Pergamon

Tetrahedron Letters 40 (1999) 3041–3044

TETRAHEDRON LETTERS

Peptidostarands: valence tautomers of cyclic peptides

Ross P. McGeary [a,*] and Dorine N. Bruget [b]

[a] *Centre for Drug Design and Development, The University of Queensland, Brisbane QLD 4072, Australia.*
[b] *Chemistry Department, The University of Queensland, Brisbane QLD 4072, Australia.*

Received 15 January 1999; accepted 9 February 1999

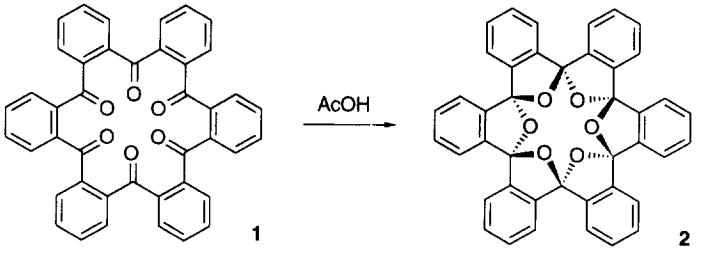
Abstract

Ab initio molecular orbital calculations, at the HF/6-31G* and MP2//HF/6-31G* levels of theory, have been performed on a hypothetical class of organic compound which we call peptidostarands. These molecules are valence tautomers of cyclic peptides. Calculations predict that cyclohexaglycine lies 76 kcal/mol lower in energy than its peptidostarand isomer, but when both molecules are derivatised with electron-withdrawing CFO groups on the nitrogen atoms, the peptidostarand becomes the more stable valence tautomer, by 19 kcal/mol. Strategies for synthesising peptidostarands are discussed.

Keywords: Crown ethers; Isomerisation; Peptides and polypeptides; Polycyclic heterocyclic compounds

Recently Lee *et al.* reported the serendipitous discovery of a new class of star-shaped 2*n*-crown-*n* ethers which resulted from the facile acid-catalysed rearrangement of cyclic polyketones (**1**) (Scheme 1) [1-3]. These compounds, called *starands*, have been characterised by spectroscopic, crystallographic and theoretical studies [1-4]. The six oxygen atoms of [1$_6$]starand (**2**) define a pre-organised, near-spherical cavity of diameter 1.02 Å, whereas its larger homologue, [1$_8$]starand, possesses a rigid cavity of diameter 2.43 Å [2]. These compounds are expected to play an important role in host–guest chemistry. Indeed, [1$_6$]starand (**2**) has been reported to bind Li^+ selectively, while [1$_8$]starand shows strongest binding affinity towards Rb^+ [3].

Scheme 1

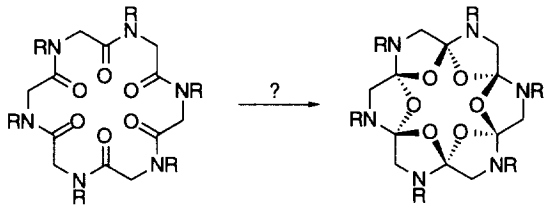


These reports prompted us to consider related systems which contain heteroatoms. In particular, we were interested in the potential for cyclic peptides (**3**) to undergo bond isomerisation to give polyspirocyclic acetals (**4**), which we call *peptidostarands* (Scheme 2).

* Email: R.McGeary@mailbox.uq.edu.au

0040-4039/99/$ - see front matter
PII: S0040-4039(99)00319-6

Scheme 2



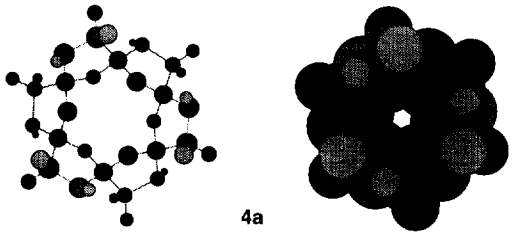
3a (R=H)
3b (R=CHO)
3c (R=CFO)

4a (R=H)
4b (R=CHO)
4c (R=CFO)

Peptidostarands (**4**) are attractive candidates for synthesis because their cyclic peptide precursors (**3**) can be prepared readily. Furthermore, the range of available α-amino acids would allow a multitude of functional groups to be incorporated into these molecules. Peptidostarands of various sizes would also be expected to form complexes with different sized metal ions. Prior to attempting to synthesise these peptidostarands, we elected to examine these molecules by *ab initio* methods, to gain some insights into their energies relative to their cyclic peptide precursors, and to examine possible ways of derivatising them so as to selectively stabilise the peptidostarands over the cyclopeptides, if necessary. We present here our preliminary calculations on these molecules and suggest potential synthetic routes to this novel class of organic compound.

Structures and stabilities of cyclohexaglycine (**3a**) and its isomeric peptidostarand (**4a**) were investigated initially at the HF/3-21G**, then at the HF/6-31G* level of theory [5]. Geometries were fully optimised, and vibrational frequencies of these molecules indicate that the calculated geometries are minima on the potential energy hypersurfaces. We, and others [6,7] find that the lowest energy conformation of **3a** has S_6 symmetry, and contains six intramolecular hydrogen bonds (γ-turns). The predicted geometry of **4a** at the HF/6-31G* level of theory also has S_6 symmetry. As well as the anomeric stabilisations afforded by the acetal oxygen lone electron pairs, all the nitrogen lone pairs of electrons in **4a** are oriented so as to participate in anomeric stabilisations into the σ* orbitals of the adjacent C–O bonds. All the C–H bonds of **4a** can be considered as either axial or equatorial (Figure 1). Peptidostarand **4a** possesses a cavity of diameter 0.98 Å, similar in size to that of **2** [1].

Figure 1
Fully optimised (HF/6-31G*) geometry of peptidostarand **4a**. A space-filling diagram is displayed at right, clearly showing the spherical cavity.



4a

Cyclohexaglycine (**3a**) is calculated to be 86 kcal/mol lower in energy than peptidostarand **4a**. When unscaled zero point corrections were considered, the difference in energy between **3a** and **4a** was found to be 90 kcal/mol. To examine the effects of electron correlation on the energies of **3a** and **4a**, we performed single point Møller–Plesset second-order perturbation (MP2) calculations at the optimised HF/6-31G* geometries (MP2//HF/6-31G*). At this level of theory **3a** is calculated to be 76 kcal/mol lower in energy than **4a**.

Most of the stabilising energy of the cyclic peptide relative to the peptidostarand presumably arises from the resonance energy of the peptide bonds, amounting to approximately 20 kcal/mol per amide bond [8-11]. It follows then that any derivatisation at nitrogen that can reduce or eliminate the amide bond resonance energy of the cyclic peptides may lead to the peptidostarand structures being energetically favoured. *N*-substitution of amide bonds with electron-withdrawing groups can prevent the nitrogen's lone pair of

electrons from delocalising into the amide bond, by preferential conjugation with the *N*-substituent. There is ample evidence that *N*-acylation of amides and lactams diminishes the double-bond character of amide bonds by this means [12]. Thus, acylation of cyclic peptide nitrogen atoms could be one way of making peptidostarand structures more stable than their isomeric cyclopeptides. To examine this possibility we have calculated the energies of both hexa-*N*-formylcyclohexaglycine **3b** and the hexa-*N*-formyl[6]peptidostarand **4b**. We find that, at the HF/3-21G** level of theory, the substituted peptidostarand **4b** is 12 kcal/mol more stable than **3b**. However, when these geometries were reoptimised at the HF/6-31G* level of theory the relative stabilities were reversed, and the substituted cyclopeptide **3b** was found to lie 17 kcal/mol lower in energy than the peptidostarand **4b**. Because of this discrepancy, we performed MP2 calculations on both **3b** and **4b** at the optimised HF/6-31G* geometries (MP2//HF/6-31G*). We found then that **3b** is 16 kcal/mol lower in energy than **4b**, which confirms the HF/6-31G* result (Table).

Clearly, the strategy of introducing electron-withdrawing substituents on the nitrogen atoms provides more stabilisation energy to the peptidostarand (**4b**) than to the cyclic peptide (**3b**). More powerful electron-withdrawing groups than formyl could be anticipated to provide even greater stabilisation energy to the peptidostarand than to the cyclopeptides. While several substituents come readily to mind, for reasons of computational efficiency we chose the fluoroformyl (CFO) group as our model.

Comparison of the hexa-*N*-fluoroformylcyclohexaglycine (**3c**) and its isomeric peptidostarand (**4c**) shows that, at the HF/3-21G** level of theory, **4c** is 39 kcal/mol lower in energy. When these molecules were fully optimised at the HF/6-31G* level of theory, the energy difference was found to be 19 kcal/mol. These results are summarised in the Table.

Table
Relative energies of the cyclic peptides (**3**) and the peptidostarands (**4**) at various levels of theory

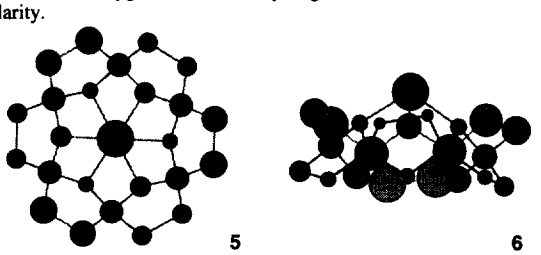
Molecule	HF/3-21G** (kcal/mol)	HF/6-31G* (kcal/mol)	MP2//HF/6-31G* (kcal/mol)
3a (R=H)	0	0	0
4a (R=H)	69	86	76
3b (R=CHO)	12	0	0
4b (R=CHO)	0	17	16
3c (R=CFO)	39	19	-
4c (R=CFO)	0	0	-

The results of these calculations allow us to suggest potential synthetic routes to peptidostarands from cyclic peptides. Strongly electron-withdrawing groups are seen to have the most dramatic stabilisation effects on the peptidostarands (Table), and so *N*-substituents such as *tert*-butoxycarbonyl (Boc), tosyl or trifluoroacetyl might be the most synthetically feasible derivatives of cyclic peptides. We expect that these derivatives would undergo facile rearrangement to peptidostarands, by analogy with the reactions of the starands shown in Scheme 1. Another means of stabilising peptidostarands could be by protonating or quaternising the basic nitrogen atoms of the peptidostarands.

Yet another approach could be to exploit the expected metal binding properties of peptidostarands to prepare stable metal ion complexes. We have briefly examined this possibility by calculating the binding enthalpy of the peptidostarand **4a** with the lithium ion. When a Li^+ ion is placed in the centre of the cavity of **4a** (endohedral binding), the binding enthalpy associated with the resulting fully optimised complex (**5**) is -74 kcal/mol. While the diameter of the cavity of **4a** (0.98 Å) is slightly smaller than that usually occupied by a Li^+ (1.46-2.12 Å [13,14]), we find that the metal ion fits within the cavity of **4a** with minimal

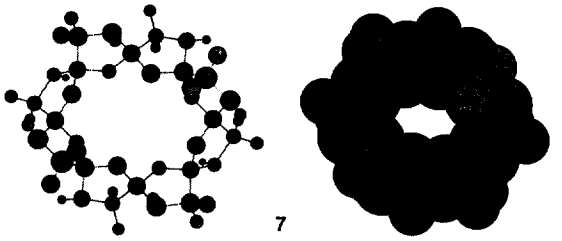
distortion of the oxygen atoms (Figure 2). This phenomenon has been reported previously for the spherands, which are able to accommodate ions that appear to be too large to fit within their cavities [15]. We have also studied the exohedrally bound **4a**–Li^+ complex (**6**), and we find that the binding enthalpy is slightly larger (-87 kcal/mol) (Figure 2).

Figure 2
Fully optimised (HF/6-31G*) geometries of the complexes between **4a** and Li^+. At left is the endohedral complex (**5**) showing the metal ion within the cavity of the peptidostarand. In the endohedral complex (**6**) at right, the Li^+ sits 1.0 Å above the plane of the oxygen atoms. All hydrogens have been omitted for clarity.



5 **6**

Figure 3
Fully optimised (HF/6-31G*) geometry of peptidostarand **7**. A space-filling model of **7** is shown at right.



7

The larger peptidostarand (**7**), the valence tautomer of cyclooctaglycine, has also been examined using *ab initio* calculations, and the fully optimised structure is shown in Figure 3. While not as symmetrical as **4a**, this peptidostarand still exhibits alternating up-down orientations of the N–H bonds which maximises anomeric stabilisations. The cavity of **7** is ovoid in shape, with shortest diameter 1.41 Å. This size is suitable for accommodating a range of transition metal ions [14].

In conclusion, we have characterised by *ab initio* calculations a new class of polyspirocyclic acetals. We have compared their energies with those of their isomeric cyclopeptides, and we have designed derivatives which we predict will be amenable to synthesis.

Acknowledgements

We thank Dr. Ian Bytheway for helpful discussions. A generous allocation of supercomputer time at the High Performance Computing Facility at The University of Queensland is gratefully acknowledged. This research was supported by a University of Queensland Foundation Award.

References

[1] Lee WY, Park CH, Kim S. J Am. Chem. Soc. 1993;115:1184-1185.
[2] Lee WY, Park CH. J. Org. Chem. 1993;58:7149-7157.
[3] Lee WY. Synlett 1994:765-776.
[4] Cho SJ, Hwang HS, Park JM, Oh KS, Kim KS. J. Am. Chem. Soc. 1996;118:485-486.
[5] *Gaussian 94* (Revisions B.2 and D.1): Frisch MJ, Trucks GW, Schlegel HB, Gill PMW, Johnson BG, Robb MA, Cheeseman JR, Keith TA, Petersson GA, Montgomery JA, Raghavachari K, Al-laham MA, Zakrzewski VG, Ortiz JV, Foresman JB, Cioslowski J, Stefanov BB, Nanayakkara A, Challacombe M, Peng CY, Ayala PY, Chan W, Wong MW, Andres JL, Replogle ES, Gomperts R, Martin RL, Fox DJ, Binkley JS, Defrees DJ, Baker J, Stewart JP, Head-Gordon M, Gonzalez C, Pople JA. Gaussian, Inc., Pittsburgh PA 1995.
[6] Böhm HJ, Brode S. J. Comp. Chem. 1995;16:146-153.
[7] Santos MA, Brennan RL, Drew MGB. J. Mol. Struct. (Theochem). 1993;286:109-123.
[8] Greenberg A, Hsing HJ, Liebman JF. J. Mol. Struct. (Theochem). 1995;338:83-100.
[9] Williams JO, Van Alsenoy C, Schäfer L. J. Mol. Struct. (Theochem.). 1981;76:171-177.
[10] Kallies B, Mitzner R. J. Chem. Soc., Perkin Trans. 2. 1996:1397-1401.
[11] Greenberg A, Chiu YY, Johnson JL, Liebman JF. Struct. Chem. 1991;2:117-126.
[12] Evans PA, Holmes AB, Collins I, Raithby PR, Russell K. J. Chem. Soc., Chem. Commun. 1995:2325-2326.
[13] Cotton FA, Wilkinson G. Advanced Inorganic Chemistry, 5th ed. New York: Wiley-Interscience, 1988:1386.
[14] Emsley J. The Elements, 2nd ed. Oxford: Oxford University Press, 1991.
[15] Trueblood KN, Knobler CB, Maverick E, Helgeson RC, Brown SB, Cram DJ. J. Am. Chem. Soc. 1981;103:5594-5596.