Pergamon

Tetrahedron Letters 40 (1999) 5983–5986

TETRAHEDRON LETTERS

Conformational Analysis of (*R,S*)-4-Amido-2,4-dimethyl-butyric Acid Derivatives

Reinhard W. Hoffmann,* Miguel A. Lazaro, Francisco Caturla, Eric Framery
Philipps-Universität Marburg, Fachbereich Chemie
D - 35032 Marburg

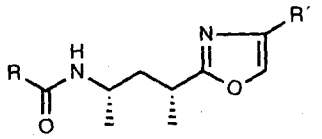
Ingrid Valancogne, Christian A. G. N. Montalbetti
Department of Chemistry, Unversity of Newcastle upon Tyne, Bedson Building
GB - Newcastle upon Tyne NE1 7RU

Received 25 May 1999; accepted 21 June 1999

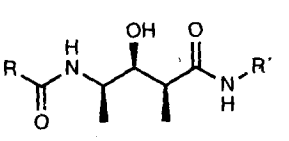
Keywords: Conformation; Hydrocarbon backbone

Abstract: *NMR spectra of various N-acyl derivatives of (R,S)-4-amino-2,4-dimethyl-butyric acid show these compounds to be biconformational, populating the conformers 4 and 5 of the molecular backbone. Both predominant conformers have the amide group gauche to the main chain.*

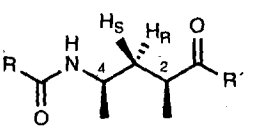
The molecular backbone of biologically active compounds serves to position functional groups three-dimensionally in space for optimal interaction with the corresponding receptor. It is noteable that nature uses flexible molecular backbones, which may have in many instances a preferred conformation. For example, in polypeptides nature combines α-amino acids as modules into flexible functional molecules with a pre-defined conformation. In search for non-natural analogs, oligomers of ß-amino acids[1] have been studied with respect to distinct folding preferences. Recently, oligomers of γ-amino acids have been investigated in the same vein,[2] revealing distinct preferences for the formation of helical structures. In a few instances nature also relies on γ-amino acids as flexible linker units to confer a particular conformation to biologically active molecules. This is evidenced by the $^3J_{H,H}$-NMR coupling constants along the backbone of calyculin C, [3] cf. **1**, or bleomycin A_2,[4] cf. **2**.



1 Linker unit in calyculin C



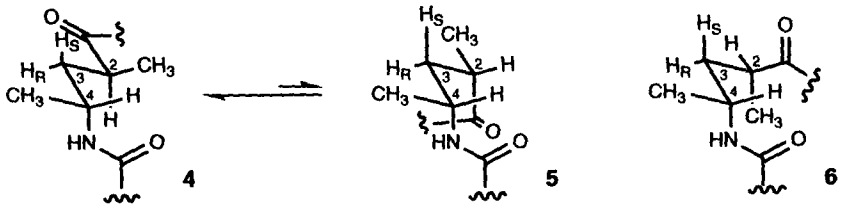
2 Linker unit in bleomycin A_2



3

The linker unit in both natural products is a derivative of (*R,S*)-4-amino-2,4-dimethyl-butyric acid (**3**). MM3* calculations on **3** (R = CH_3, R' = OMe) suggest that two backbone-conformations **4**, and **5** contribute predominantly to the local conformer population, whereas conformer **6** should be of sufficiently higher energy (+ 7 kJ mol^{-1} relative to **4**) to be neglected.

PII: S0040-4039(99)01226-5



Conformation **4** corresponds to that deduced for calyculin C [3] or bleomycin A_2 [5] in solution from the NMR data. It corresponds as well to that found in the crystalline state for bleomycin A_2.[6] We became interested to learn, whether this conformational preference is intrinsic to the backbone segment **3**, or whether it is imposed to a large extent from the remainder of the molecule, i.e. the flanking groups R and R'. Knowledge of this sort is a prerequisite for the use of compounds **3** as spacer units in a modular approach to larger flexible molecules with defined shape.[8]

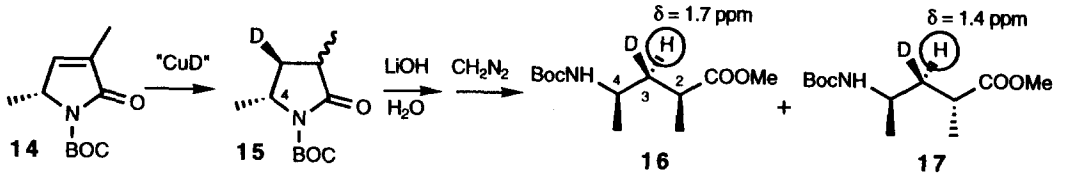
We therefore studied the conformational behaviour of a series of derivatives of **3** and related compounds[9] by ^{1}H NMR spectroscopy (cf. table) The relevant vicinal H,H-coupling constants between the hydrogen atoms at C-2, C-3, and C-4 could not be determined in all cases completely, because of signal overlap or line broadening due to the presence of amide rotamers.

Table: NMR Coupling constants of (*R,S*)-4-Amido-2,4-dimethyl-Butyric Acid Derivatives

		Solvent	Temp (K)	C-3-H (pro-*R*) δ (ppm)	C-3-H (pro-*R*) ^{3}J to H-2	C-3-H (pro-*R*) ^{3}J to H-4	C-3-H (pro-*S*) δ (ppm)	C-3-H (pro-*S*) ^{3}J to H-2	C-3-H (pro-*S*) ^{3}J to H-4
1 [a]	RCONH, R = (Calyculin C)	C_6D_6	298	2.18	1.5	13.0	1.84	12.5	1.5
7 [b]	BocNH, COOMe	$CDCl_3$	298	1.94	6.2	9.6	1.68	6.7	n.d.
8	BocNH, COOMe	$CDCl_3$	298	1.7	7	10	1.4	7 [c]	n.d.
9	CbzNH, COOMe	$CDCl_3$	333	1.85	7.2	9.6	1.48	6.7 [c]	4.8
10	FmocNH, COOH	$CDCl_3$	333	1.87	7.2	9.8	1.48	n.d.	n.d.
11	CF_3CO, NHFmoc, COOH	$CDCl_3$	298	1.89	8.0	9.9	1.49	n.d.	n.d.
12	Br, NHFmoc, COOH	$CDCl_3$	328	1.86	7.6	10.3	1.49	6.5	3.9
13	FmocNH, COO^tBu	C_6D_6	298	1.11	6.6	8.7	1.01	7.7	n.d.

a) Values from ref. [3] ; b) values from ref. [7] ; c)Taken from the coupling pattern of the C-2-H signal; n.d. = not determined

In order to get more detailed information on the nature of the preferred conformer, the NMR-chemical shifts of the individual diastereotopic protons at C-3 of **8** were assigned by a stereospecific labelling procedure:



Starting from the pyrrolinone **14**[7,10] reduction with "copper deuteride"[11] provided a (1:1.5)-mixture of the C-2-epimeric pyrrolidinones **15**, the spectral data of which corresponded to those reported by Koskinen.[7,10] We presume that the deuterium atom has been incorporated in this reduction anti to the C-4 methyl group of **15**. The pyrrolidinones were transformed into the esters **16** and **17** by treatment of **15** with LiOH followed by diazomethane. The esters **16** and **17** could then be separated by preparative HPLC. Comparison of the ^{1}H-NMR-spectra of **16** and of **8** showed that deuteration has led to the disappearance of the ^{1}H-NMR-signal at δ = 1.4 ppm and had, moreover, simplified the coupling pattern of the C-3-H NMR signal at δ = 1.7 ppm. This allowed an assignment of chemical shifts to the individual diastereotopic protons at C-3 in **8**. This assignment is in line with the one made for the diastereotopic protons in the corresponding segment **1** of calyculin C.[3] In view of the consistency between **8** and **1**, the chemical shifts of the compounds **9** to **12** have been assigned by analogy.

It is clear from the data in the table, that the conformational preference of the compounds **7** to **13** is lower than that of the corresponding segment **1** in calyculin C. It appears, however, that the same local conformer **4** is preferentially populated, albeit to a lesser extent. The consistently high $^3J_{H,H}$-coupling constants between C-4-H and C-3-$H_{(pro\ R)}$ indicate that the local conformation around the bond C-3/C-4 is fairly uniform. In turn, there is conformational heterogeneity regarding the C-2/C-3 bond. This is manifest from the low alteration of the values of the two C-2-H to C-3-H coupling constants. We therefore conclude that the 4-amino-2,4-dimethyl-butyrate segment in the compounds **7** to **13** is biconformational, with the conformations **4** and **5** populated to a similar extent. The backbone segment **3** present in compounds **7** to **13** has therefore a (moderate) intrinsic preference to populate a distinct conformation. This preference is increased in calyculin C or bleomycin A_2 by an (as not yet determined) effect of the groups flanking the segment **3**.

Acknowledgements: This work has been supported by the European Commission through the TMR network ERB FMRX CT 960011.

References

1 a) U. Koert *Angew. Chem.* **109**, 1922 (1997); *Angew. Chem. Int. Ed. Engl.* **36**, 1836 (1997); b) D. Seebach and J. L. Matthews *J. Chem. Soc., Chem. Commun.*, 2015 (1997); c) D. Seebach, K. Gademann, J. V. Schreiber, J. L. Matthews, T. Hintermann, B. Jaun, L. Oberer, U. Hommel and H. Widner *Helv. Chim. Acta* **80**, 2033 (1997); d) S. H. Gellman *Accts. Chem. Res.* **31**, 173 (1998); e) Y.-D. Wu and D.-P. Wang *J. Am. Chem. Soc.* **120**, 13485 (1998); f) X. Daura, K. Gademann, B. Jaun, D. Seebach, W. F. van Gunsteren and A. E. Mark *Angew. Chem.* **111**, 249 (1999); *Angew. Chem. Int. Ed. Engl.* **38**, 236 (1999); g) K. Gademann, B. Jaun, D. Seebach, R. Perozzo, L. Scapozzo and G. Folkers *Helv. Chim. Acta* **82**, 1 (1999); h) D. H. Appella, J. J. Barchi Jr., S. R. Durell and S. H. Gellman *J. Am. Chem. Soc.* **121**, 2309 (1999); i) B. W. Gung, D. Zou, A. M. Stalcup and C. E. Cottrell *J. Org. Chem.* **64**, 2176 (1999).

2 a) T. Hintermann, K. Gademann, B. Jaun and D. Seebach *Helv. Chim. Acta* **81**, 983 (1998); b) S. Hanessian, X. Luo, R. Schaum and S. Michnick *J. Am. Chem. Soc.* **120**, 8569 (1998).

3 Y. Kato, N. Fusetani, S. Matsunaga, K. Hashimoto and K. Koseki *J. Org. Chem.* **53**, 3930 (1988).

4 a) T. Owa, A. Haupt, M. Otsuka, S. Kobayashi, N. Tomioka, A. Itai, M. Ohno, T. Shiraki, M. Uesugi, Y. Sugiura and K. Maeda *Tetrahedron* **48**, 1193 (1992); b) D. L. Boger and H. Cai *Angew. Chem.* **111**, 470 (1999); *Angew. Chem. Int. Ed. Engl.* **38**, 448 (1999).

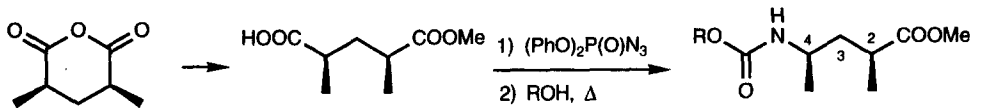
5 D. L. Boger, T. M. Ramsey, H. Cai, S. T. Hoehn and J. Stubbe *J. Am. Chem. Soc.* **120**, 9149 (1998).

6 S. M. Lui, D. E. Vanderwall, W. Wu, X.-J. Tang, C. J. Turner, J. W. Kozarich and J. Stubbe *J. Am. Chem. Soc.* **119**, 9603 (1997).

7 P. M. Pihko and A. M. P. Koskinen *J. Org. Chem.* **63**, 92 (1998).

8 a) R. W. Hoffmann *Angew. Chem.* **104**, 1147 (1992); *Angew. Chem. Int. Ed. Engl.* **31**, 1124 (1992); b) R. W. Hoffmann, M. Stahl, U. Schopfer and G. Frenking *Chem. Eur. J.* **4**, 559 (1998).

9 The synthesis of **8** has been described before by Koskinen[7,10] starting from alanine. Our synthesis was based on the monoester **19**,[12] which is readily obtained from meso-2,4-dimethylglutaric anhydride **18** and may easily be resolved,[13] if required. Curtius degradation of **19**[14] in the presence of alcohols led us to the various N-acylated derivatives **8-10** and **13** listed in the table.



18 **19** **8 - 10**

The amides **11** and **12** were prepared by attaching the amido acid **10** to 2-chlorotrityl resin and coupling with the second amino acid by standard methods using *O*-benzotriazolyl-*N,N,N',N'*-tetramethyluronium tetrafluoroborate (TBTU) as coupling reagent.

10 A. M. P. Koskinen and P. M. Pihko *Tetrahedron Lett.* **35**, 7417 (1994).

11 M. F. Semmelhack, R. D. Stauffer and A. Yamashita *J. Org. Chem.* **42**, 3180 (1977).

12 For leading references see: P. J. Kocienski, R. C. D. Brown, A. Pommier, M. Procter and B. Schmidt *J. Chem. Soc., Perkin Trans. 1*, 9 (1998).

13 a) R. W. Hoffmann, H.-J. Zeiß, W. Ladner and S. Tabche *Chem. Ber.* **115**, 2357 (1982); b) M. Sefkow, A. Neidlein, T. Sommerfeld, F. Sternfeld, M. A, Maestro and D. Seebach *Liebigs Ann. Chem.*, 719 (1994).

14 K. Ninomiya, T. Shioiri and S. Yamada *Tetrahedron* **30**, 2151 (1974).