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Bioorganic Chemistry

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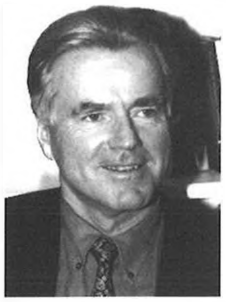
Abstract. The behavior of short-lived radicals, radical ions, and biradicals in biological and chemical systems has been studied. It turned out that these highly reactive intermediates react selectively. The rules that we have found are applied to biological (enzyme reactions), chemical (total synthesis of natural products; peptide folding), and physical (DNA chips) aspects of life sciences.



Bernd Giese was born in Hamburg, Germany, in 1940. He studied chemistry at the Universities of Heidelberg, Hamburg and Munich where he completed his Ph.D. in 1969 under the direction of *R. Huisgen*. He then worked for two years on the synthesis of antidiabetics in the company *BASF*. Subsequently, he carried out his habilitation at the Universities of Münster and Freiburg. From 1978 to 1988, he was full professor at the Technische Hochschule Darmstadt and accepted his present position at the University of Basel in 1989. He is editor of *Synlett*. For further details of his research, see: http://www.chemie.unibas.ch/~giese/index.html.

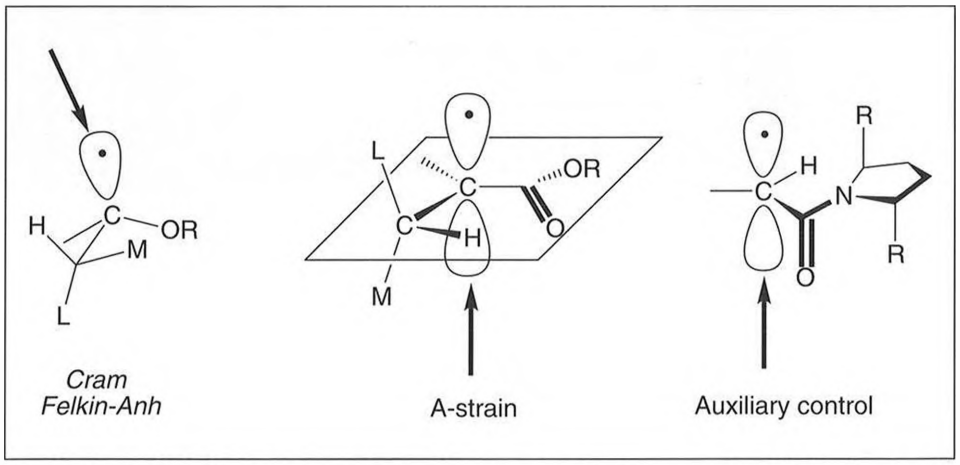
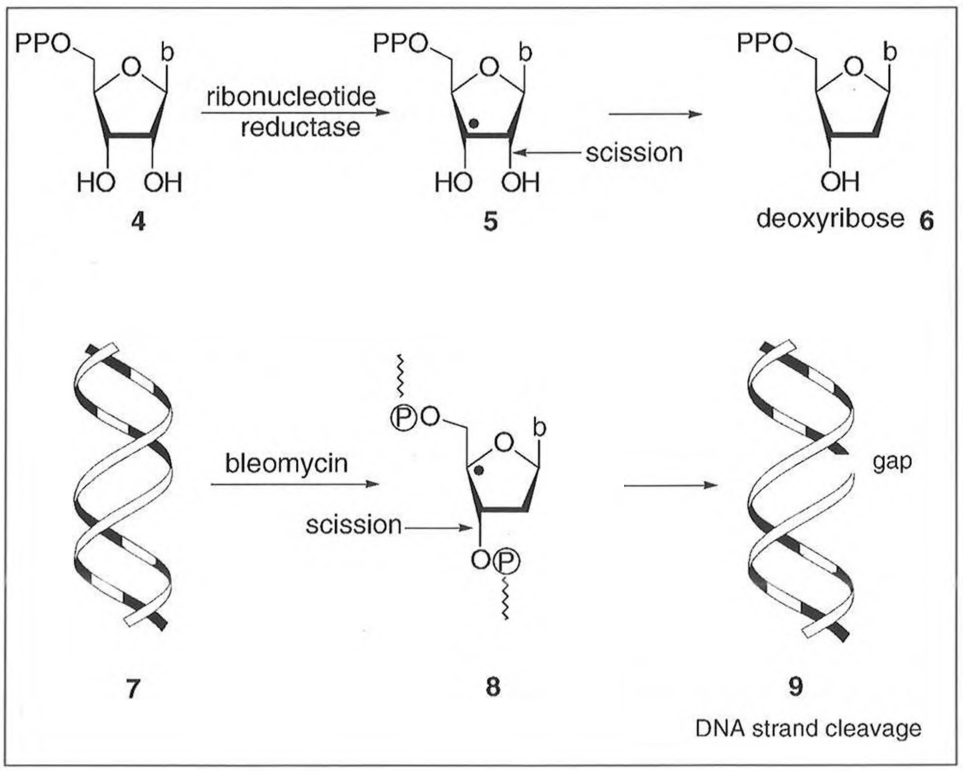


Fig. 1. *Rules of stereoselective reactions of acyclic radicals*

Scheme 1



1. Organic Synthesis

1.1. *Methods*

We have developed rules for the application of radical reactions in organic synthesis. Because of the high reactivity of radicals, it is important to control their selectivities. Our work has shown that the stereoselectivity of radical reactions follows the

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general rules known for ionic reactions of cyclic and acyclic molecules (*Fig. 1*) [1].

1.2. *Total Synthesis*

Over the last few years, we have synthesized the enzyme inhibitors **1**–**3** (*Fig. 2*). The first total synthesis of soraphen A (**1**) used carbohydrates as starting materials [2]. Stereoselective C,C- and C,H-bond formation reactions are the decisive steps of the syntheses of trehazolin (**2**) and tetrahydrolipstatin (**3**) [3].

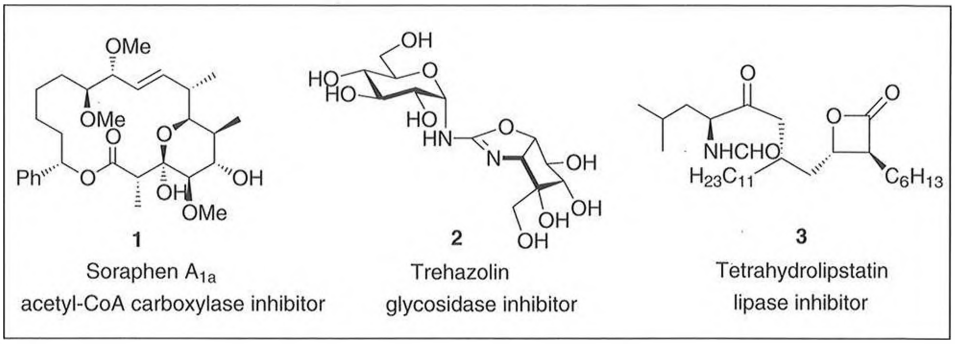


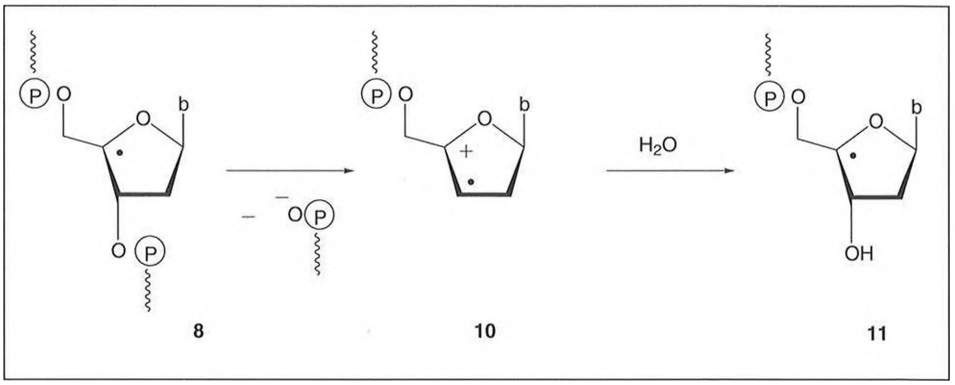
Fig. 2. *Natural products (enzyme inhibitors) synthesized in the nineties*

2. Radicals in Biochemical Reactions

Radicals play an important role in the life cycle of DNA. We are studying how ribonucleotide reductase generates deoxyribose **6** from **4** *via* radical **5** [4], and how antibiotics (bleomycin, enediynes) cleave DNA **7** *via* radicals like **8** to **9** (*Scheme 1*) [5].

It turned out that in 4'-DNA radical **8**, the radical center acts as the neighbor group for the hydrolysis reaction **8**→**11**. The application of this effect has led to a new photocleavable linker in the solid-phase synthesis [6] (*Scheme 2*).

Scheme 2



3. Charge Transfer Through DNA

A new assay for studying charge transfer through DNA was developed [7]. In this assay, we site-selectively oxidized a guanine (G) to the radical cation $G^{+\bullet}$ and measured the charge transfer through DNA double strands. Depending upon the base sequence, the rate of the charge transfer exhibits a strong or a weak distance dependence. We suggested a charge-hopping between guanine bases where each hopping step depends strongly upon the distance between the adjacent Gs (strands **12**→**15**) (*Fig. 3*). Nevertheless, long-distance charge transport occurs (strand **18**) if the individual hopping distances between G bases are short [7]. Thus, charge transfer through DNA is sequence-dependent. This method will be applied for the determination of DNA sequences in DNA chips.

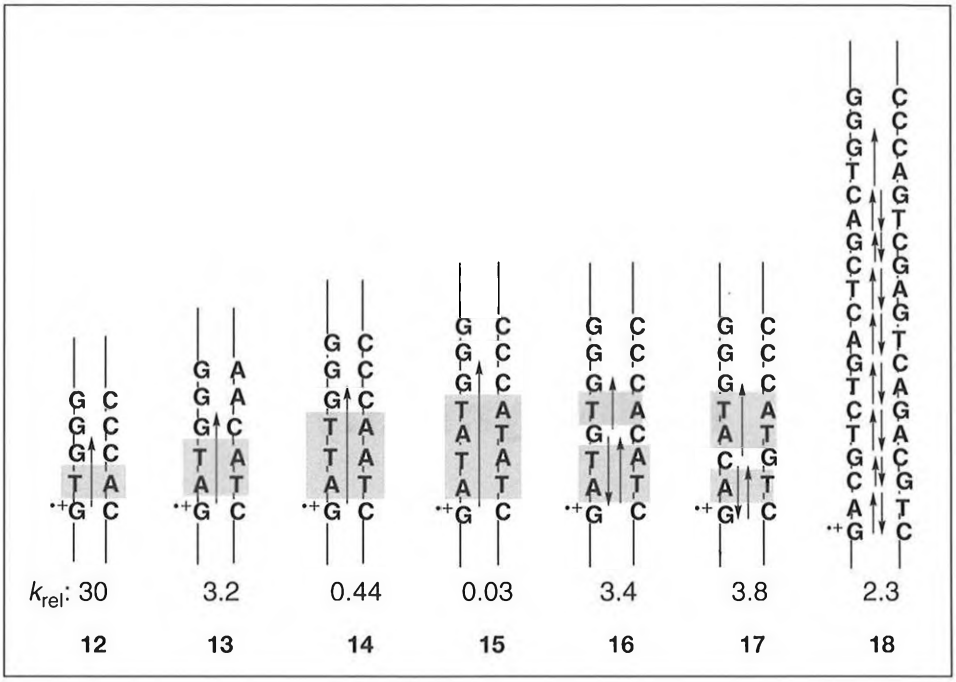
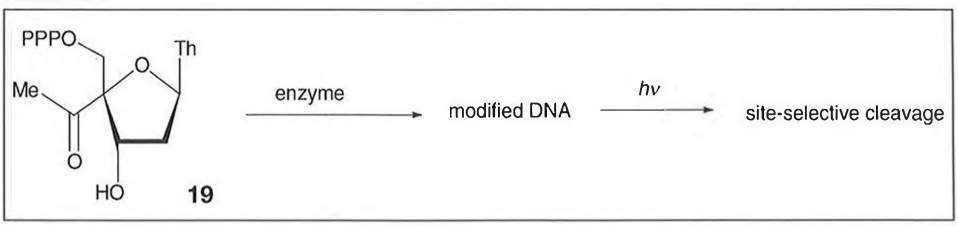


Fig. 3. *Relative rates (k_{rel}) of charge transfer through DNA strands* via *superexchange* (**12**–**15**) *or hopping* (**16**–**18**) *mechanisms*

4. Enzymatic DNA-Chain Elongation

We have studied the influence of various deoxyribose substituents on enzymatic DNA-chain elongations. It turned out that nucleotide **19** can be incorporated enzymatically into the growing DNA strand [8]. The rate of incorporation gives insight into the active site of the enzyme

Scheme 3



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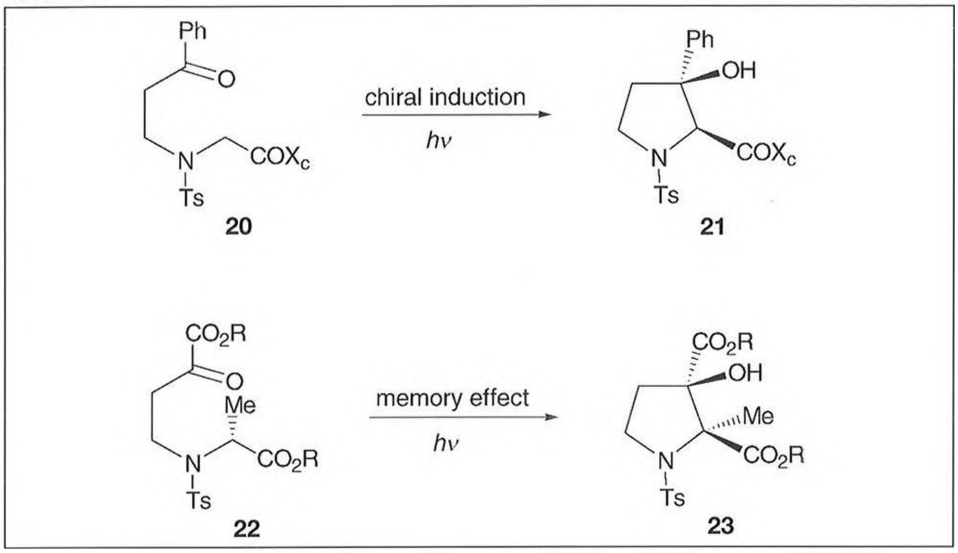
Scheme 4



[9]. Irradiation of the modified DNA strand induces selective cleavage at the modified site (*Scheme 3*). Application of this method to biotechnological problems is in progress.

5. Photochemical Reactions

Cyclic amino acids induce β-turns in peptides. We have developed a method for selective photocyclization reactions of modified amino acids **20** and **22** to **21** and **23**.

Depending upon the reaction conditions and substituents, either triplet or singlet biradicals are intermediates. The triplet biradical exhibits a strong asymmetric induction whereas the singlet biradical shows a memory effect. These reactions are applied to the cyclization of amino acids in peptides [10].

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