the density gradients, and the spin densities; MGGA functionals depend on the spin kinetic energy densities τ_σ , the spin density gradients, and the spin densities; and HMGGA functionals depend on τ_σ , HF exchange, the density gradients, and the spin densities. GGE methods combine GGA exchange with LSDA correlation, and in the newer GGSC approach [17], the Kohn-Sham operator is defined by

$$F = F^{\text{SE}} + F^{\text{GCE}} + F^{\text{LC}} + (Y/100) F^{\text{GCC}} \quad (1)$$

where F^{SE} is the Slater local exchange functional [14], F^{GCE} is the gradient correction to the LSDA exchange, F^{LC} is the LSDA correlation functional, F^{GCC} is the gradient correction to the LSDA correlation, and Y is the percentage of the gradient correction to correlation. In the sole GGSC functional tested in this study (MOHLYP), Y is set to 50, as was done in previous work. [17,52] For each theory level we list the percentage X of Hartree-Fock exchange, and the inclusion of the kinetic energy density τ_σ in the exchange and/or correlation functionals. We incorporate methods with broad variation in X , where $X = 0$ to 56 for DFT levels, and $X = 100$ for HF theory itself.

2.3. Experimental reference structures

Benchmark equilibrium internuclear distances (r_e) for creatininium C-C, C-N and C-O bonds are taken from published X-ray structures of creatininium nitrate, **(1)** [5] and creatininium dihydrogen arsenate, **(2)** [6] (Fig. 2). These researchers report a consistent experimental uncertainty of 0.002 Å in C-C, C-N and C-O interatomic distance for both structures. The imino group of the creatinine imidazolyl moiety (atom N1, Fig. 1) is protonated in both cases and engages in hydrogen bonding with an oxygen atom in the corresponding anion; however, the dihydrogen arsenate anion participates in two equidistant hydrogen bonds with the organic cation, whereas nitrate engages in only one H-bond with the protonated imino nitrogen (Fig. 2). The anion-cation hydrogen bonds in **(2)** are 0.117 Å shorter than the single analogous hydrogen bond in **(1)**. Stronger hydrogen bonding in **(2)** is also expected given the higher proton affinity of dihydrogen arsenate: H_3AsO_4 ($\text{p}K_a = +2.26$) is a much weaker acid than HNO_3 ($\text{p}K_a = -1.4$). [53] Differences in intramolecular bond lengths between the two experimental structures help to elucidate the effects of their respective H-bonding patterns. Bond distances in the planar imidazolyl ring of **(1)** do not vary significantly from those found in similar hybrid salts incorporating protonated imidazolyl groupings [5]; however, stronger hydrogen bonding in **(2)** relative to **(1)** slightly shortens the C1-N2, C2-C3, C2-N1 and C2-O1 bonds, slightly lengthens the C4-N3 bond, significantly lengthens the C1-N1 bond and does not affect the C3-N3 bond. Relatively shorter C1-N2 ($\Delta r_e = r_e(\mathbf{2}) - r_e(\mathbf{1}) = -0.006$ Å) and C2-N1 ($\Delta r_e = -0.009$ Å) interatomic distances in **(2)** than in **(1)** can be attributed to increased electron density on each nitrogen atom engaging in H-bonding with the H_2AsO_4^- anion, as can the relatively large increase in C1-N1 bond distance ($\Delta r_e = 0.012$ Å). The fairly short C2-N1 bond length in both structures also suggests conjugation involving the C2-O1 carbonyl [6], which is consistent with the existence of various tautomeric forms of creatinine and creatininium in aqueous solution. [5] Additional hydrogen bonds between adjacent cations exist in both structures, and while these are longer and weaker than those involved in anion-cation interactions, they may still affect intramolecular bond lengths in solid-phase X-ray structures. [5,6] Notably, while $\Delta r_e(\text{C1-N1})$ is indeed significant, the average absolute deviation in bond length $|\Delta r_e|$ over all C-C, C-N and C-O bond distances is only 0.006 Å (0.005 Å without C1-N1).

2.4 Computational Details

DFT, AM1, PM3 and MNDO calculations were performed using *Gaussian03* or a locally modified version of *Gaussian03* [54], on the Minnesota Supercomputing Institute core resources, on an Alienware MJ-12 dual-CPU workstation running under the SUSE Linux Professional 9.3 OS, and on a Dell OptiPlex 745 workstation running under the SUSE Linux

Professional 10.1 OS. PM6 calculations were done using MOPAC 2007 [55] on a Dell Inspiron 600m machine running Windows XP. SCC-DFTB calculations were carried out using DFTB/DYLAX [42-44] and DFTB+ [44] on the Minnesota Supercomputing Institute core resources. Certain visualizations were done using ChemCraft v1.5 (build 266) [56] on an Alienware Sentia machine running Windows XP.

3. Results and Discussion

All density functionals, HF theory, SEMO methods, and SCC-DFTB were tested against experimental benchmark C-C, C-N and C-O bond lengths obtained from the aforementioned creatininium nitrate and creatininium dihydrogen arsenate crystal structures. The quality of our results was gauged by mean unsigned error (MUE) in bond length, representing the averages of the absolute deviations from experimental reference values, and by mean signed error (MSE) in bond length, which is used to detect systematic deviations. MUEs and MSEs were obtained for each method with respect to benchmark bond lengths from each set of experimental parameters. Table 3 lists MUEs for DFT and HF equilibrium bond lengths as evaluated against both experimental structures; Table 4 gives analogous results for SEMO and SCC-DFTB methods. The respective mean signed errors (MSEs) in bond distance are given in Supplementary Information.

The overall performance of each technique was assessed by mean mean unsigned error (MMUE), i.e., the mean of all MUEs for bond lengths (in Å) with respect to both sets of benchmark values:

$$MMUE = \frac{MUE(1) + MUE(2)}{2}, \quad (2)$$

where MUE(1) = MUE against reference bond lengths from experimental creatininium nitrate, and MUE(2) = MUE against corresponding bond lengths from experimental creatininium dihydrogen arsenate. Table 5 gives MMUEs for all twenty-eight methods studied. We also define (a) the average unsigned error per bond as the mean of all unsigned deviations over all methods for a particular bond with respect to each corresponding reference value; and (b) the average mean unsigned error (AMUE) as the mean of all MUEs over all methods with respect to each benchmark dataset.

We find that density functional theory distinctly outperforms SCC-DFTB and semiempirical methods for protonated creatinine; 86% of the density functionals we tested perform better in terms of bond distance MMUE than all SCC-DFTB and NDO methods examined in this study. DFT MMUEs range from 0.0126 Å to 0.0358 Å, with 76% of density functionals displaying MMUEs below 0.02 Å, whereas NDO methods yield MMUEs between 0.0363 Å and 0.0448 Å. DFTB/DYLAX and DFTB+ both give very similar raw bond distances (± 0.001 Å) and show the same overall absolute deviation in bond length (0.0203 Å), placing SCC-DFTB above all the NDO methods we tested but below 17 of 21 density functionals.

The MPW1B95 functional exhibits the best overall performance in terms of MMUE in bond distance, followed closely by PBEh, mPW1PW, SVWN5, and B97-2 (Table 5). These functionals yield MMUEs of 0.0126 Å, 0.0129 Å, 0.0133 Å, 0.0142 Å and 0.0144 Å, respectively. The same five functionals are also most accurate with respect to (1) and (2) individually, albeit in a slightly different order. Against the creatininium nitrate structure, the top functionals are MPW1B95, PBEh, mPW1PW, SVWN5 and B97-2; evaluated against the arsenate structure, their respective ranking is PBEh, mPW1PW, MPW1B95, B97-2 and SVWN5 (Table 3). It is important to note that variations in MMUE between these top five methods are very small, e.g., only 0.0003 Å between MPW1B95 and PBEh. Errors of this magnitude cannot be reliably used to differentiate between methods in the present case,

especially since the published experimental error for both benchmark structures is much larger (0.002 Å). (In additional tests not reported here, we found that it was impossible to distinguish between DFT methods in terms of their ability to predict creatininium C-C, C-N and C-O bond angles; the vast majority of functionals yielded bond angles that varied by less than a degree. However, DFT methods were still more accurate for bond angles than SCC-DFTB and NDO.) For the purposes of this study, it is more illustrative to rank groups of functionals, which differ more distinctly in terms of unsigned error in bond distance. Here we classify the top five functionals as more or less equally suitable for creatininium geometries, with the next three functionals (M05, M06 and M06-L, all with MMUE = 0.0146 Å) in “second place,” and the remaining two functionals out of the top ten (MPW1KCIS, MMUE = 0.0153 Å and M05-2X, MMUE = 0.0154) ranked third overall.

The presence of the kinetic energy density τ_{σ} may be helpful for DFT methods but does not seem to be required; while 60% of the ten best DFT levels (including the best overall method, MPW1B95) incorporate τ_{σ} in the exchange and/or correlation functional, four of the top five methods do not. However, our results indicate that Hartree-Fock exchange is a clear prerequisite for accurate prediction of creatininium geometries. All density functionals with $X > 0$ have MMUE < 0.02 Å, and the four functionals that perform comparatively poorly, i.e., have MMUE > 0.272 (better than NDO but worse than SCC-DFTB), have no Hartree-Fock exchange. All top ten density functionals have $X > 15$, with the notable exceptions of SVWN5 and M06-L, two local functionals with respective MMUEs of 0.0142 and 0.0146. Additionally, eight of the ten best functionals are hybrid generalized-gradient approximation (HGGA) or hybrid meta generalized-gradient approximation (HMGGA) methods; our data show that both hybrid and nonhybrid GGA functionals perform much more favorably for the creatininium system than generalized-gradient exchange (GGE) and generalized-gradient exchange with scaled correlation (GGSC) functionals (Tables 1 and 5). The GGSC method tested in this study, MOHLYP, performs worst among DFT methods for creatininium bond lengths (MMUE = 0.0358 Å), and is not significantly better than the most favorable semiempirical method (MNDO, MMUE = 0.0363 Å). However, MOHLYP more likely falls short for this system because it was parameterized against a transition-metal training set.

It is interesting to compare average mean unsigned errors (AMUEs) and average unsigned errors for particular bonds in creatininium with respect to each set of experimental values. The AMUE in bond distance over all bonds and all methods tested against (1) (AMUE(1)) is 0.0205 Å; the corresponding AMUE as compared to (2) (AMUE(2)) is 0.0227 Å. (Importantly, these overall errors are factors of 10.25 and 11.35 larger than the published experimental errors for C-C, C-N and C-O bonds in (1) and (2).) AMUE(2) is larger than AMUE(1) by 0.0022 Å, but errors in individual bond lengths were not consistently greater with respect to (2) than (1); in fact C1-N3, C2-O1 and C4-N3 bonds were on average predicted more accurately for (2). The larger magnitude of AMUE(2) over all methods is largely due to less favorable prediction of C2-N1 (0.0583 Å vs. 0.0493 Å for (1)), and to a lesser extent, C1-N2 (0.0262 Å vs. 0.0202 Å for (1)). In fact, the chief contributor to AMUE(1), AMUE(2) and MMUEs for individual methods is the error in C2-N1 bond length, which is not surprising given the significant distortion of this bond in both crystal structures due to hydrogen bonding. (One can speculate that the calculated structures would be closer to the structure of the creatininium ion in the gas phase, but unfortunately experimental benchmark values for this species are not available.) All methods we examined systematically overestimate the C2-N1 bond distance, some by as much as 0.097 Å (PM3). Similarly, 71% of all methods underestimate (“overbind”) the C1-N1 bond distance. Methods that overestimate (“underbind”) C1-N1 are also those with the highest MMUE: MOHLYP, DFT levels with the VWN correlation functional, and all four NDOs. The average of AMUE(1) and AMUE(2) is 0.0216 Å and represents the mean absolute deviation in bond length from both experimental structures across all methods and all bonds. 81% of

density functionals yield MMUEs less than 0.0216, while 100% of IEHT and NDO methods tested have MMUEs greater than this average value.

5. Conclusions

In this paper we have tested geometric parameters for protonated creatinine (creatininium) obtained by a variety of DFT methods and other molecular orbital methods against corresponding intramolecular bond distances from two experimental datasets. While the accuracy of the DFT levels we tested varied considerably as measured by mean mean unsigned error (MMUE), density functional theory predicted bond distances much better than semiempirical and iterative extended Hückel theories we evaluated. We found that overall absolute errors in NDO bond length were a factor of 2.2 – 2.7 larger than *ab initio* Hartree-Fock, and a factor of 2.7 – 3.3 worse than the average performance of the top five DFT methods. The average unsigned deviation in bond length between the two experimental reference structures (creatininium nitrate and creatininium dihydrogen arsenate) is 0.006 Å, and experimental bond lengths obtained by solid-phase X-ray diffraction are altered by distinctive intramolecular hydrogen bonding interactions not accounted for in our simulations. Still, the same methods that do well with respect to the nitrate structure also accurately predict geometries for the arsenate structure. Since most density functionals in the top 30% of methods studied exhibit very similar MMUEs (some deviate from each other by less than the experimental error for the reference structures), we rank the top ten methods by groups rather than individually. The best performing group of functionals comprises MPW1B95, PBEh, mPW1PW, SVWN5 and B97-2; any of these functionals can be recommended to accurately reproduce geometric parameters for creatininium. The M05, M06, and M06-L functionals have slightly higher but still quite favorable MMUEs and may still be suitable for creatininium; the MPW1KCIS and M05-2X functionals are ranked third overall but demonstrate distinctly better performance than IEHT and NDO methods. (The SVWN5 and M06-L local functionals may be used when reduced computational cost is desired, e.g., for larger systems or longer simulations.) All ten of these functionals proved superior to the widely used B3LYP level of theory, which has a MUE of 0.0178 Å. We found that the performance of a particular functional for the creatininium system is enhanced by Hartree-Fock exchange, and that hybrid GGA and hybrid meta GGA methods are generally favored. We are currently engaged in the next stages of our validation study and are evaluating creatininium charge distributions, dipole moments, and proton affinities using the top ten DFT levels from this work, to pinpoint the functionals that will most accurately calculate relative hydrogen bond strengths between creatininium and a putative receptor.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Protonated creatinine (creatininium), illustrating the atom numbering convention followed in this study.

Figure 2. Experimental X-ray structures of creatinium nitrate (1) [5] and creatinium dihydrogen arsenate (2) [6].

Table 1

Summary of DFT methods examined in this work.^a

Method	Type	<i>X</i>	τ in E or C?	References
B3LYP	HGGA	20	Neither	9-11
B97-2	HGGA	21	Neither	15
M05	HMGGA	28	Both	12
M05-2X	HMGGA	56	Both	13
M06	HMGGA	27	Both	14
M06-2X	HMGGA	54	Both	14
M06-L	MGGA	0	Both	7
MOHLYP	GGSC	0	Neither	9,16,17
MPW1B95	HMGGA	31	Correlation	18-20
mPW1KCIS	HMGGA	15	Correlation	20-24
mPW1PW ^b	HGGA	25	Neither	20,25
mPWVWN5	GGE	0	Neither	20,26
O3LYP	HGGA	11.61	Neither	9,16,27
PBEh ^c	HGGA	25	Neither	28,29
PBEVWN5	GGE	0	Neither	26,28
SVWN5	LSDA	0	Neither	26,30
TPSS	MGGA	0	Both	31
TPSSH	HMGGA	10	Both	32
TPSSVWN5	GGE	0	Exchange	26,31
X3LYP	HGGA	21.8	Neither	11,22,23,33
VSXC	MGGA	0	Both	8

^a GGA: generalized-gradient approximation; GGE: generalized-gradient exchange; GGSC: generalized gradient exchange with scaled correlation; HGGA: hybrid GGA; HMGGA: hybrid meta GGA; LSDA: local spin density approximation; MGGA: meta GGA; *X* = percentage of Hartree-Fock exchange; E = exchange, C = correlation.

^b Same as mPW0, mPW1PW91 and MPW25.

^c Same as PBE0 and PBE1PBE.

Table 2

Benchmark equilibrium internuclear distances (r_e , Å) for creatininium compounds from experiment.

Bond	$r_e(1)^a$	$r_e(2)^b$
C1-N1	1.362	1.374
C1-N2	1.311	1.305
C1-N3	1.315	1.321
C2-C3	1.510	1.503
C2-N1	1.376	1.367
C2-O1	1.206	1.201
C3-N3	1.452	1.452
C4-N3	1.449	1.451

^a Creatininium nitrate [5];

^b creatininium dihydrogen arsenate [6]

Table 3

Mean unsigned errors (MUE, Å) in DFT and HF creatininium bond distances.

Method	MUE (1) ^a	MUE (2) ^b
B3LYP	0.0165	0.0191
B97-2	0.0131	0.0158
HF	0.0145	0.0186
M05	0.0133	0.0159
M05-2X	0.0138	0.0171
M06	0.0133	0.0159
M06-2X	0.0150	0.0179
M06-L	0.0133	0.0159
MOHLYP	0.0354	0.0363
MPW1B95	0.0104	0.0148
MPW1KCIS	0.0140	0.0166
mPW1PW	0.0120	0.0146
mPWVWN5	0.0271	0.0280
O3LYP	0.0144	0.0170
PBEh	0.0115	0.0144
PBEVWN5	0.0268	0.0276
SVWN5	0.0126	0.0158
TPSS	0.0190	0.0216
TPSSh	0.0164	0.0190
TPSSVWN5	0.0280	0.0291
V5XC	0.0179	0.0205
X3LYP	0.0160	0.0186

^aTested against creatininium nitrate [5] benchmarks

^btested against creatininium dihydrogen arsenate [6] benchmarks

Table 4

Mean unsigned errors (MUE, Å) in NDO and SCC-DFTB creatininium bond distances.

Method	MUE (1) ^a	MUE (2) ^b
DFTB/DYLAX	0.0188	0.0219
DFTB+	0.0188	0.0219
AM1	0.0368	0.0381
MNDO	0.0359	0.0368
PM3	0.0439	0.0435
PM6	0.0450	0.0446

^aTested against creatininium nitrate [5] benchmarks;

^b tested against creatininium dihydrogen arsenate [6] benchmarks

Table 5

Mean mean unsigned errors (MMUE, Å) in DFT, HF, NDO and SCC-DFTB creatininium bond distances.

Method	MMUE
MPW1B95	0.0126
PBEh	0.0129
mPW1PW	0.0133
SVWN5	0.0142
B97-2	0.0144
M05	0.0146
M06	0.0146
M06-L	0.0146
MPW1KCIS	0.0153
M05-2X	0.0154
O3LYP	0.0157
M06-2X	0.0164
HF	0.0166
X3LYP	0.0173
TPSSh	0.0177
B3LYP	0.0178
VSXC	0.0192
TPSS	0.0203
DFTB/DYLAX	0.0203
DFTB+	0.0203
PBEVWN5	0.0272
MPWVWN5	0.0276
TPSSVWN5	0.0286
MOHLYP	0.0358
MNDO	0.0363
AM1	0.0374
PM3	0.0437
PM6	0.0448