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Memory Effect of Chirality in the Photocyclization of Modified Dipeptides

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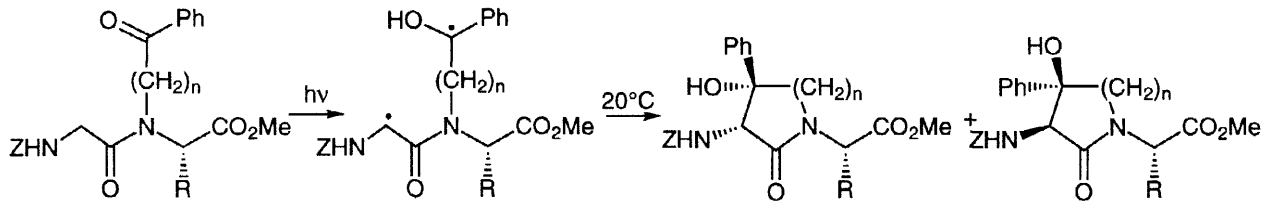
Abstract: *Photocyclizations of dipeptides **5** and **8** occur mainly with retention of configuration at the stereogenic center of alanine. This memory effect of chirality is explained by a hindered rotation in the two intermediate biradicals **9** and **10** that slows down the equilibration of the radicals.* © 1998 Elsevier Science Ltd. All rights reserved.

Recently, we have demonstrated that photochemical cyclizations of the modified dipeptides **1** into glycine are regio- and stereoselective and follow a remarkable asymmetric induction if valine is the inducing amino acid.[1] Intermediates are biradicals **2** that are formed in a regioselective H-abstraction step from the triplet state of the phenyl ketone. After the triplet-singlet intersystem crossing the biradical **2** cyclizes and yields **3** as main product.



n = 1	10	:	1 (R = Pr^i, 51%)
n = 2	7.4	:	1 (R = Pr^i, 67%)

Scheme 1

We have now observed that selective photochemical cyclization reactions can occur also if both amino acids of the dipeptides are substituted.[2] Thus, the modified ala-val dipeptide **5** yields mainly pyrrolidinone **6** as cyclization product.[3] The isomer ratio **6**:**7** of 16:1 at –15°C demonstrates that the C,C-bond formation occurs with high retention at the stereogenic center of alanine. In order to check whether this stereoselectivity is caused by the asymmetric induction of valine we have synthesized the *R,S*-ala-val dipeptide **8**. This dipeptide also cyclized with high stereoselectivity, but now isomer **7** was the main cyclization product (**6**:**7**, <1:20, 0°C). Again, the product with retention of configuration at the alanine was formed preferentially.[4]

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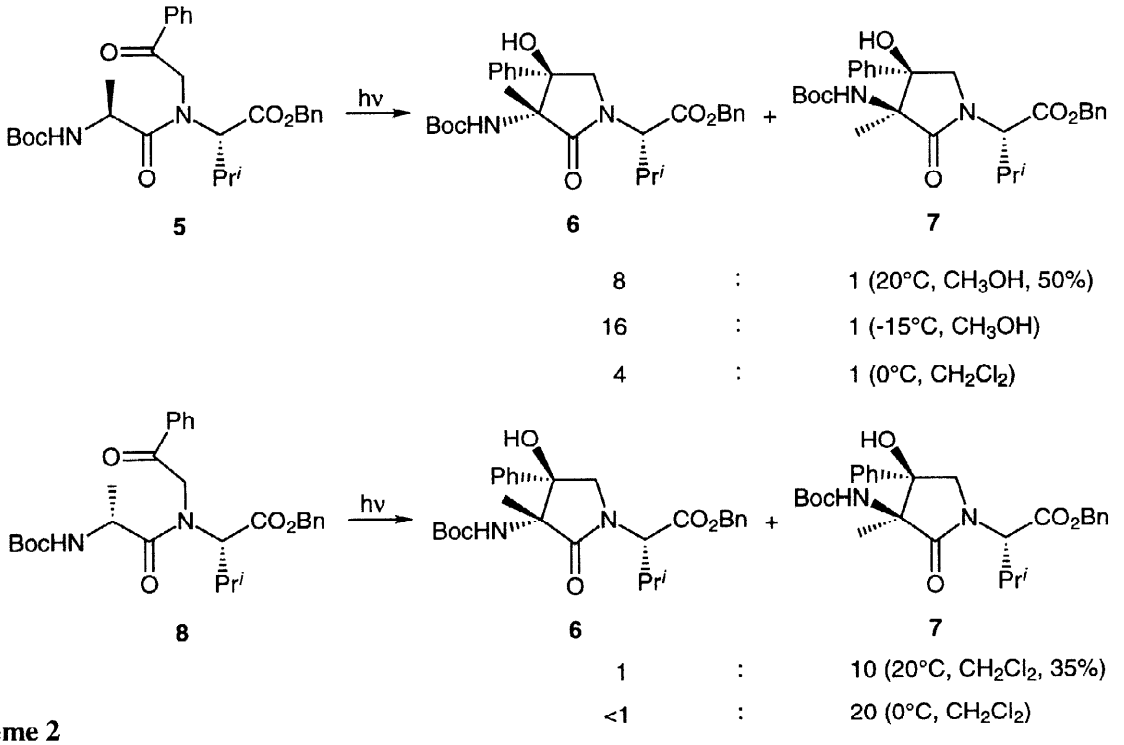
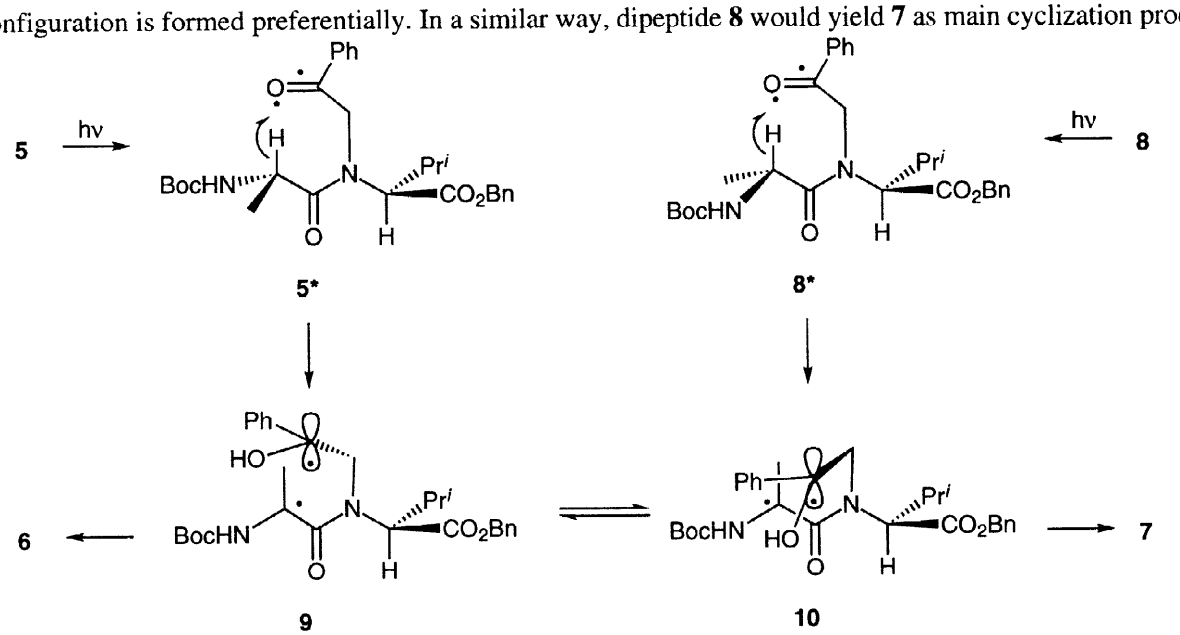


Scheme 2

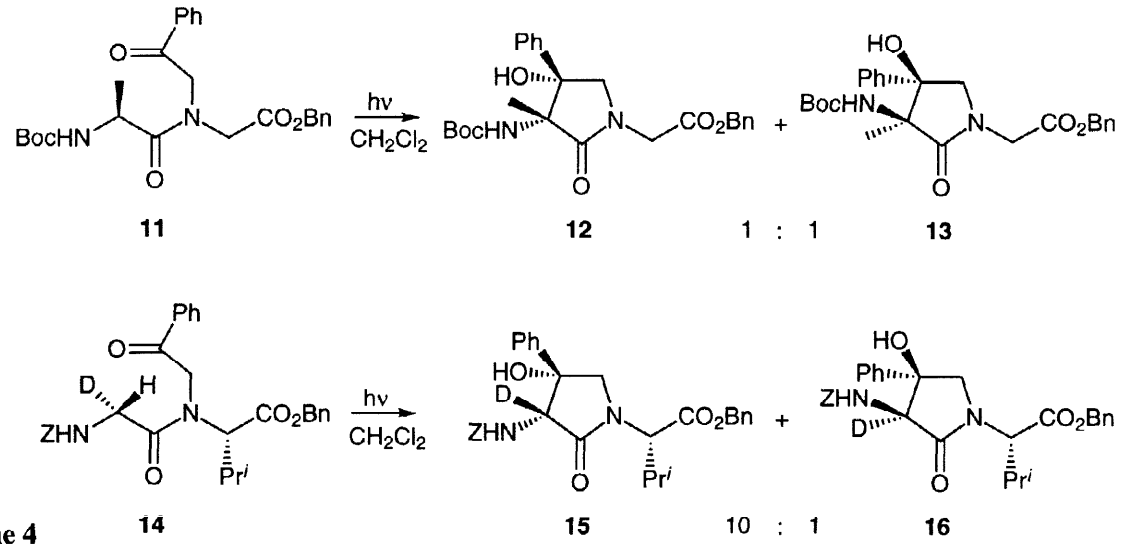
The experimental results show that the intermediate biradicals formed from dipeptides **5** and **8** must differ from each other during their reaction time scale and that they possess a memory of the configuration of their precursors. A possible explanation of this memory effect[5,6] is given in Scheme 3: The H-abstraction by the photochemical excited ketone **5***[7] leads to biradical **9** in which the hydroxybenzyl radical is positioned at the *re*-side of the alanyl radical. If the triplet-singlet intersystem crossing[8] and the subsequent radical combination is faster than the rotation around the N–CH_2 bond (**9** ⇌ **10**), then the cyclized product **6** with retention of configuration is formed preferentially. In a similar way, dipeptide **8** would yield **7** as main cyclization product.



Scheme 3

In biradicals **9** and **10** the rotation around the N–CH_2 bond is presumably hindered by the alkyl substituents of the amino acids. In order to check this we synthesized modified dipeptides **11** and **14** containing

glycine or selectively deuterated glycine[9] as one of the amino acids. The photochemical cyclization of **11** led to products **12** and **13** in a 1:1 ratio.[10] Thus, the memory effect of chirality is completely lost. Obviously, the equilibration of the intermediate biradicals is faster than the triplet-singlet interconversion with subsequent cyclization.



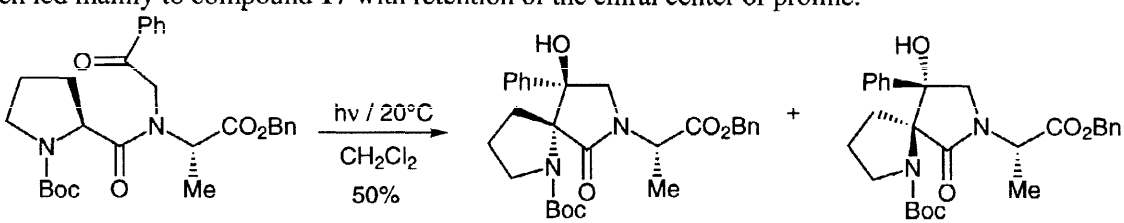
11 **12** **13**

14 **15** **16**

Scheme 4

The photochemistry of selectively deuterated[9] dipeptide **14** is also very instructive. In Scheme 4 only the deuterated cyclization products following the H-abstraction are shown. The preferred formation of the pyrrolidinone **15** is in accord with the asymmetric induction found for the undeuterated dipeptide **1** (Scheme 1)[1], but the H-abstraction and the C,C bond formation occur on opposite sides of the glycine. This means that the asymmetric induction by valine (**1**→**3** or **14**→**15**) and not the memory effect of chirality governs the photocyclization of **14**.

These experiments offer strong support for the explanation that the memory effect is caused by a hindered rotation around the N–CH_2 bond that slows down the equilibration between **9** and **10**. Therefore, the intersystem crossing with subsequent cyclization is faster than the equilibration, and the biradicals **9** and **10** preserve the memory of the alanine chirality. That this memory effect could be a general phenomenon in photocyclizations of substituted peptides with bulky amino acids is demonstrated by the cyclization of dipeptide **16** which led mainly to compound **17** with retention of the chiral center of proline.[11,12]



16 **17** **18**

Scheme 5

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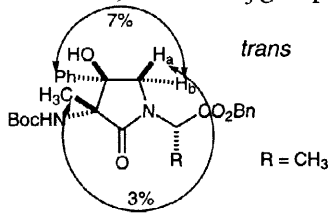
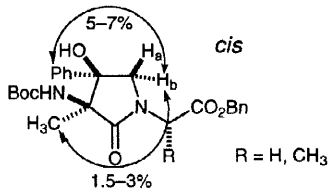
References and Notes

1. C. Wyss, R. Batra, C. Lehmann, S. Sauer, B. Giese, *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2529.
2. Synthesis and photocyclization of the modified dipeptides **5**, **8**, **11**, **14**, and **16** followed the conditions described in ref. 1.
3. The relative configurations of **6**, **7**, and **12** were elucidated by NOE experiments. Moreover, the chemical shifts (^{1}H- and ^{13}C-NMR) of the CH_3 group are characteristic for the *trans*- and the *cis*-pyrrolidinone rings:





Chemical Shifts δ (ppm) of the CH_3 group at the pyrrolidinone ring

trans product	R	^{1}H	^{13}C	*cis* product	R	^{1}H	^{13}C
19	H	1.60	19.2	**12,13**	H	0.98	22.2
20	Me	1.52	18.8	**21**	Me	0.89	21.7
6	Pr^i	1.39	19.0	**7**	Pr^i	0.93	22.0

Compounds **19–21** are not mentioned in the communication because **19** is formed only in minute amounts[10] and **20+21** are formed with only low selectivity from the modified ala-ala dipeptide. The absolute configuration of the *trans* product **6** is based on the X-ray crystal structure[12] of the trifluoroacetate salt of the protonated *trans* product **17** and the comparison of NMR data: in general, a methylene proton H_a, which is *cis* to the OH group of the pyrrolidinone ring, absorbs at lower field than a geminal proton H_b which is *trans* to the OH group (data not shown). In addition, the *cis* proton H_a of **17** (product of „memory effect") absorbs at lower field (δ = 4.41 ppm) than the *cis* proton H_a of **18** (δ = 4.05 ppm). Similar differences in chemical shifts of H_a are also found in the *trans* photocyclization products from the modified ala-val (δ = 3.80 and 3.68 ppm) and ala-ala (δ = 3.66 and 3.60 ppm) dipeptides. From the *trans* product **6** a *cis* carbamate was synthesized by treatment with $SOCl_2$ which inverted the alcoholic carbon center. This *cis* carbamate was a diastereomer of the *cis* carbamate formed directly from **7** by deprotection of the Boc group and cyclization with N,N'-carbodiimide.
4. The photocyclizations of dipeptides **5** and **8** occur also into the isopropyl group of valine. This leads to pyrrolidine derivatives in 11% (from **5**) and 36% (from **8**), respectively. Diastereomers of **6** and **7**, in which the configuration of the alcoholic carbon center is inverted, are formed only in traces.
5. For a discussion of the term „memory effect", see: J. C. Scaiano, *Tetrahedron* **1982**, *38*, 819; A. G. Griesbeck, H. Mauder, S. Stadtmüller, *Acc. Chem. Res.* **1994**, *27*, 70; K. Fuji, T. Kawabata, *Chem. Eur. J.* **1998**, *4*, 373.
6. To our knowledge only two other examples of retention of the stereochemistry in type-II photocyclization reactions of acyclic systems are known: S. Kohmoto, T. Kreher, Y. Miyaji, M. Yamamoto, K. Yamada, *J. Org. Chem.* **1992**, *57*, 3490; W. Weigel, S. Schiller, G. Reck, H. G. Henning, *Tetrahedron Lett.* **1993**, *34*, 6737.
7. After conformational analysis (MacroModel software, Amber force field, Monte Carlo search method) one finds conformations for **5** and **8** in which the distance between the benzoyl oxygen and the hydrogen at the chiral center of alanine are close enough for H-abstraction (2.6–2.9 Å). These calculated conformations are used in Scheme 3 for the photoexcited molecules **5*** and **8***, see also ref. 1.
8. The photocyclization could be completely prevented by 2,5-dimethylhexadiene as triplet quencher.
9. L. S. Hegedus, E. Lastra, Y. Narukawa, D. C. Snustad, *J. Am. Chem. Soc.* **1992**, *114*, 2991.
10. The *trans* products were formed only in minute amounts.
11. The main cyclization product **17** (from **16**) corresponds to the main cyclization product **6** (from **5**). However, the minor products **18** and **7** differ from each other by different configurations at the alcohol center. In order to understand these differences, work with other amino acids in different solvents will be carried out.
12. The structure was proven by the X-ray crystal structure of the trifluoroacetate salt of the protonated *trans* product **17**. Crystallographic data have been deposited at the Cambridge Crystallographic Data Centre.