Theoretical proposal for an organometallic route to *cis*-peptides†

Robin Chaudret,[a] Georges Trinquier,[b] Romuald Poteau*[c] and Laurent Maron[c]

Received (in Montpellier, France) 27th February 2009, Accepted 24th April 2009
First published as an Advance Article on the web 12th May 2009
DOI: 10.1039/b904139g

We show by means of quantum chemistry calculations that organolanthanide catalysis can be a way to obtain *cis*-amide bonds, thus providing clues for the synthesis of new peptidic materials.

Recently[1] we have proposed, through quantum chemistry calculations, that peptides based on chains of *cis*-amide bonds can be considered as stable systems. Our main contribution was to show that considering the connection of *cis*-peptide plaques as sterically impracticable is not relevant and that assembling peptide plaques that are *already* prepared in their *cis* conformation is an exothermic process. Yet, this new kind of peptidic material remains a concept, since we did not supply clues on how to prepare *cis*-peptide plaques. We show, by the application of density functional theory, the closeness of free energy pathways which lead to *cis* or *trans*-amide compounds with the assistance of a cerium complex. It could be considered that it is still too early for computational chemistry to demonstrate the viability of a synthetic pathway. This proposed multi-step synthetic pathway must actually be considered as an attempt to stimulate interactions between experimentalists and theoreticians. This work is aimed at suggesting consideration of the possibility of obtaining new peptidic materials with *cis*-amide bonds *via* an organometallic synthetic route. Although metal complexes are widely used as catalysts in various reactions, organometallic catalysis is far from routinely used in the field of peptide synthesis. As a matter of fact, following the seminal work of Merrifield,[2] the advances in peptide synthesis that have occurred during the last few decades are based on solid-phase methods.[3] Polymerization of such *cis* units could give rise to new candidates in peptidomimetics. Such a field is of growing interest since it is expected to propose protease resistant substances.

Amide bonds preferentially exist in *trans* conformations, the *cis* conformation being rarely observed in peptides. The reason lies (i) in the energy difference between the two conformations, close to 2.3 kcal mol^{-1} if one considers the parent representative of the amide bond, *i.e.* *N*-methylacetamide (NMA); (ii) in apparently obvious steric clashes between groups attached to the α carbon, which disfavor *cis* bonds.[4] It is the role of quantum chemistry to assess such discouraging postulates, widely accepted in the realm of peptides. In that context, density functional theory (DFT) based methods, accepted by the computational chemistry community as a reliable tool for the study of conformations or chemical reactions, may provide new insights, well beyond the initial intuition of Corey and Pauling.[5] We proposed cyclic arrangements for *cis*-polypeptides, which actually appear to be thermodynamically stable for sizes around six peptide units and beyond.[1a] The stability criteria are based on isodesmic reactions for joining all-*cis* plaques (–C_αHR–CO–NH–C_αHR′–) into polypeptides. Moreover, a conformational search on all-*cis* opened chains led to stable regular helical structures.[1b] Such calculations do not go against common sense in that, as expected, the *cis* world lies higher in energy than the *trans* world. Nevertheless, our conformational explorations of energy landscapes, together with the stability criteria, provide a picture of a high energy plateau and thus suggest an evolution of the *cis* instability paradigm. Considering the stability of the opened or closed *cis* peptides, the 14 kcal mol^{-1} barrier to overcome in order to reach the more stable *trans* form in the case of NMA, and the presumable transferability of this barrier height to amide bonds in polypeptides, one can assess that these systems should be locked in these arrangements. This is an interesting result, but this *cis* world is actually unreachable due to the cliff height which is at least 2.3 × *N* kcal mol^{-1}, where *N* is the number of amide bonds. We shall first consider a prototype of the peptide bond, namely the *N*-methylacetamide compound, for which we examine the possibility to favour its *cis* conformation with the assistance of a lanthanide complex.

Molecules existing as *E* and *Z* forms can be conveniently isomerised by photochemical processes or by reduction reactions. In the context of the latter reaction, we have considered the following issue: does the gain of one or more electrons have a significant impact on the *trans–cis* isomerisation of a peptide bond? Firstly, we shall indicate the free energies obtained for neutral NMA, in order to validate the level of calculation. The energy difference between *cis* (Fig. 1a) and *trans* conformers as well as the barrier height are slightly overestimated (2.6 kcal mol^{-1} and 19.6 kcal mol^{-1}). Interestingly, the addition of one electron inverts the stability since the more stable *cis* conformer of NMA$^-$ becomes more stable by 2.2 kcal mol^{-1} with respect to the more stable *trans*-NMA$^-$. Moreover the barrier height is significantly lowered (down to 3.8 kcal mol^{-1} with respect to the *trans*-counterpart of the most stable *cis* geometry[6]). Addition of a second electron leads to a more puzzling result: the *trans* conformer dissociates whereas the *cis*

[a] *Université Pierre et Marie Curie (Paris 6), Laboratoire de Chimie Théorique, CNRS, UMR 7616, CC 137, Place Jussieu, 75252 Paris cedex 05, France*
[b] *Université de Toulouse, UPS, LCPQ, IRSAMC, CNRS, UMR 5626 (IRSAMC), 118 route de Narbonne, F-31062 Toulouse, France*
[c] *Université de Toulouse, INSA, UPS, LPCNO, IRSAMC, CNRS, UMR 5215 (IRSAMC), 135 avenue de Rangueil, F-31077 Toulouse, France. E-mail: romuald.poteau@univ-tlse3.fr; Fax: +33 561559664*
† Electronic supplementary information (ESI) available: 3D version of Fig. 3a and b, Cartesian coordinates and absolute energies of all compounds. See DOI: 10.1039/b904139g

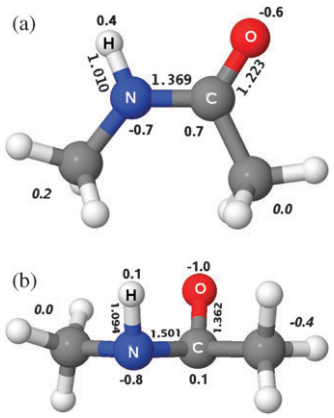

Fig. 1 Optimized DFT structure of (a) *cis*-NMA and (b) *cis*-NMA^{2-}. The numbers are the atomic charges obtained by a natural population analysis (values in italic for methyl charges). Some bond lengths are also given (in Å).

structure still exists. The resulting *cis* geometry exhibits a pyramidal N atom negatively charged (Fig. 1b), there is no longer a π bond between oxygen and carbon which, respectively, possess three and one lone pairs. Nevertheless it is undoubtedly reminiscent of the *cis* conformer. As provided by a natural population analysis,[7] NMA^{2-} exhibits three lone pairs on the negatively charged oxygen atom ($q_O \sim -1$), and the neighbouring carbon atom holds one lone pair, available for bonding, but not for conjugation with the nitrogen lone pair due to the pyramidalisation of both N and C atoms.

The results obtained for NMA^{n-} ($n = 1$ or 2) led us to design a system able to provide at least one electron to NMA in order to possibly yield the *cis* conformer. We propose a lanthanide complex in the role as electron provider, namely a metallocene of cerium. Our calculations show that the $[Cp_2CeNMA]^-$ complex is a minimum, both in the *cis* and *trans* conformations of NMA. Since the oxidation numbers of the cerium atom and Cp groups are +III and −I, respectively, NMA is formally NMA^{2-}, as confirmed by NPA calculations on the complex.[8] Unlike free NMA^{2-}, the complex $[Cp_2Ce(trans\text{-}NMA)]^-$ is a minimum on the potential energy surface, but it is less stable than its *cis* counterpart by 1.1 kcal mol^{-1}. Moreover, the barrier height between *cis* and *trans* conformers is reduced by a factor greater than two with respect to free neutral NMA (Fig. 2). At this point, it appears that a metallocene of cerium is a good candidate for favouring *cis*-NMA and to establish an equilibrium *trans* ⇌ *cis*. We have now (i) to build a relevant chemical pathway leading to Cp_2CeNMA^- and (ii) to find a way to get neutral NMA from the cerium complex.

Back to some fundamentals of lanthanocene chemistry, monomeric Cp'_2CeH (with $Cp' = C_5H_2{}^tBu_3$) is a stable species, and the insertion of CO is strongly exoergic,[9] yielding, in the presence of H_2, Cp_2CeOMe after a series of elementary reactions that occur after formation of the formyl complex $Cp_2Ce(\eta^2\text{-}CHO)$. In the following, we will consider the reactivity of Cp_2CeMe, which will appear as a relevant precursor leading to Cp_2CeNMA. It is experimentally known that even though Cp_2CeMe is dimeric, the reactive species is monomeric.[10] As a consequence, we shall consider it as a prototype for evaluating

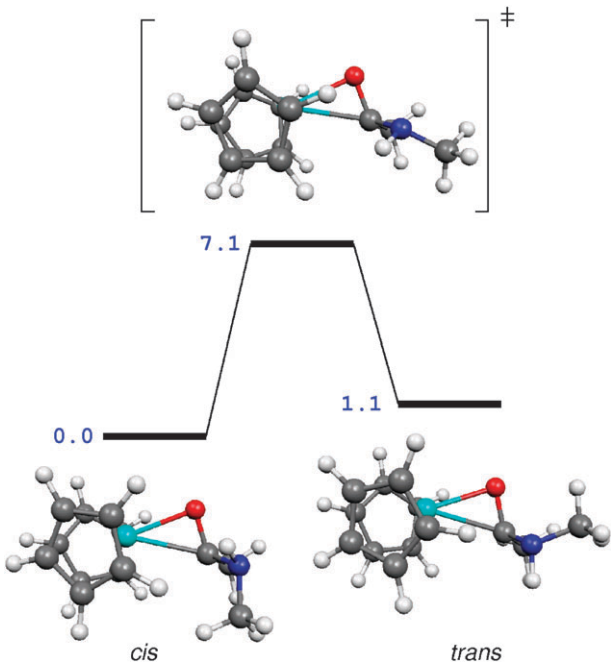

Fig. 2 Equilibrium between the *cis* and *trans*-Cp_2CeNMA^- conformers (energies in kcal/mol).

the possibility to synthesize peptide bonds by means of lanthanide chemistry. Insertion of CO into the Ce–C bond is also exoergic by −19.5 kcal mol^{-1}, to be compared to −13.9 kcal mol^{-1} for the insertion of CO into the Ce–H bond.[9] The formation of the η^2-acetyl complex proceeds with a low activation energy (3.7 kcal mol^{-1}), the transition state being an η^1-acetyl complex. This is in agreement with the known fact that the Ln–C bond is more reactive than the Ln–H bond, as proved both experimentally[11] and theoretically.[12–14] After this primary reaction, we shall now consider a complete reaction pathway, leading to the formation of free neutral NMA (Fig. 3). We propose to introduce a sodium-amide compound Na–NHMe. According to the large positive charge of Ce, Na–NHMe will easily dissociate into $HNMe^-$ and a sodium cation, which will behave as a counterion, whereas the anion will have a strong affinity with the cerium complex. As frequently done in theoretical works, the counterion is not considered. The reaction, which yields *cis*- and *trans*-NMA complexes **D**, proceeds by the low-lying transition states **C** which are slightly lower for the *cis* configuration (Fig. 3a). These transition states connect on the other side to adducts $[Cp_2Ce(NHMe)(acetyl)]^-$ **B**, which are very stable by *ca.* 73 kcal mol^{-1}. However, the resulting products **D** of the addition of $NHMe^-$ to the acetyl complex are higher in energy with respect to the pre-reaction adducts **B** by 11 kcal mol^{-1} (*cis*) and 13 kcal mol^{-1} (*trans*). Considering also the activation energy (*ca.* 20–22 kcal mol^{-1}), the complex will probably remain trapped as the $[Cp_2Ce(NHMe)(acetyl)]^-$ adduct and unfortunately not as a NMA–[Ce] complex. A reaction which helps to go beyond the adduct is thus needed. The resulting complexes **D** being anionic, it should be possible to regenerate Cp_2CeMe—and to simultaneously liberate neutral NMA—by using a methyl cation transfer agent. We propose to use the dimethylchlorinium ion,

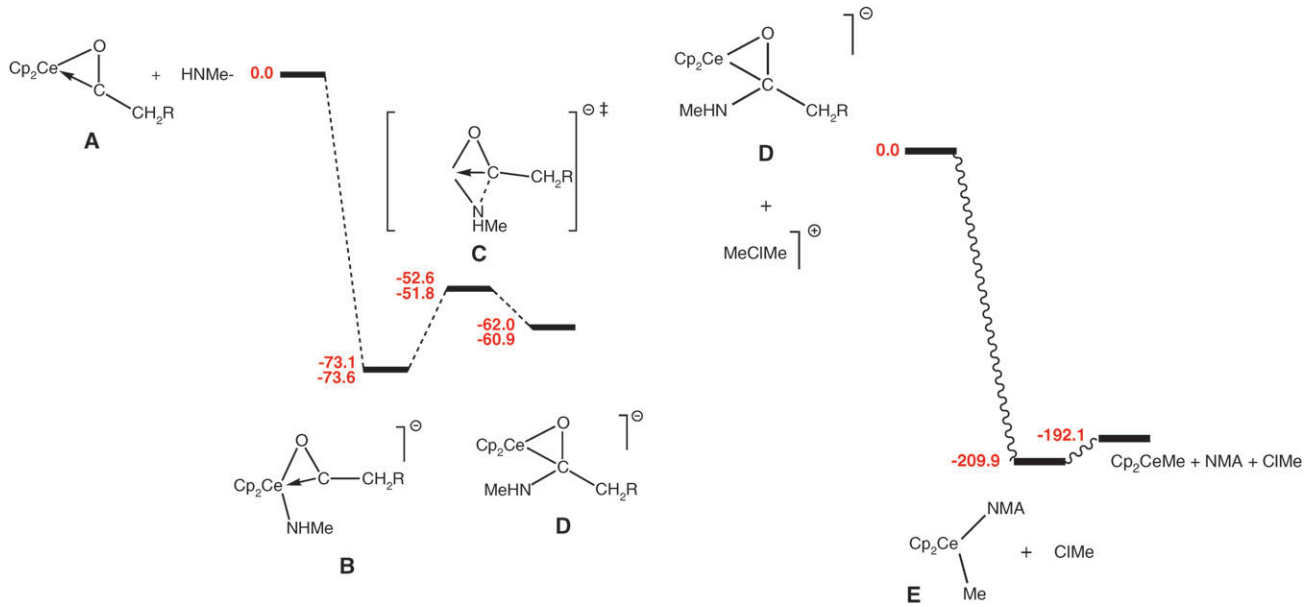

Fig. 3 Free energy pathways for producing neutral amide compounds MeHN–$COCH_2R$ (energies in kcal mol^{-1}). (a) Formation of a $[Cp_2Ce(NHMe)(acetyl)]^-$ adduct. the energies correspond to *cis* (first line) and *trans* (second line) conformers, with R = Me. For the sake of clarity, only one pathway is represented. The first species, namely $Cp_2Ce(\eta^2$-acetyl), can be formed after insertion of CO into the Ce–C bond of Cp_2CeMe (see text); (b) liberation of neutral NMA *via* a S_N2 reaction (all energies are calculated for the *cis* case).

which is known to play that role.[15] Transition states of S_N2 reactions are low, solvent dependent, and not easy to locate on potential energy surfaces. Consequently, we have only calculated thermodynamical data of this reaction, which provides a complex **E** with both neutral NMA and methyl coordinated to Cp_2Ce, and which lies *ca.* 210 kcal mol^{-1} below **D** in the case of the *cis* form (Fig. 3b; similar energies are expected for the production of *trans*-NMA). This additional reaction fulfils what was expected: overcoming the trapping of the reaction in the energy basin of the adducts **D**. The last step would consist of the release of neutral NMA. Since a straightforward release of NMA from complex **E** is calculated to be endergonic by 18 kcal mol^{-1}, assistance is required. Considering the strong exoergicity of the reaction of $HNMe^-$ with **A** as generalizable, liberation of NMA should be easily achieved by a reaction with any negative ligand.

Starting from the fact that *cis*-peptide bonds could be favored with respect to *trans* bonds by providing electrons to a peptide plaque, we propose a metallocene of cerium as an electron–donor. A complete reaction mechanism is investigated, beginning with the insertion of CO in Cp_2CeMe and leading, after sequential addition of $HNMe^-$ and dimethylchlorinium, to neutral *cis* and *trans*-NMA and a cerium complex *via* two chemical pathways. They are in close competition, the *cis* pathway being slightly more stable in its first part. Consequently, the two conformers should be obtained in similar quantities, and it should be easy to separate them with a specific trap.[16] In previous works we showed that the *cis* world, although thermodynamically higher in energy than the *trans* world, is however populated by viable cyclic or opened polypeptides with rather regular shapes. The present results suggest that homogeneous catalysis supported by lanthanide complexes could be a *voie d'entrée* to the *cis* world. In this preliminary work, we only assess the possibility to isomerize a single peptide bond. Isodesmic reactions show that the association of peptide plaques already prepared in their *cis* conformation is almost as stable as the association of *trans* plaques.[1] In other words, polymerization reaction to *cis*-polypeptides could be achievable from a thermodynamical point of view, provided that a peptide bond is already available in its *cis* conformation. Polymerization of NMA seems unrealizable, since the breaking of C_α–H bonds preliminary to the insertion of a new peptide plaque is not achievable. We need both to circumvent that problem and to start from already prepared *cis* plaques. Theoretical investigations of polymerization reactions of *cis*-polypeptides by ring opening reactions catalyzed by lanthanide complexes are in progress, in order to provide additional arguments which could stimulate experimental works.

We thank the CALcul en MIdi-Pyrénées (CALMIP) for generous allocations of computer time. L. M. is a member of the Institut Universitaire de France (IUF).

Computational details

All calculations of the molecules in their ground state were carried out with GaussianXX (XX = 98[17a] or 03[17b]). The large core effective core potentials specifically designed for rare earth atoms with an oxidation number +3 (Ln^{III}) and their associated basis set developed by the Stuttgart–Dresden groups were used for the cerium element.[18] Gaussian basis sets of hydrogen and main group elements are of double-ζ plus polarization quality. All structures were optimized without symmetry constraints, in order to avoid explorations of potential energy surfaces driven by such constraints. We systematically explored the potential energy surfaces in the framework of density functional theory (DFT) methods, using the B3PW91 functional. All energetic data given in this paper

are free energies calculated at 298 K within the harmonic approximation.

References

1 (*a*) R. Poteau and G. Trinquier, *J. Am. Chem. Soc.*, 2005, **127**, 13875–13889; (*b*) R. Poteau and G. Trinquier, *J. Org. Chem.*, 2007, **72**, 8251–8258.
2 R. B. Merrifield, *J. Am. Chem. Soc.*, 1963, **85**, 2149–2154.
3 (*a*) F. Albericio, *Curr. Opin. Chem. Biol.*, 2004, **8**, 211–221; (*b*) B. L. Nilsson, M. B. Soellner and R. T. Raines, *Annu. Rev. Biophys. Biomol. Struct.*, 2005, **34**, 91–118.
4 S. Mathieu, R. Poteau and G. Trinquier, *J. Phys. Chem. B*, 2008, **112**, 7894–7902.
5 L. Pauling and R. B. Corey, *Proc. Natl. Acad. Sci. U. S. A.*, 1952, **38**, 86–93.
6 Note that there are several pathways on the potential energy surface of NMA^-. Systematic scans of the PES have been performed in order to carefully check that *cis*-NMA^- is the more stable conformer. Actually, the lowest *trans* conformer lies 2.2 kcal mol^{-1} above the most stable *cis*-NMA^- structure.
7 A. E. Reed, R. B. Weinstock and F. Weinhold, *J. Chem. Phys.*, 1985, **83**, 735–746.
8 E. D. Brady, D. L. Clark, J. C. Gordon, P. J. Hay, D. W. Keogh, R. Poli, B. L. Scott and J. G. Watkin, *Inorg. Chem.*, 2003, **42**, 6682–6690.
9 E. L. Werkema, L. Maron, O. Eisenstein and R. A. Andersen, *J. Am. Chem. Soc.*, 2007, **129**, 2529–2541.
10 M. Ephritikine, *Chem. Rev.*, 1997, **97**, 2193–2242.
11 P. L. Watson and G. W. Parshall, *Acc. Chem. Res.*, 1985, **18**, 51–56.
12 L. Maron, L. Perrin and O. Eisenstein, *J. Chem. Soc., Dalton Trans.*, 2002, 534–539.
13 N. Barros, O. Eisenstein and L. Maron, *Dalton Trans.*, 2006, 3052–3057.
14 E. C. Sherer and C. J. Cramer, *Organometallics*, 2003, **22**, 1682–1689.
15 M. A. Freitas and R. A. J. O'Hair, *J. Org. Chem.*, 1997, **62**, 6112–6120.
16 E. L. Werkema, E. Messines, L. Perrin, L. Maron, O. Eisenstein and R. A. Andersen, *J. Am. Chem. Soc.*, 2005, **127**, 7781–7795.
17 (*a*) M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, V. G. Zakrzewski, J. A. Montgomery, Jr., R. E. Stratmann, J. C. Burant, S. Dapprich, J. M. Millam, A. D. Daniels, K. N. Kudin, M. C. Strain, O. Farkas, J. Tomasi, V. Barone, M. Cossi, R. Cammi, B. Mennucci, C. Pomelli, C. Adamo, S. Clifford, J. Ochterski, G. A. Petersson, P. Y. Ayala, Q. Cui, K. Morokuma, P. Salvador, J. J. Dannenberg, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. Cioslowski, J. V. Ortiz, A. G. Baboul, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. Gomperts, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. G. Johnson, W. Chen, M. W. Wong, J. L. Andres, C. Gonzalez, M. Head-Gordon, E. S. Replogle and J. A. Pople, *GAUSSIAN 98 (Revision A.11)*, Gaussian, Inc., Pittsburgh, PA, 2001; (*b*) M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Montgomery, Jr., T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. G. Johnson, W. Chen, M. W. Wong, C. Gonzalez and J. A. Pople, *GAUSSIAN 03 (Revision C.01)*, Gaussian, Inc., Wallingford, CT, 2004.
18 (*a*) M. Dolg, H. Stoll, A. Savin and H. Preuss, *Theor. Chim. Acta*, 1989, **75**, 173–194; (*b*) M. Dolg, H. Stoll and H. Preuss, *Theor. Chim. Acta*, 1993, **85**, 441.

