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Evaluation of Density Functionals, SCC-DFTB, Neglect of Diatomic Differential Overlap (NDDO) Models and Molecular Mechanics Methods for Prolyl-Leucyl-Glycinamide (PLG) and Structural Derivatives

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Abstract

Prolyl-leucyl-glycinamide (PLG) is a unique endogenous peptide that modulates dopamine receptor subtypes of the D₂ receptor family within the CNS. We seek to elucidate the structural basis and molecular mechanism by which PLG and its analogues modulate dopamine receptors, toward the development of new therapeutics to treat Parkinson's disease, tardive dyskinesia and schizophrenia. As a first step toward establishing a validated protocol for accurate computational modeling of PLG and associated peptidomimetic analogues, we evaluated the accuracy of density functional theory (DFT), wavefunction theory (WFT), and molecular mechanics (MM) calculations for PLG and for a library of structurally related small molecules. We first tested twelve local and nonlocal density functionals, Hartree-Fock (HF) theory, four “semiempirical” methods of the neglect of diatomic differential overlap (NDDO) type, and one self-consistent-charge nonorthogonal tight-binding (SCC-DFTB) method as implemented in two software suites, against coupled-cluster benchmark geometries for 4-methylthiazolidine, a small molecule that comprises key structural features present in our PLG analogue library. DFT and HF calculations were done with the MG3S augmented polarized triple-zeta basis set. We find that for 4-methylthiazolidine bond distances, DFT significantly outperforms NDDO, and both SCC-DFTB versions we evaluated perform worse than HF theory and are less accurate than 83% of the density functionals tested. The top five functionals for 4-methylthiazolidine were M05-2X, mPW1PW, B97-2, M06-2X, and PBEh, with mean unsigned errors (MUEs) in bond length of 0.0017, 0.0020, 0.0023, 0.0025 and 0.0027 Å, respectively. The widely used B3LYP functional ranked 11th out of twelve functionals evaluated, slightly below SCC-DFTB, and is significantly less accurate for 4-methylthiazolidine bond distances (MUE = 0.0095 Å) than the best local functional (M06-L, MUE

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= 0.0030 Å), which is far less computationally costly. Based on that initial analysis, we obtained new M05-2X benchmark geometric parameters for PLG and a library of eleven peptidomimetic derivatives, which we in turn used to examine the accuracy of thirty-four popular molecular mechanics (MM) force fields, four NDDO approaches, and SCC-DFTB for the full compound structures. Here, we found that ~70% of the MM force fields tested superior to the best semiempirical and SCC-DFTB codings. Moreover, AMBER-type force fields proved most accurate among MM methods for this class of small-molecule peptidomimetics; the AMBER-type methods comprised eight out of the top ten molecular mechanics options we tested.

Keywords

PLG; peptidomimetics; molecular mechanics; DFT; CCSD; NDDO

1. Introduction

Prolyl-leucyl-glycinamide (PLG) is a tripeptide that modulates specific dopamine receptor subtypes of the D₂ receptor family within the CNS, by affecting sensitivity in a more controlled and subtle manner than direct-acting receptor agonists and antagonists. [1,2] Changes in dopamine receptor sensitivity have been implicated in such diseases as Parkinson's and schizophrenia; therefore, an understanding of PLG's mechanism of receptor modulation may lead to new therapeutic approaches for treating diseases such as those that involve the dopaminergic system. [3,4] PLG is known to modulate the D₂ and D₄ dopamine receptors via affinity enhancement of agonists to these receptors, and also induces a shift of the receptor from a low-affinity state to a high-affinity state. The PLG interaction site was found to be located on the dopamine D₂ receptor; [5-7] but the exact location and structural features of this allosteric site remain unknown.

Computational techniques have proven useful for the elucidation of active-site structural features and associated molecular mechanisms; [8-10] however, systematic validation studies, which have not yet been reported for this class of dopamine receptor modulators, are required to assess the accuracy of specific *in silico* techniques for these compounds. Ligand binding modes to the dopamine D₂ receptor will likely involve hydrogen bonding and hydrophobic interactions; therefore a suitable computational method must, at a minimum, accurately model the associated geometric parameters and charge distributions for the ligand. As a first step in this overall validation process, here we evaluate both types of electronic structure calculations, density functional theory (DFT) and wave function theory (WFT), together with a series of molecular mechanics (MM) methods, for PLG and PLG-analog geometric parameters. As experimental geometric parameters for the full analog library are not available, and as the structures are too large for full coupled-cluster optimization, we first obtained CCSD(T) [11] reference geometries for 4-methylthiazolidine (Figure 1), a small five-membered ring system incorporating structural characteristics common to the majority of compounds in our dataset. A series of 12 less expensive DFT levels, together with Hartree-Fock (HF) theory, five neglect of diatomic differential overlap (NDDO) methods, and one iterative extended Hückel theory (IEHT) method, were consequently assessed for 4-methylthiazolidine against these coupled-cluster parameters. Next, the most accurate method from that analysis was applied to yield new best estimates of bond lengths for our compound database comprising the full structures of PLG and eleven peptidomimetic derivatives [5-7] (Table 1), against which 34 MM force-field bond-length parameter sets were finally evaluated. Benchmark parameters for 4-methylthiazolidine were obtained by coupled-cluster calculations with single, double and quasiperturbative triple excitations (CCSD(T) [11]). Density functionals examined here include the two most accurate functionals [12-15] for the prediction of bond distances in an extensive study [15]

of density functionals for a structurally diverse assortment of molecules containing H, C, N, and O. Here we also include three more recently developed, highly accurate functionals [16,17], plus seven DFT levels with and without the kinetic energy density τ_σ in the exchange and/or correlation functionals, and incorporating various percentages of Hartree-Fock exchange. [18-31] The NDDO approaches tested here include AM1 [32-35], MNDO [36,37], PM3 [38], and PM6 [39]; and the IEHT method we evaluate is self-consistent-charge density-functional tight-binding (SCC-DFTB) as coded in two software packages: DFTB/DYLAX [40-42] and the closely related DFTB+ update [43].

2. Theoretical Approach

2.1 Basis Sets

The CCSD(T), DFT and HF calculations in this study use the valence-optimized, augmented and polarized MG3S triple-zeta basis set [44], which is 6-311+G(2df,2p) for H, C, N, and O. [45-48] This basis set is the same as G3Large [49] without the core polarization functions, and is identical to MG3 [44] without diffuse functions on hydrogen.

2.2. Density Functionals

The density functionals we tested are listed in Table 2, together with two important properties: the percentage X of Hartree-Fock exchange, and whether or not the kinetic energy density τ_σ was included in the exchange and/or correlation functionals. Included here are the two most accurate functionals for geometric parameters from Ref. 15: M06-L and B3LYP, as well as the more recently developed functionals M05-2X [16], M06 [17] and M06-2X [17]. M05-2X is of particular interest as it has proven highly accurate for the prediction of geometries, dipole moments and bond dissociation energies in a variety of biocenters [50,51] as well as for bond lengths in protonated creatinine (creatininium) [52], which features a five-membered imidazoline ring that is similar to certain PLG analog substructures. The complete set of twelve functionals addressed in this work includes one local spin density approximation (LSDA), four hybrid generalized-gradient approximation (HGGA), one meta GGA (MGGA), and six hybrid meta GGA (HMGGA) methods (see Table 2). LSDA functionals depend on the spin densities; HGGA functionals depend on the amount of Hartree-Fock exchange, the spin densities and the spin density gradients; MGGA functionals depend on the spin densities and their gradients, plus the kinetic energy density τ_σ ; and HMGGA functionals depend on all four quantities: kinetic energy density, Hartree-Fock exchange, spin densities, and spin density gradients. In this paper we evaluate methods with Hartree-Fock exchange percentages ranging from 0 to 56 (DFT) and 100 (HF theory).

2.3 Molecular Mechanics Force Fields

We assessed a broad array of MM force fields for the PLG-analogue dataset, as implemented in five molecular modeling and discovery software suites (see below). These include variations on the AMBER [53-58], OPLS [59,60], ESFF [61], UFF/Universal [62-65], MMFF94 [66-72], Tripos [73], CHARMM [74-77], COMPASS [78-81], CFF/CVFF [82-94], Engh-Huber [95], RULE [96], PEF95SAC [97], and Dreiding [98] force fields. General MM optimizations were done in the gas phase and incorporated at least 1000 steps of conjugate-gradient minimization with an energy change convergence criterion of $0.001 \text{ kcal mol}^{-1} \text{ \AA}^{-1}$.

2.4 Computational Details

CCSD(T), HF, AM1, PM3, MNDO, and DFT calculations were performed using *Gaussian03* or a locally modified version of *Gaussian03* [99] on the Minnesota Supercomputing Institute (MSI) core resources, and on a Dell OptiPlex 745 workstation running under the Suse Linux Professional 10.1 OS. PM6 calculations were carried out using

MOPAC 2007 [100] on a Dell Inspiron 600m workstation running under Windows XP. SCC-DFTB calculations were done using DFTB/DYLAX [40-42] and DFTB+ [43] on the MSI core resources. Molecular mechanics calculations were performed using MOE 2007.09 [101], SYBYL 7.2 [102], InsightII 2000.1 [103], MacroModel 9.1 [104], and Cerius2 4.10L [105] on MSI quad-core Intel Xeon and dual-core AMD Opteron workstations running under Suse Linux Enterprise Desktop 10.2. Visualizations were done using these versions of MOE, SYBYL, InsightII and MacroModel, as well as ChemCraft v 1.5 (build 266) [106] and *GaussView* 4.1.2 [99], on the MSI Xeon and Opteron workstations. Molecules for MM calculations were constructed in the respective software suites, and structures for QM calculations were generated using *GaussView* 4.1.2.

3. Results and Discussion

3.1 4-methylthiazolidine

CCSD(T)/MG3S benchmark C-C, C-N, C-S, C-H, and N-H bond lengths (fifteen parameters total, Table 3) were used to test all twelve density functionals and Hartree-Fock theory for 4-methylthiazolidine. The accuracy of each method was assessed by mean unsigned error (MUE) in bond distance, which represents the average absolute deviation from calculated coupled-cluster reference values. Table 4 gives MUEs in fifteen DFT and HF equilibrium bond lengths, and Table 5 gives corresponding results for two density-functional tight-binding software releases and four semiempirical neglect of diatomic differential overlap (NDDO) methods.

Not surprisingly, we find that density functional theory proves superior for reproducing 4-methylthiazolidine bond distances: 83% of the density functionals we evaluated yielded lower MUEs than both SCC-DFTB codings and all four semiempirical methods. DFT mean unsigned errors in bond distance ranged from 0.0017 Å to 0.0107 Å, while NDDO methods gave MUEs from 0.0133 Å to 0.0415 Å. Raw bond lengths obtained from DFTB/DYLAX and DFTB+ optimizations were almost identical, and both SCC-DFTB packages gave very similar absolute deviations in bond distance (0.0085 Å for DYLAX and 0.0087 Å for DFTB+), placing both of these significantly ahead of the NDDO methods but below 10 out of 12 density functionals we assessed. In additional tests, we found that it was not possible to reliably differentiate between DFT methods in terms of their ability to reproduce bond and torsional angles for this system, as DFT MUEs in these angles varied from each other by less than one degree; bond and torsional angles were therefore not used to prioritize methods. Density functional theory yielded MUEs in bond angles from 0.128 degree (M06-2X) to 0.735 degree (B3LYP). We did, however, find that the general ranking of method type by bond and torsional angle MUE paralleled that obtained by examining errors in bond length, with DFT outperforming DFTB (MUE = 1.464 – 1.483 degrees) and exhibiting significantly better accuracy than NDDO (MUE = 2.087 – 3.609 degrees).

The best density functional for 4-methylthiazolidine bond lengths is M05-2X, followed by mPW1PW, B97-2, and M06-2X. M05-2X is the clear leader: its MUE differs from that of the next best functional by 0.0003 Å and from B97-2 by 0.0006 Å (Table 4). Next in ranking, the PBEh and M06-L functionals also exhibit slightly less favorable but very similar performance, with MUEs of 0.0027 Å and 0.0030 Å respectively. The seventh-ranked MPW1KCIS functional gave a MUE in bond length of 0.0038 Å, placing it almost 0.001 Å in accuracy below M06-L, which is a less costly local functional. Five density functionals ranked below Hartree-Fock theory, with the SVWN5 functional performing worst among DFT methods (MUE = 0.0107 Å). Mean unsigned errors for NDDO methods ranged from 0.0133 Å (PM3) to 0.0415 Å (MNDO), demonstrating that these methods are distinctly less accurate for 4-methylthiazolidine than SCC-DFTB and DFT.

Our results indicate that a higher percentage X of Hartree-Fock exchange in DFT methods generally correlates with better performance. The top five DFT methods have at least 21% Hartree-Fock exchange, and the two best functionals, M05-2X and mPW1PW, are hybrid meta GGA and hybrid GGA functionals, respectively, with $X \cdot 25$. The worst functional, SVWN5, is a local spin density approximation method that cannot incorporate Hartree-Fock exchange. A notable exception is the M06-L local meta GGA functional, which ranked sixth overall despite $X = 0$. For this 4-methylthiazolidine system, hybrid meta GGA and hybrid GGA functionals perform better overall than meta GGA and LSDA functionals. Although the top DFT method includes the kinetic energy density τ_G in both the exchange and correlation functionals, there appears to be no strong requirement for τ_G : the second- and third-ranked DFT levels do not incorporate τ_G at all, and TPSSH, which places third from last, includes the kinetic energy density in both functionals. Interestingly, the commonly used B3LYP functional ranked next to last for 4-methylthiazolidine bond distances, surpassing only SVWN5 and exhibiting a MUE (0.0095 Å) slightly worse than SCC-DFTB (0.0087 Å).

3.2. PLG analog library

The M05-2X functional and the MG3S basis set were consequently used to obtain benchmark bond lengths for PLG and the eleven PLG analog compounds shown in Table 1. Bonds to hydrogen were omitted from the analysis. Thirty-four codings of popular MM force fields, plus AM1, MNDO, PM3, PM6, DFTB/DYLAX, and DFTB+, were tested against these best estimates. Once again, we gauge the quality of our results by mean unsigned error (MUE) in bond distance. Table 6 lists MUEs in MM bond lengths for all force field implementations tested, and Table 7 provides MUEs for NDDO and SCC-DFTB approaches. Here, we found that the majority of MM force fields proved more accurate than the semiempirical QM approaches: the best NDDO method, AM1, reproduced our compound set geometries less accurately than 68% of the molecular mechanics force fields we evaluated. The least accurate NDDO approach, PM3, performed worse than all but one MM method (RULE). SCC-DFTB also proved less suitable for the PLG-analog systems than most MM force fields; the older DFTB/DYLAX implementation in particular returned very large errors in bond length (MUE = 0.1739 Å). The AMBER89 force field as coded in MOE 2007.09 exhibits the best overall performance for PLG and its analogs in terms of MUE in bond distance, followed closely by the Kollman All-Atom force field in SYBYL 7.2 (MUE = 0.0096 Å and 0.0097 Å, respectively). Eight of the top ten MM methods tested are AMBER-type force fields; however, it is important to note that variations between these top ten methods (and between the majority of MM methods examined overall) are very small, e.g., only 0.0031 Å between the top-ranked AMBER89 and MMFFs (MOE 2007.09), which placed twentieth. Many of the force fields also performed similarly against the DFT benchmarks, e.g., MMFF94s, OPLS2001, and MMFF94x all yielded a MUE in bond length of 0.0124 Å; the force fields ranked third through seventh yielded MUEs of ~0.011 Å; and those placing eighth through twenty-second gave MUEs of ~0.012 – 0.013 Å. Such small differences in errors cannot be reliably utilized to distinguish between the appropriateness of individual methods in the current case. Once again, it was impossible to differentiate between MM methods in terms of their ability to reproduce PLG and PLG-analog C-C, C-N, C-S, and C-O bond and torsional angles, as the majority of force fields gave angles, including those incorporating ring atoms, that differed by less than one degree. Specifically, we found that MUEs in bond angles among force fields ranged from 1.873 degrees (MMFF as implemented in SYBYL) to 3.318 degrees (Engh-Huber in MOE), with 79.4% of force fields demonstrating MUEs between 1.87 and 2.87 degrees.)

In the present study, it is more appropriate to rank and prioritize groups of force fields, which vary more distinctly in terms of bond distance errors, than individual methods.

Consequently, we recommend the top seven MM methods as equally suitable to reproduce PLG-analog and similar peptidomimetic geometries (MUE = 0.0096 Å – 0.0111 Å); six of these methods utilize AMBER-type force fields that were parameterized for large biopolymers and include peptide, protein and nucleic acid parameters. Placing second in groups of force fields for the PLG-analog systems are the OPLS and MMFF-type methods, along with the ESFF, Universal, UFF VALBOND and Tripos force fields, followed by the CHARMM27, CHARMM22, CFF91, COMPASS, Dreiding, Engh-Huber, CVFF95, CVFF and PEF95SAC methodologies in “third place.” (It is arguable as to whether CHARMM27 should be classified with the second or third grouping of force fields; we have classified it as part of the latter as its MUE in bond distance differs from that of Tripos by 0.0026 Å, but varies from that of CHARMM22 by 0.0019 Å.) The RULE force field as implemented in MOE 2007.09 was the least accurate approach for this system, with a bond-distance MUE of 0.0430 Å compared to the M05-2X/MG3S best estimates.

5. Conclusions

In this study, we have first evaluated geometric parameters for 4-methylthiazolidine obtained by a selection of density functionals and other less costly molecular orbital methods against corresponding coupled-cluster benchmark bond distances. While the accuracy of the density functionals we examined for this system varied significantly in terms of mean unsigned error (MUE), DFT reproduced bond lengths much more reliably than the iterative extended Hückel theories and semiempirical NDDO methods we tested – with the notable exceptions of the B3LYP and SVWN5 functionals, which performed better than all four NDDO methods but worse than both DFTB codings. Our results indicate that the performance of a given density functional for 4-methylthiazolidine is enhanced by an increase in Hartree-Fock exchange, and that hybrid GGA and hybrid meta GGA functionals are generally preferred. We found that mean unsigned errors in NDDO bond distances were a factor of 3.1 – 9.6 larger than *ab initio* Hartree-Fock, and a factor of 6 – 18 larger than the average absolute error of the top five density functionals.

The best overall method from that analysis, the M05-2X density functional, was then used to generate new benchmark geometries for prolyl-leucyl-glycinamide (PLG) and a series of peptidomimetic analogues developed in our laboratory, many of which contain functionalities similar to 4-methylthiazolidine. We tested a wide array of commercially available molecular mechanics force field implementations together with NDDO and SCC-DFTB for their ability to reproduce the PLG-analogue benchmark values. While AM1, DFTB+, and PM6 performed best among non-MM methods, we do not recommend any of the semiempirical or SCC-DFTB techniques we tested for our compound set due to relatively high errors in bond distance compared to the best-performing MM force fields. However, since many of these force fields demonstrated similar absolute errors, with some deviating from each other by less than 0.0001 Å, we prioritize the MM methods by groups rather than by individual force field. Here, we found that AMBER-type force fields from three commercial software toolkits ranked at or near the top, followed roughly by MMFF-type force fields, with those in the CFF, CVFF and COMPASS families (MM methods parameterized for a broader range of compound structures and elements) generally disfavored. Our conclusions suggest that the molecular mechanics requirements of small peptidomimetics may resemble those of larger peptides and biopolymers rather than small druglike molecules or organic compounds, as the best force fields for our PLG-analogue compound set are also those that were parameterized and optimized specifically for larger proteins.

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Figure 1.
4-methylthiazolidine, illustrating the atom numbering convention followed in this study.

Table 1

Prolyl-leucyl-glycinamide (PLG) and eleven structurally related PLG analogues. [5-7]

Compound	Structure
PLG	

47

Compound	Structure
96	
100	

Compound	Structure

107	

Compound	Structure
108	

120

Compound	Structure
140	

Compound	Structure
149	
162	

Compound	Structure
164	
169	

Table 2 Summary of the DFT methods assessed in this study^a

functional	Type	X	τ in E or C?	References
B3LYP	HGGA	20	neither	12_14
B97-2	HGGA	21	neither	18
M05-2X	HMGGA	56	both	16
M06	HMGGA	27	both	17
M06-2X	HMGGA	54	both	17
M06-L	MGGA	0	both	15
MPW1B95	HMGGA	31	correlation	19_21
MPW1KCIS	HMGGA	15	correlation	21_25
mPW1PW ^a	HGGA	25	neither	21_26
PBEh ^b	HGGA	25	neither	27_28
SVWN5	LSDA	0	neither	29_30
TPSSh	HMGGA	10	both	31

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

^b Same as mPW0, mPW1PW91, and MPW25.

Table 3

CCSD(T)/MG3S best estimates of fifteen bond distances (in Å) for 4-methylthiazolidine (Figure 1)

Bond	Distance (Å)
S1-C2	1.820
S1-C5	1.822
C2-C3	1.524
C3-N4	1.462
N4-C5	1.456
C3-C6	1.526
C2-H7	1.087
C2-H8	1.086
C3-H9	1.091
N4-H10	1.011
C5-H11	1.086
C5-H12	1.092
C6-H13	1.090
C6-H14	1.089
C6-H15	1.090

Table 4

Mean unsigned errors (MUEs) in fifteen DFT and HF bond distances for 4-methylthiazolidine (Figure 1), tested against CCSD(T)/MG3S benchmarks

functional	MUE, Å
M05-2X	0.0017
mPW1PW	0.0020
B97-2	0.0023
M06-2X	0.0025
PBEh	0.0027
M06-L	0.0030
MPW1KCIS	0.0038
HF	0.0043
M06	0.0062
MPW1B95	0.0075
TPSSh	0.0080
B3LYP	0.0095
SVWN5	0.0107

Table 5

Mean unsigned errors (MUEs) in fifteen NDDO and SCC-DFTB bond distances for 4-methylthiazolidine (Figure 1), tested against CCSD(T)/MG3S benchmarks

method	MUE, Å
DFTB/DYLAX	0.0085
DFTB+	0.0087
PM3	0.0133
PM6	0.0142
AM1	0.0155
MNDO	0.0415

Table 6

Mean unsigned errors (MUEs) in molecular mechanics bond distances (in Å) for prolyl-leucyl-glycinamide (PLG) and eleven PLG analog compounds, tested against M05-2X/MG3S values

MM Force Field	MUE, Å
AMBER89 ^a	0.0096
Kollman All-Atom ^b	0.0097
AMBER99 ^a	0.0109
AMBER94 ^a	0.0110
AMBER7 FF02 ^b	0.0110
TAFF ^a	0.0110
AMBER7 FF99 ^b	0.0111
AMBER4.1 FF95 ^b	0.0116
AMBER ^c	0.0116
ESFF ^c	0.0120
OPLS2005 ^d	0.0121
Universal ^e	0.0122
OPLS-AA ^d	0.0123
MMFF94s ^a	0.0124
OPLS2001 ^d	0.0124
MMFF94x ^a	0.0124
MMFFs ^b	0.0126
MMFF94 ^a	0.0126
MMFF ^b	0.0126
MMFFs ^a	0.0127
MMFF ^a	0.0128
UFF VALBOND ^e	0.0130
Tripos ^b	0.0138
CHARMM27 ^a	0.0164
CHARMM22 ^a	0.0183
CFF91 ^e	0.0198
CFF91 ^c	0.0211
COMPASS ^e	0.0214
Dreiding ^e	0.0214
Engh-Huber ^a	0.0217
CVFF95 ^e	0.0230
CVFF ^c	0.0252
PEF95SAC ^a	0.0255

MM Force Field	MUE, Å
RULE ^a	0.0430

^aMOE 2007.09 [101];

^bSYBYL 7.2 [102];

^cInsightII 2000.1 [103];

^dMacroModel 9.1 [104];

^eCerius2 4.10L [105]

Table 7

Mean unsigned errors (MUEs) in NDDO and SCC-DFTB bond distances (in Å) for prolyl-leucyl-glycinamide (PLG) and eleven PLG analog compounds, tested against M05-2X/MG3S values

Method	MUE, Å
AM1	0.0163
DFTB+	0.0173
PM6	0.0189
MNDO	0.0266
PM3	0.0285
DFTB/DYLAX	0.1739