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Ab initio calculations on peptide-derived oxazoles and thiazoles: Improved molecular mechanics parameters for the AMBER* force field

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Summary

Ab initio calculations at the RHF/6-31G* and MP2/6-31G*//RHF/6-31G* levels of theory are performed for 2-methyl-4-carboxamido-oxazoles and -thiazoles, including rotational profiles for the ring-carboxamide bond, which showed the expected conjugation and hydrogen bonding effects. On the basis of these data, newly optimised stretch, bend and torsional parameters for the AMBER* force field are derived, along with CHELPG-fitted partial atomic charges.

Introduction

In recent years, a wide range of novel and unusual cyclopeptides containing oxazoline-, thiazole- and thiazoline-based amino acids have been isolated from marine organisms and from certain bacteria, fungi and plants [1], e.g. lissoclinamide 4 **1** [2], patellamide D **2** [3], and cyclodidemnamide **3** [4] (see Scheme 1). These cyclopeptides display a range of biological properties, particularly immunoregulatory, antibiotic and antitumoural, but including enzyme-inhibitory activity. In recent publications we have highlighted the potential for cyclopeptides [5] and related marine natural products [6] to chelate and transport metal ions in vivo using the various hetero-atom ligands associated with their macrocyclic cavities [7–9]. As part of these ongoing synthetic and metal-binding studies [10–12] amongst cyclopeptides [13] we required a reliable set of molecular mechanics force-field parameters for a range of heterocyclic amino-acid-derived residues.

Although some comparative MO studies have been published for simple (i.e. mono- or unsubstituted) oxazole and thiazole systems [14–16] no ab initio data of a level consistent with that used to derive the AMBER* field as a whole, and with that now available for all 20 naturally occurring amino acid residues (i.e. RHF/6-31G* minimum) [17–19], have yet been recorded for the 1-alkyl, 4-carboxamido type O,N and O,S heterocycle systems present in the natural products of interest. On the other hand, the study of peptides by both ab initio and molecular mechanics methods is a well-established and rapidly expanding research area [20] (see Scheme 2).

A comprehensive ab initio study of peptide amino acid residues was reported by Jorgensen and co-workers in 1995 [19]. These workers calculated rotational energy profiles at the RHF/6-31G* level for a wide range of peptide residue dihedral angles, and thus were able to obtain the necessary data for a reparameterisation of the OPLS force field. More recently, Friesner and co-workers [21] have assessed the extent to which peptide conformational energies obtained using a selection of common molecular mechanics force fields (AMBER, OPLS, CHARMM, MMFF and MM3) are in agreement with results from ab initio calculations performed on RHF/6-31G** geometries using localised MP2 methods. We chose to use the AMBER* force field [22–24] utilised in MacroModel v. 5.5 [25] for reparameterisation, in view of its ready availability, diverse application in peptide modelling and use in previous studies on macrocyclic heterocycle-containing peptides [3]. In addition, the recent ab-initio-based reparameterisation of this force

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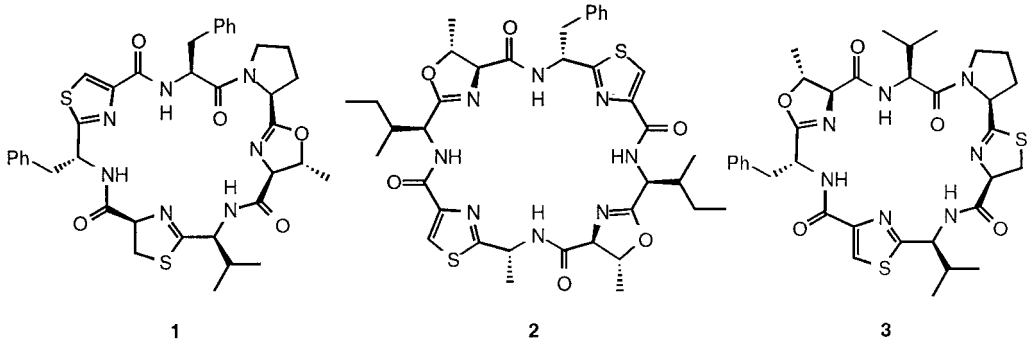

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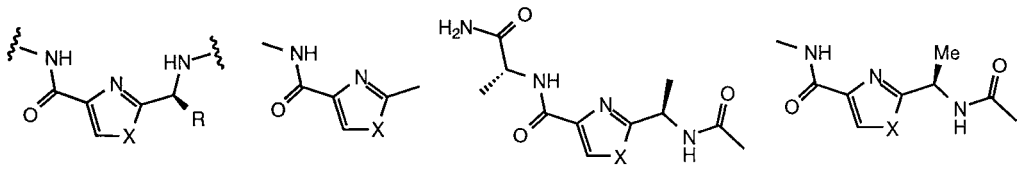
Scheme 1. Examples of five-ring heterocycles containing peptide macrocycles.



4 (X=O) **5** (X=S) **6** (X=O) **7** (X=S) **8** (X=O) **9** (X=S) **10** (X=O) **11** (X=S)

Scheme 2. The peptide-derived five-ring heterocycle subunits **4** and **5** found in the synthetic targets, the simplified models **6** and **7** used for ab initio geometry optimisations, and the model systems **8** and **9** (used for partial charge derivation) and **10** and **11** (used for torsion parameter revision).

field for proline residues by Still and co-workers [18] was particularly appealing to us, given the presence of such residues in all of the Lissoclinamide series. Proline has in fact received considerable attention of late, with high-level ab initio/molecular mechanics studies both of the free amino acid and its *N*-acetyl, L-proline amide form having been published [26, 27]. We wish to report some preliminary results of these investigations for model oxazole and thiazole substructures of types **4** and **5**, represented by the model systems **6** and **7**.

Ion chelation considerations

Although a considerable volume of peptide–ion interaction modelling work exists in the literature [28], this has mainly concerned interactions between alkali metal ions and either the carbonyl groups of the peptide backbone or of side-chain carboxylate anions [29]. Both sets of interactions are usually treated for convenience as being purely ionic in character, and thus able to be modelled as interactions between point charges [30]. With the exception of zinc and copper carboxylates, until very recently [31] very little work had been done concerning the interactions between transition metal ions and peptide nitrogen atoms, although these are thought to play an important role in the biochemistry of marine natural products [5]. Indeed, complexes containing copper ions chelated to thiazole and oxazoline rings have recently been isolated and characterised [7, 8]. In related work, Wipf et al. [9] have isolated a silver ion complex of the tris-oxazoline metabolite Westiellamide. Whilst an ab initio study of covalent interactions between **4** and **5** and third-row transition element cations is beyond the scope of the present study, better quality partial atomic charges than those currently available are highly desirable. We sought to determine these using the CHELPG fitting method and to integrate these charges into the revised AMBER* force field. The oxazole/thiazole chelation examples which have so far been reported have involved replacement of the amide *cis*-hydrogen with a metal cation, and so accurate determination of the partial charges at this site and on the hetero-ring nitrogen atom (which also plays a role in chelation) is of particular importance, as is the geometry of the atoms immediately surrounding the putative chelation site. The studies described in this paper thus concentrate on: (i) obtaining new global minima for the systems **6** and **7**; (ii) revision of the existing AMBER* stretch and bend parameters to take account of the new optimum geometry; and (iii) calculation of ab initio rotational energy profiles for the ring-

carboxamide bonds, and fitting of the values obtained to suitable AMBER* torsion parameters. In addition, all the revised and new parameters are calculated using CHELPG-fitted atomic charges, derived from MP2/6-31G*//RHF/6-31G* calculations on model structures **8** and **9**.

Methods

Ab initio calculations were carried out using the Gaussian 92 suite of programs [32] utilising standard basis sets, except for the single point MP2 calculations on **8** and **9**, for which Gaussian 94 was utilised. For the dihedral drives only the dihedrals θ_1 and θ_2 were constrained, with all other geometrical parameters being optimised at the RHF/6-31G* level for each value of θ_n. Molecular mechanics calculations were carried out using the AMBER* force field [24] as implemented in v. 5.5 of MacroModel [25]. The initial stretching, bending, torsional and non-bonded interaction parameters for both the models **10** and **11** of **6** and **7** were thus drawn from the original AMBER force field [22, 23], with amide parameters from AMBER* (1992 revision) [24] and others from separate work on imine [33] and dehydroalanine [34] systems. The hydrogen bonding interaction between the amide hydrogen atoms and the hetero-ring nitrogen was modelled using the standard 6-12 Lennard-Jones parameters described by Kollman and co-workers [35]. The fitting of the ab initio energies for the ring-amide bond rotational profiles to suitable AMBER* torsion parameters was carried out using the *torfit* program, v. 2.0 [36].

Results and discussion

4-Carboxamido-oxazoles

Ab initio data

Although not present in the *Lissoclinum* peptides, amino-acid-derived 4-carboxamidooxazoles of type **6** are present in a number of closely related natural products which have attracted both medicinal and synthetic interest [2,37–39]. The global minimum obtained for this system by optimisation at the RHF/6-31G* level is shown in Figure 1. The atomic coordinate data in Z-matrix format together with CHELPG partial atomic charges at both the MP2 and RHF levels of theory and the corresponding charges from the unrevised AMBER* force field are given in Table 1a.

The global minimum shows, not unexpectedly, an essentially planar structure, with the carboxamide substituent deployed so as to enable hydrogen bond formation between the *cis*-amide hydrogen and the ring nitrogen atom, with a bond length of 2.389 Å. The ring bond lengths and angles show close similarities to the corresponding data obtained by Shaffer and Wierschke [15] for the parent oxazole at the same level of theory, although there appears to be a slight decrease in length for all five ring bonds, probably due to the increased π-delocalisation caused by adding the carboxamido substituent.

The ab initio torsional profiles for the ring-carbonyl bond obtained at the MP2/6-31G*//RHF/6-31G* and RHF/6-31G*//RHF/6-31G* levels of theory are shown in Graph 1a, together with molecular mechanics energies using the unrevised AMBER* force field. The results clearly show that, as expected, the hydrogen-bonded global minimum is preferred over the alternative planar arrangement (with $\theta_1 = 180°$), with a very substantial ~8 kcal/mol difference in energy, and that a barrier to free rotation of 9–10 kcal/mol exists, with $\theta_1 = 90°$ being the most disfavoured geometry. These results mirror the observed preference for $\theta_1 = 0°$ type geometries observed in oxazole-containing natural products [13].

AMBER reparameterisation*

Charges. The use of CHELPG fitting to the MP2/6-31G* electrostatic potential is consistent with the methods used for the AMBER* force field as a whole, although it may be noted that Kollman and co-workers have adopted RESP fitting [40,41] to the RHF/6-31G* electrostatic potential (i.e. *not* the MP2 density) as the method of choice for the recent 'second generation' AMBER94 field [42]. This approach is stated to give a 10–15% overestimation of dipole moments with respect to the gas-phase values, its use being justified on the grounds that solvation in water gives rise to a similar increase in polarisation and thus the derived charges are more suitable for aqueous-phase mechanics calculations. It is interesting to note that a cursory comparison between the RHF and MP2 charge values shown in Table 1a appears to show a similar 10–15% increase in polarisation for RHF/6-31G*-derived charges with respect to those obtained from the MP2-correlated wave function. This suggests that the MP2-derived values may be a 'truer' representation of gas-phase polarisations, although of course comparisons between results obtained using different fitting methods must be treated with caution. Charges

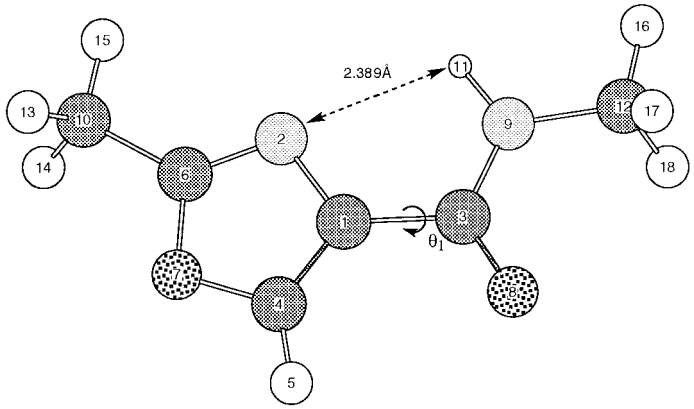


Figure 1. Minimum energy conformation for the model 4-carboxamido-oxazole structure **6**. The hydrogen bond length and the dihedral angle [C(8)-C(1)-C(6)-C(12), θ_1] under study are indicated.

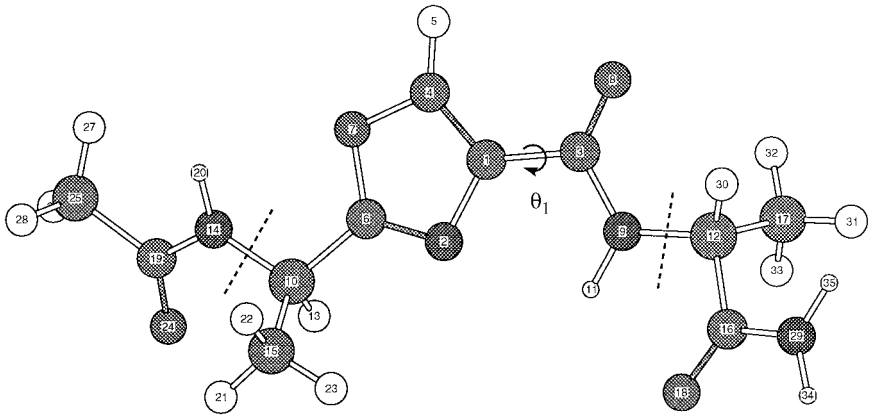


Figure 2. Tetrapeptide-derived charge derivation model structure **8**, shown with $\theta_1 = 0°$. The boundaries of subfragment **8a** are indicated by broken lines.

obtained by fitting using the same group's earlier ESP method (as implemented in Gaussian 94) also show this trend, however. As the critical hydrogen bond interaction tends to occur endo to the macrocyclic ring in compounds such as **1**–**3**, we reasoned that any attempt to 'pre-polarise' the molecule to offset solvation effects would be unjustified, and, given the likely detrimental effect (due to non-bonding interaction inaccuracies) on AMBER*, modelling of the crucial θ_1 torsion could not be justified. MP2/6-31G*-derived charges are, therefore, used throughout this article.

The most notable discrepancies between these ab-initio-derived charges and those from AMBER* occur for the oxazole ring atoms in **6** and for the atoms immediately adjacent to them, particularly C10. A reparameterisation for the oxazole subtype is clearly necessary, with normalisation of any resulting modifications to ensure that overall neutrality is maintained across the fragment. As **6** is typically found as part of a peptide backbone, some idea of the effect of the discrepancies at the C10 and C12 carbon atoms on the all-atom partial charges for alkyl side chain and amide nitrogen substituents is necessary (and, conversely, of the effect of such substituents on the partial charges in the fragment). In order to assess the extent of these effects, the model system Ac-Ala-Oxz-Ala-NH_2 **8** (Figure 2) was chosen and optimised using AMBER*, the oxazole moiety being restrained to the global minimum geometry from **6**. The value of the dihedral angle N2-C6-C10-N14, and thus the extent to which hydrogen bonding occurs between the alanine amide hydrogen H20 and N2, can be expected to have a significant effect on the CHELPG-fitted charges obtained for the subfragment **8a** of interest, as well as on the energy profile for the θ_1 torsion angle. As the torsional profile data calculated from **6** do

Table 1a. Coordinate data for the **6** global minimum, in Z-matrix format. CHELPG charges at the RHF/6-31G* and MP2/6-31G* levels for the global minimum are also given, together with the standard charges from the AMBER* force field

Z-matrix								Charges		
Atom		n	R_n (Å)	n	A_n (°)	n	D_n (°)	RHF	MP2	AMBER*
1	C	–	–	–	–	–	–	0.119	−0.1380	0.0000
2	N	1	1.3901	–	–	–	–	−0.7179	−0.6602	−0.1398
3	C	1	1.4837	2	124.194	–	–	0.6015	0.4500	0.4998
4	C	1	1.3335	2	108.627	3	−180.003	−0.0330	−0.0486	−0.0970
5	H	4	1.0657	1	134.247	2	180.022	0.1865	0.1663	0.1500
6	C	2	1.2710	1	104.724	3	179.978	0.8202	0.7381	0.2928
7	O	4	1.3495	1	107.522	5	180.011	−0.3360	−0.2866	−0.1060
8	O	3	1.2040	1	121.714	4	0.032	−0.6131	−0.5106	−0.4998
9	N	3	1.3416	1	114.788	8	180.016	−0.3477	−0.2841	−0.5198
10	C	6	1.4882	2	128.727	1	180.007	−0.4725	−0.4738	−0.2146
11	H	9	0.9940	3	118.151	1	−0.111	0.2788	0.2603	0.2479
12	C	9	1.4454	3	121.577	11	−179.800	−0.1944	−0.2034	0.1573
13	H	10	1.0842	6	110.420	2	−120.292	0.1291	0.1281	0.0382
14	H	10	1.0842	6	110.420	13	−119.368	0.1293	0.1283	0.0382
15	H	10	1.0802	6	109.225	13	120.315	0.1444	0.1442	0.0382
16	H	12	1.0818	9	108.553	3	179.919	0.0979	0.1015	0.0382
17	H	12	1.0831	9	111.010	16	119.741	0.1078	0.1066	0.0382
18	H	12	1.0831	9	111.020	16	−119.756	0.1072	0.1061	0.0382

not take account of possible hydrogen bond interactions between N2 and H20, such an interaction must be minimised in any charge derivation model, even though in molecules such as **8** lacking other conformational restraints a doubly hydrogen-bonded N2 is the most likely outcome in the global minimum energy conformation, with the N2-C6-C10-N14 dihedral being close to zero. However, in macrocyclic peptide rings such as those in **1**–**3** the N2-C6-C10-N14 angle is less predictable, and thus we reasoned that obtaining accurate torsion parameters for θ_1 was of greater importance than allowing for conformation dependence in charge assignments for atoms taking part in any hypothetical N2-H20 bond. N2-C6-C10-N14 was therefore restrained to 180°, in order to minimise N2-H20 non-bonded interactions during charge derivation.

The following observations may be made regarding the fragment charges obtained for **8a**:

(1) The sum of the CHELPG-derived partial charges across the fragment is close to the zero required for AMBER* compatibility.

(2) The partial atomic charges for the alanine α-hydrogen (H13) and methyl group (C15 and H21–H23) atoms show negligibly small differences from the all-atom AMBER* charges, suggesting that these unrevised charges may be used *unchanged* in any revised field (an important point as they were originally chosen to allow the substitution of alternative amino acid side chains).

(3) Adjustment of the remaining charges to achieve fragment neutrality consistent with the AMBER* force field gave the revised charge set shown in Table 1b.

Torsion parameters. The relative energies obtained using the unrevised AMBER* force field (Graph 1a, curve c) for the various conformers of **6** clearly undershoot those obtained at the MP2/6-31G*//RHF/6-31G* level (Graph 1a, curve b) for higher values of θ_1, whilst significantly *overestimating* at lower, more highly populated values, a more serious error from our perspective given the predominance of the hydrogen-bonded conformation in the natural products of interest. We began our reparameterisation efforts by adjusting the optimum values of the previously reported stretching and bending parameters to reflect the new global minimum, whilst in general retaining the force constants in lieu of future redetermination (the general rigidity of the ring system

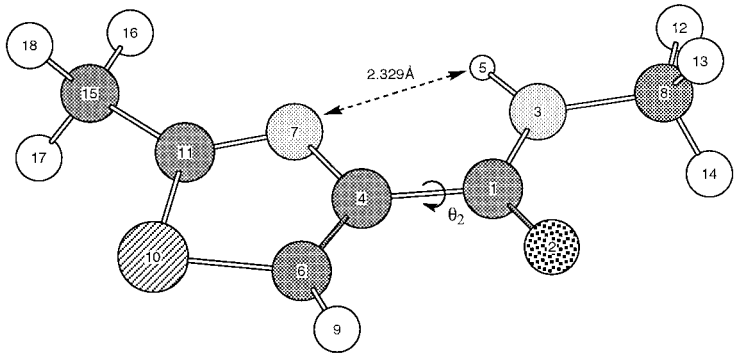


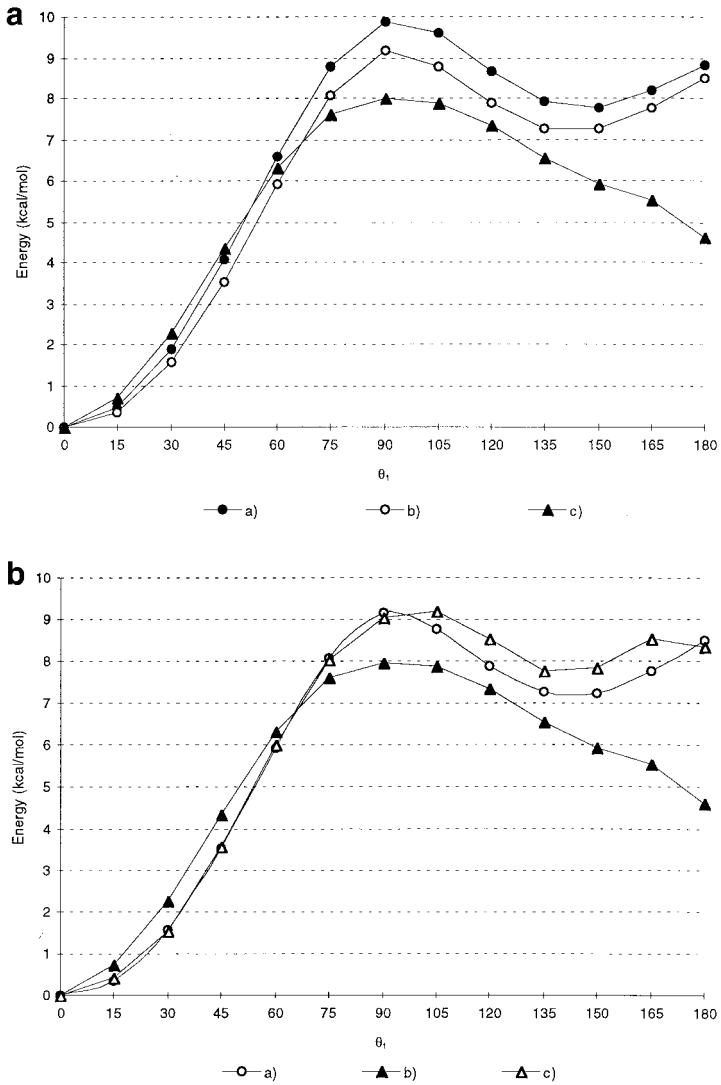
Figure 3. Minimum energy conformation for the model 4-carboxamido-thiazole structure **7**. The hydrogen bond length and the dihedral angle [C(7)-C(6)-C(1)-N(3), θ_2] under study are indicated.

Table 1b. Unrevised AMBER*, CHELPG-fitted MP2/6-31G*//RHF/6-31G* and revised AMBER* charges for carboxamido-oxazole fragment **8b** of model system **8** (Figure 2)

Atom		AMBER*	MP2	Revised
1	C	0.0000	0.1769	0.1698
2	N	−0.1398	−0.6461	−0.6532
3	C	0.4998	0.6653	0.6582
4	C	−0.0970	−0.1179	−0.1250
5	H	0.1500	0.1979	0.1908
6	C	0.2928	0.5923	0.5852
7	O	−0.1060	−0.2469	−0.2540
8	O	−0.4998	−0.6375	−0.6446
9	N	−0.5198	−0.5896	−0.5967
10	C	0.1337	0.3530	0.3459
11	H	0.2479	0.2929	0.2858
13	H	0.0382	0.0313	0.0382
15	C	−0.1146	−0.1414	−0.1146
21	H	0.0382	0.0595	0.0382
22	H	0.0382	0.0263	0.0382
23	H	0.0382	0.0151	0.0382
Total		0.0000	0.0311	0.0000

convinced us that errors in these values were of much less significance than inaccuracies in the torsion parameters for the freely rotatable ring-carbonyl bond). The stretching force constants for the various C-C and C-N bonds were however reinterpolated from the bond length data using the algorithm described in the original (united atom) AMBER paper. The AMBER* partial charges were also replaced with those calculated from model **8**. To maximise the transferability of the calculation results to systems such as the target molecules, the *N*-acetyl alanine fragment present in model **8** was appended at C10 to give a hybrid AMBER* model system of structure **10** (Scheme 2), allowing the new oxazole fragment charges to be used without the need to derive empirically unnecessary charges for the 2-methyl-4-carboxamido-1,3-oxazole methyl group present in **6**. The ab initio geometries for the oxazole and *N*-methylcarboxamide portions of **10** were retained, however. Of initial concern was the breaking of the plane of symmetry present in **6** by introduction of the Ac-Ala functionality; however, repetition of the $\theta_1 = 0°$ to $\theta_1 = 180°$ calculations using the C15 epimer of **10** gave agreement to within 0.02 kcal/mol at each point, indicating that the steric and long-range electrostatic effects of introducing the new moiety on the θ_1 torsional profile are not significant.

The relative (a) ab initio energies for θ_1 in **6**, (b) unrevised AMBER* energies for θ_1 in **10**, and (c) revised AMBER* energies for θ_1 in **10** are shown in Graph 1b, with the energy profile required for the torsional energy term in revised AMBER* (i.e. the difference between the ab initio energies and the sum of the non-torsional terms in AMBER* using the revised partial charges from **8**) shown in Graph 2 (curve a). The anomaly seen for the $\theta_1 \approx 180°$ region in **6** is reproduced essentially unchanged for **10**, as is the more problematic overestimation (even without an energetic contribution from any torsion parameters) of the increase in energy when moving from $\theta_1 = 0°$ to $\theta_1 = 15°$. Given the inability of AMBER* to incorporate geometry-dependent non-bonded interactions, rather than purely distance-dependent 6–12 or 10–12 models, correction of this highly localised discrepancy must be undertaken by means of torsion parameters. This poses a significant problem in terms of adjusting the standard v_1–v_3 parameters, as the effective



Graph 1. (a) Plot of relative energies for varying values of dihedral angle θ_1 in the model oxazole system **6**: (a) at the RHF/6-31G*//RHF/6-31G* level; (b) at the MP2/6-31G*//RHF/6-31G* level; and (c) from the unrevised AMBER* force field. (b) Plot of relative ab initio energies for varying values of dihedral angle θ_1 in oxazole systems **6**/**10**: (a) for **6**, at the MP2/6-31G*//RHF/6-31G* level; (b) for **10**, from the unrevised AMBER* force field; and (c) for **10**, from the revised AMBER* force field.

periodicity of rotation required to simulate an effect spanning a 30–40° region would need to be $n = 4$ or greater. Indeed our attempts to reparameterise using the standard AMBER model give only marginal improvements in fit, even when angular offsets were employed for v_1–v_3. However, more recent implementations of AMBER* (in MacroModel v. 4.5 and onwards) allow the use of a six-term torsional energy expression of the form

$$E = \frac{v_1}{2}(1 + s\cos\theta) + \frac{v_2}{2}(1 - s\cos 2\theta) + \frac{v_3}{2}(1 + s\cos 3\theta) + \frac{v_4}{2}(1 - s\cos 4\theta) + \frac{v_5}{2}(1 + s\cos 5\theta) + \frac{v_6}{2}(1 - s\cos 6\theta)$$

where s is the sign of the relevant force constant v_n. Use of this model in reparameterisation of the ring-carboxamide bond gave accurate reproduction of the barrier height and agreement to within 0.1 kcal/mol for values of θ_1 up to and including 90°, with agreement to within 0.75 kcal/mol for the less significant higher energy conformations with $\theta_1 > 100°$ (Graph 1b, curve c). The revised stretch, bend and torsion parameters

Table 1c. Revised AMBER* parameters for 4-carboxamido-oxazole fragment **8a**. The underlined force constants are reinterpolated from the bond length data using the standard algorithm [22]

Bond		Length (Å)	Force constant (kcal/mol)
7	4	1.3495	400.0000
4	5	1.0657	340.0000
4	1	1.3335	570.0000
1	3	1.4837	353.0000
1	2	1.3901	415.0000
3	8	1.2040	570.0000
3	9	1.3416	475.0000
9	11	0.9940	434.0000
2	6	1.2710	570.0000
6	10	1.4882	345.0000
6	7	1.3380	400.0000

Bond angle			Optimum (°)	Force constant (kcal/mol)
7	4	1	107.5220	70.0000
7	4	5	118.2310	35.0000
7	6	2	113.6370	70.0000
7	6	10	117.6420	70.0000
5	4	1	134.2470	35.0000
4	7	6	105.4960	70.0000
4	1	3	127.1780	85.0000
4	1	2	108.6270	70.0000
1	3	8	121.1740	80.0000
1	3	9	114.7880	70.0000
1	2	6	104.7240	70.0000
3	1	2	124.1940	70.0000
3	9	11	118.1510	35.0000
8	3	9	124.0390	80.0000
2	6	10	128.7270	70.0000

Dihedral				$\nu_1/2$	$\nu_2/2$	$\nu_3/2$	$\nu_4/2$
2	3	4	5	0.9548	2.0875	−0.0006	−0.3982
2	3	4	6	−0.2480	0.3631	0.2196	−0.3056
5	4	3	7	0.0000	0.0000	0.0000	0.0000
6	4	3	7	0.0000	0.0000	0.0000	0.0000

for the **8a** fragment are given in Table 1c; in this case the use of ν_5 and ν_6 terms in addition to ν_1–ν_4 did not significantly improve the fit, and so they are omitted.

4-Carboxamido-thiazoles

In contrast to N,O heterocycles such as **6**, the reliability of the 6-31G* basis set has not yet been adequately demonstrated for sulphur-containing systems such as **5** and **7**/**9**, and so ab initio calculations at this level of theory must be treated with more caution. The generally encouraging agreement with theory which has been reported for simple thiazoles [14,15] and for cysteine [17], however, encouraged us to attempt reparameterisation of the ring-carbonyl dihedral as for the oxazole case. The case of cysteine is particularly en-

Table 2a. Coordinate data for the **7** global minimum, in Z-matrix format. CHELPG charges at the MP2/6-31G* and RHF/6-31G* levels for the global minimum are given, together with the standard charges from the AMBER* force field

Z-matrix								Charges		
Atom		n	R_n (Å)	n	A_n (°)	n	D_n (°)	RHF	MP2	AMBER*
1	C	–	–	–	–	–	–	0.6291	−0.4759	0.4998
2	O	1	1.2038	–	–	–	–	−0.6235	−0.5168	−0.4998
3	N	1	1.3414	2	123.832	–	–	−0.3721	−0.3144	−0.5198
4	C	1	1.4940	2	121.180	3	179.996	0.1180	0.1418	0.0000
5	H	3	0.9937	1	118.152	2	180.026	0.2629	0.2513	0.2479
6	C	4	1.3402	1	123.195	2	−0.004	−0.1809	−0.1716	−0.1257
7	N	4	1.3809	1	121.066	6	179.998	−0.5657	−0.5269	−0.0950
8	C	3	1.4450	1	121.496	5	179.957	−0.1433	−0.1526	−0.1573
9	H	6	1.0688	4	127.181	1	−0.007	−0.2132	0.1852	−0.1500
10	S	6	1.7222	4	109.497	9	179.993	−0.0795	−0.0626	−0.0486
11	C	7	1.2751	4	111.666	1	179.998	0.4316	0.3936	0.2193
12	H	8	1.0817	3	108.566	1	179.878	0.0886	0.0923	0.0382
13	H	8	1.0829	3	111.023	12	119.767	0.0930	0.0922	0.0382
14	H	8	1.0829	3	111.008	12	119.761	0.0928	0.0918	0.0382
15	C	11	1.4992	7	124.147	4	179.988	−0.1495	0.1828	−0.2146
16	H	15	1.0811	11	108.724	7	−0.037	0.0654	0.0732	0.0382
17	H	15	1.0845	11	111.041	16	119.907	0.0599	0.0651	0.0382
18	H	15	1.0845	11	111.042	16	−119.910	0.0602	0.0655	0.0382

Table 2b. Unrevised AMBER*, CHELPG-fitted MP2/6-31G*//RHF/6-31G* and revised AMBER* for carboxamido-thiazole fragment **9a** of model system **9** (Figure 4)

Atom		AMBER*	MP2	Revised
1	C	0.4998	0.7172	0.7161
2	O	−0.4998	−0.6481	−0.6491
3	N	−0.5198	−0.6631	−0.6642
4	C	0.0000	0.1458	0.1447
5	H	0.2479	0.2763	0.2752
6	C	−0.1257	−0.2345	−0.2356
7	N	−0.0950	−0.4454	−0.4464
9	H	0.1500	0.2254	0.2243
10	S	−0.0486	−0.0364	−0.0486
11	C	0.2193	0.2482	0.2471
15	C	0.1337	0.3993	0.3982
17	C	−0.1146	−0.1117	−0.1146
21	H	0.0382	0.0286	0.0382
23	H	0.0382	0.0562	0.0382
24	H	0.0382	0.0239	0.0382
25	H	0.0382	0.0178	0.0382
Net		0.0000	−0.0006	0.0000

couraging, as recent work by Hoyau and Ohanessian [31] and by O'Hair and co-workers [43] has shown that sulphur-electrophile interactions can be predicted with reasonable accuracy by such means. The global minimum obtained for **7** at the RHF/6-31G* level is shown in Figure 3. The atomic coordinate data given in Z-matrix format together with CHELPG-fitted partial atomic charges both with and without MP2 correlation are given in Table 2a.

In contrast to the oxazole, quite marked differences are noticeable between the ring bond lengths and angles and the corresponding values which have been calculated for simple thiazole at this level of theory [15]. The differences are particularly apparent around the sulphur atom. The hydrogen bond is slightly shorter (2.329 Å) than the one observed for **6**. Comparison between MP2- and RHF-derived charges shows a similar trend to that seen with the oxazole, and once again the MP2-derived charges were utilised.

A plot of the ab initio RHF/6-31G*//RHF/6-31G* and the accompanying MP2/6-31G*//RHF/6-31G* energies against angle θ_2 (Graph 3a, curves a and b) again shows the expected preference for the hydrogen-bonded global minimum over the alternative planar structure with $\theta_2 = 180°$, with a barrier to rotation

Table 2c. Revised AMBER* parameters for 4-carboxamido-thiazole fragment **9a**. The underlined force constants are reinterpolated from the bond length data using the standard algorithm [22]

Bond		Length (Å)	Force constant (kcal/mol)
10	6	1.7222	300.0000
6	9	1.0688	340.0000
6	4	1.3402	564.0000
4	1	1.4940	337.7000
4	7	1.3809	427.5000
1	2	1.2038	570.0000
1	3	1.3414	490.0000
3	5	0.9937	434.0000
7	11	1.2751	567.0000
11	10	1.4992	328.5000
11	15	1.7438	300.0000

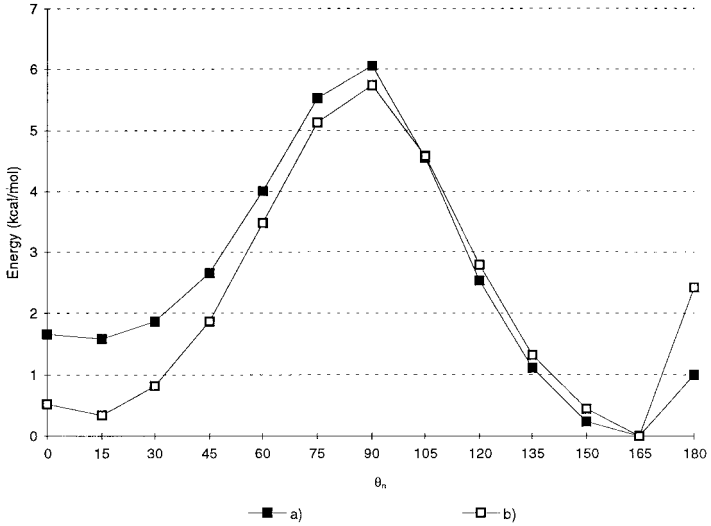
Bond angle			Optimum (°)	Force constant (kcal/mol)
10	6	4	109.4970	70.0000
10	6	9	123.3210	35.0000
10	11	7	113.8920	70.0000
10	11	15	121.9610	70.0000
9	6	4	127.1810	35.0000
6	4	1	123.1950	85.0000
6	4	7	115.7390	70.0000
6	10	11	89.2060	80.0000
4	1	2	121.1800	80.0000
4	1	3	114.9870	80.0000
4	7	11	111.6660	70.0000
1	3	5	118.1520	35.0000
1	4	7	121.0660	70.0000
2	1	3	123.8330	80.0000
7	11	15	124.1470	70.0000

Dihedral				$v_1/2$	$v_2/2$	$v_3/2$	$v_4/2$	$v_5/2$	$v_6/2$
6	4	1	2	0.0000	2.4356	−0.0003	0.4080	0.0000	0.0000
6	4	1	3	−0.1200	0.3752	0.3423	−0.3860	0.0462	−0.0748
7	4	1	2	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
7	4	1	3	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000

very similar in magnitude to that for the oxazole system. This suggests that the increased aromaticity of thiazole **7** with respect to oxazole **6** has little effect on the magnitude of the barrier, and that reparameterisation should be feasible using similar methods. Our experience with using the unrevised AMBER* field for aromatic (as opposed to aliphatic) sulphur has suggested that omission of the lone pairs gives more accurate results, and so monopolar sulphur is assumed throughout the reparameterisation process.

AMBER reparameterisation*

Charges. Analogous to the oxazole case a comparison of AMBER* partial charges and those obtained from the fragment **9a** of the tetrapeptide-derived model thiazole **9** (Figure 4) was made, with the Ala-NH to thiazole nitrogen hydrogen bond again being



Graph 2. Required energy profiles for the torsional terms in revised AMBER* for (a) θ_1 in **6**/**10** and (b) θ_2 in **7**/**11**.

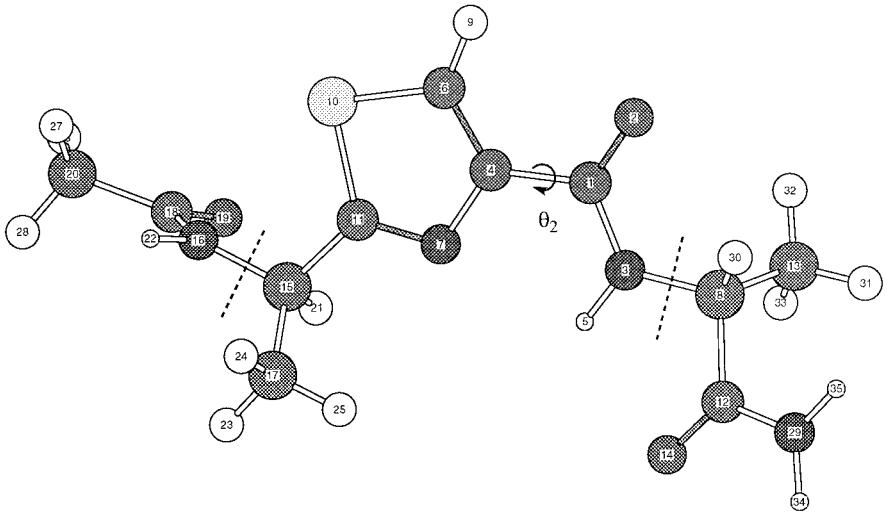
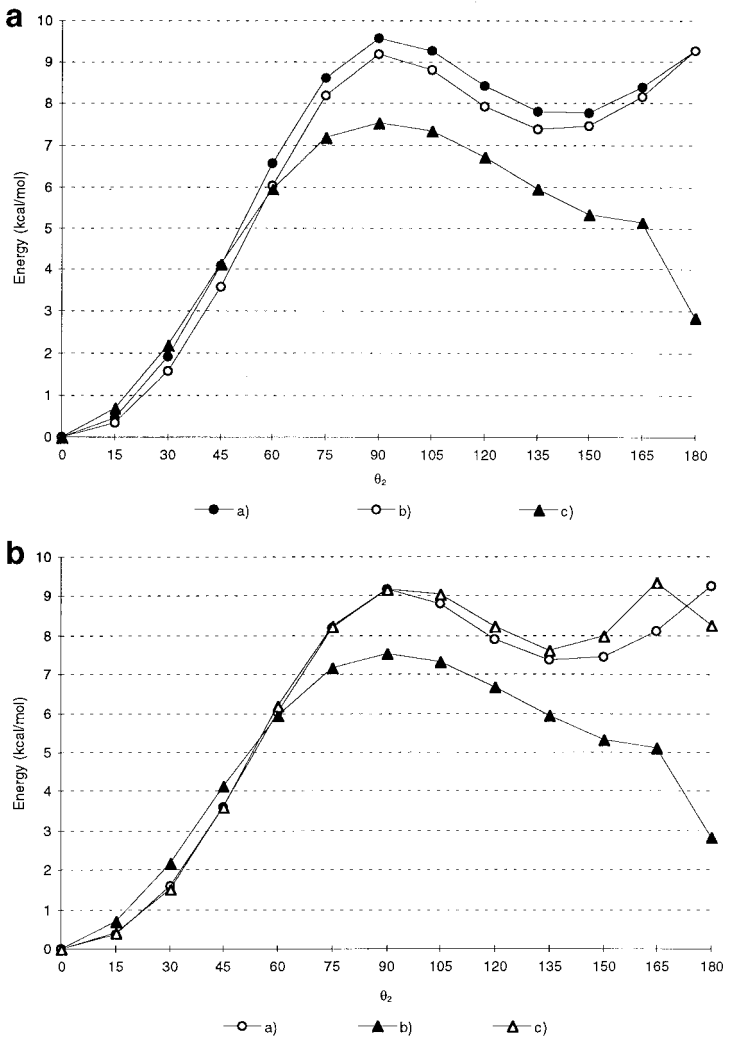


Figure 4. Tetrapeptide-derived charge derivation model structure **9**, shown with $\theta_2 = 0°$. The boundaries of subfragment **9a** are indicated by broken lines.

suppressed by restricting the N16-C15-C11-N7 dihedral angle to 180° during optimisation of the acylalanine moiety with AMBER* (the thiazole moiety being restrained to the global minimum geometry from **7**). As with **8a**, the fragment **9a** of interest was found to be almost neutral, with little variation from standard all-atom AMBER* charges for the alanine residue attached to the oxazole in the 2-position. The fact that the ab-initio-derived sulphur atom partial charge was almost identical to its AMBER* counterpart suggests that the standard AMBER* thiophene sulphur atom charge model may also be applicable when the sulphur lone pairs are included in calculations for steric reasons, as is often necessary for AMBER* calculations on biopolymers. Slight adjustment to give overall neutrality gave the revised partial charges indicated in the right-hand column of Table 2b.

Torsion parameters. As with the oxazole case, a hybrid model system **11** (Scheme 2) was employed for parameter revision, allowing the direct use of **9a**-derived charges without invalidating the relative



Graph 3. (a) Plot of relative ab initio energies for varying values of dihedral angle θ_2 in the model thiazole system **7**: (a) at the RHF/6-31G*//RHF/6-31G* level; (b) at the MP2/6-31G*//RHF/6-31G* level; and (c) from the unrevised AMBER* force field, with monopolar sulphur. (b) Plot of relative ab initio energies for varying values of dihedral angle θ_2 in thiazole systems **7**/**11**: (a) for **7**, at the MP2/6-31G*//RHF/6-31G* level; (b) for **11**, from the unrevised AMBER* force field with monopolar sulphur; and (c) for **11**, from the revised AMBER* force field with monopolar sulphur.

ab initio energies for the dihedral angle of interest. The unrevised AMBER* energies for the various values of θ_2 in **7** (Graph 3a, curve c) show, as with the oxazole, a pattern of overestimation of the difficulty of small torsional perturbations and underestimation of the energies for higher values of θ_2. In this case, however, the latter is more serious, with an erroneous value for $\theta_2 = 180°$ some 6.41 kcal/mol below the MP2/6-31G* value, and only 2.84 kcal/mol above the global minimum. Such an error could easily be a source of problems in mechanics/dynamics work, leading to the false prediction of fundamentally incorrect local minima. Therefore, revision of the torsion parameters to avoid this is of comparable importance to correction of the errors around the global minimum. Fortunately, the application of revised fragment charges from **9a**, adjustment of the ideal values for the various bond stretch and angle bend parameters based on the **7** global minimum (with C-C and C-N reinterpolation, based on the bond length data, for the former where appropriate), and finally torsion parameter fitting to the six-term model for **11** again gave much improved agreement with the ab initio data, with errors of <0.1 kcal/mol for $\theta_2 = 0°$ to $\theta_2 = 90°$

and of <1 kcal/mol for the remaining conformations (Graph 3b, curve c). The revised parameters are given in Table 2c; in contrast to the oxazole case, the use of five- and sixfold terms proved to be useful.

Conclusions

Global minima for the model oxazole and thiazole systems **6** and **7** at the RHF/6-31G* level of theory have been obtained. A study of the effects of varying the dihedral angle for the ring-carbonyl bonds showed clear discrepancies between energy differences calculated at the MP2/6-31G*//RHF/6-31G* level and those obtained using the parameters present in the currently available version of AMBER*, indicating that revision of the force field was required. Readjustment of the bond stretching and bond angle parameters to take account of the new global minima and development of new torsional parameters for the dihedral angle under study gave much better agreement with the calculated ab initio energies, and should hopefully lead to more accurate mechanics/dynamics simulations of the various macrocyclic peptide systems which incorporate these structural subunits, particularly for the critical regions around the global minimum. In addition, new and hopefully more realistic partial atomic charges have been obtained, which should assist in the modelling of transannular interactions across macrocyclic rings and also cation interactions with the systems under study.

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