Communications to the Editor

Diastereoselective [4 + 2] Cycloaddition of Singlet Oxygen in the Photooxygenation of Chiral Naphthyl Alcohols: Evidence for a Hydroxy Group-Directing Effect

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Received January 4, 1993

The directing effect of the hydroxy group has recently been observed[2] in the photooxygenation of chiral allylic alcohols, in which the incoming enophile ($^1O_2$) coordinates with the HO functionality in such a way as to result in a high threo selectivity. Stereocontrol in this ene reaction derives from the 1,3-allylic strain with the stereogenic center.

It was our interest to assess whether such assistance by the hydroxy group is also exercised in the [4 + 2] cycloaddition of $^1O_2$. An example in which low diastereoselectivity was reported[4] is that of the chiral *cis*-5,6-dihydroxy-1-methylcyclohexa-1,3-diene, in which an anti/syn ratio of 62:38 was obtained.

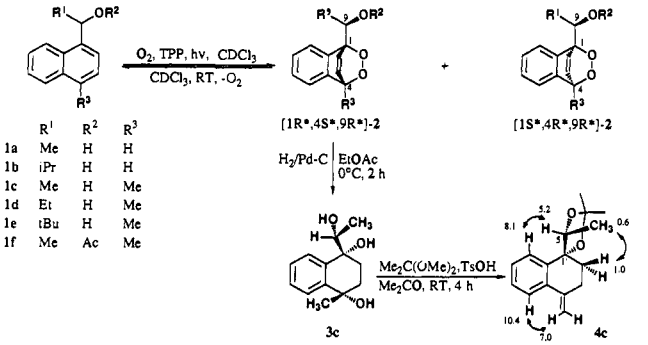
As substrates we chose the chiral naphthyl alcohols **1** (Scheme I) because, on one hand, the resulting 1,4-endoperoxides are well documented[5] and, on the other hand, steric interactions between the peri hydrogen atom at position 8 and the chirality center with the hydroxy functionality should provide substantial stereodifferentiation. That this is indeed so is readily visible in the data displayed by Table I.

The photooxygenations were performed in the usual way by using tetraphenylporphine (TPP) in $CDCl_3$ or Rose Bengal (RB) in CD_3OD as photosensitizers for singlet oxygen. In view of the appreciable thermal reversion of the endoperoxides,[5] the cycloadditions were conducted at low temperature and in deuterated solvents to permit direct NMR monitoring of product formation and assessment of the diastereomeric ratio. Only endoperoxide **2c** derived from the chiral alcohol **1c** was sufficiently persistent to permit isolation (79% yield), purification by low-temperature (−20 °C) recrystallization from ethyl ether, and complete characterization.[6]

The stereochemical assignment of the major diastereomer [1*R**,4*S**,9*R**]-**2c** was made on the basis of chemical transformations in conjunction with NOE measurements (Scheme I). Thus, catalytic hydrogenation gave the saturated triol **3c**, which on acetalation gave the acetonide **4c**. Although, unfortunately, the 4-OH group was lost through dehydration in the acetalation process **3c** → **4c**, the NOE effects shown for structure **4c** (cf. Scheme I) definitely establish the proposed configuration.

That high diastereofacial control for the $^1O_2$ [4 + 2] cycloaddition is a general phenomenon is revealed by the other chiral naphthyl alcohols (Table I). The diastereomeric ratio (dr)

Scheme I



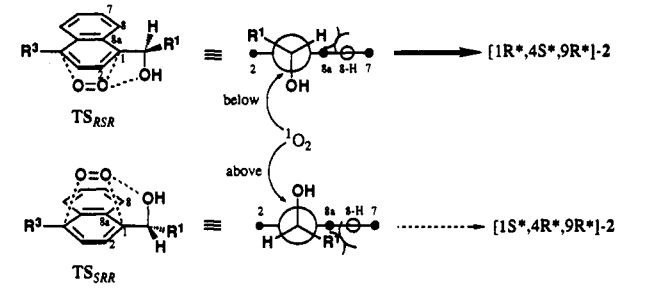
	R^1	R^2	R^3
1a	Me	H	H
1b	iPr	H	H
1c	Me	H	Me
1d	Et	H	Me
1e	tBu	H	Me
1f	Me	Ac	Me

Table I. Product Studies and Diastereoselectivities of the Photooxygenation of the Chiral Naphthyl Alcohols **1**

entry	substrate	solvent	temp (°C)	time (h)	conv (%)	yield (%)	diastereoselectivity[b] dr (%)
1	**1a**	$CDCl_3$	−30	28	65 ± 5	>90	80:20 ± 5
2	**1b**	$CDCl_3$	−30	28	28 ± 5	>95	81:19 ± 5
3	**1c**	$CDCl_3$	−35	4	>98	>98	85:15 ± 3
4	**1c**	CD_3OD	−35	28	>95	>95	55:45 ± 5
5	**1d**	$CDCl_3$	−35	6	>98	>98	88:12 ± 5
6	**1e**	$CDCl_3$	−30	2.5	30 ± 3	>98	87:13 ± 3
7	**1e**	$CDCl_3$	−5	48	60 ± 5	ca. 70	ca. 5:95
8	**1f**	$CDCl_3$	−30	6	21 ± 3	>98	56:44 ± 3

[a] Tetraphenylporphine (TPP) was used as sensitizer, except for entry 4, in which Rose Bengal was employed; photooxygenations were conducted in a test tube, and ^1H NMR spectra were taken on the crude product mixture at −20 °C. [b] Ratio of [1*R**,4*S**,9*R**]- and [1*S**,4*R**,9*R**]-**2** diastereomers; for **1a,b** these were determined by ^{13}C and for **1c–f** by ^1H NMR spectroscopy.

Scheme II



values of the respective diastereomeric endoperoxides **2** were determined directly on the crude photooxygenates by integration of the appropriate, characteristic ^1H NMR signals.

Since the steering propensity of a hydroxy group toward $^1O_2$ has been well established in the ene reaction of chiral allylic alcohols,[2] we propose a similar mechanistic rationalization for stereocontrol in the present case (Scheme II). Accepting a traditional, concerted [4 + 2] cycloaddition coordinate, although nonconcerted pathways have been recognized for several dienic substrates,[7] association of the incoming dienophilic $^1O_2$ with the hydroxy functionality[8] allows for two approaches: one from below through the transition state TS_{RSR} and the other from above through TS_{SRR}. As shown in the Newman projections of the naphthalene substrate, peri strain with the 8-H hydrogen of the naphthalene is minimal for TS_{RSR} and, therefore,

(1) Diplomarbeit, University of Würzburg, Sept 1992.
(2) Adam, W.; Nestler, B. *J. Am. Chem. Soc.* **1992**, *114*, 6549.
(3) Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841.
(4) (a) Carless, H. A. J.; Billinge, J. R.; Oak, O. Z. *Tetrahedron Lett.* **1989**, *30*, 3113. (b) Carless, H. A. J.; Oak, O. Z. *Tetrahedron Lett.* **1989**, *30*, 1719.
(5) (a) Turro, N. J.; Chow, M. F. *J. Am. Chem. Soc.* **1981**, *103*, 7218. (b) Turro, N. J.; Chow, M. F.; Kanfer, S.; Jacobs, M. *Tetrahedron Lett.* **1981**, *22*, 3. (c) von den Henkel, C. J. M.; Steinberg, H.; de Boer, T. J. *Recl.: J. R. Neth. Chem. Soc.* **1980**, *99*, 109.
(6) Both isomers **2c** exhibit the expected IR and ^1H and ^{13}C NMR spectral data; for the major isomer [1*R**,4*S**,9*R**]-**2c** also a satisfactory elemental analysis was obtained.
(7) (a) Clennan, E. L. *Tetrahedron* **1991**, *47*, 1343. (b) O'Shea, K. E.; Foote, C. S. *J. Am. Chem. Soc.* **1988**, *110*, 7167. (c) Matusch, R.; Schmidt, G. *Angew. Chem.* **1988**, *100*, 720.

0002-7863/93/1515-3766$04.00/0

the $^1O_2$ is expected to be guided by the HO group to come in from below to give preferentially the endoperoxide diastereomer [1*R**,4*S**,9*R**]-**2**. This is exactly what is observed in the photooxygenation of **1** (Table I, except for entries 4, 7, and 8).

When the photooxygenation was run in CD_3OD instead of $CDCl_3$ (cf. entries 3 and 4 in Table I), the dr dropped from 85:15 to 55:45. Alternatively, the acetylated derivative **1f** (cf. entries 3 and 8 in Table I) also displayed poor stereocontrol, i.e., the dr dropped from 85:15 to 56:44. These observations can be consistently rationalized within the context of the proposed mechanism. Both association of the hydroxy group with methanol through hydrogen bonding and acetylation reduce the nucleophilicity of the oxygen atom sufficiently that coordination with the incoming electrophilic $^1O_2$ becomes less significant.[9]

Astonishing are the results for the *tert*-butyl derivative **1e** (cf. entries 6 and 7 in Table I). For this substrate, the magnitude and even the sense of the diastereoselectivity depend on the conditions of photooxygenation, a fact which was *not* observed for the other chiral naphthalenes; thus, a high opposite diastereoselectivity is noted, i.e., a dr of ca. 5:95 versus 87:13. Careful NMR monitoring of the photooxygenation course revealed that the initially formed major stereoisomer [1*R**,4*S**,9*R**]-**2e** reverted significantly faster to the naphthalene **1e** than the minor stereoisomer [1*S**,4*R**,9*R**]-**2e**. Consequently, by adjusting the extent of conversion and/or temperature of photooxygenation, the dr values can be fixed at will. We are not aware of an analogous happenstance in the [4 + 2] cycloaddition of singlet oxygen.

In summary, the present results illustrate that a strategically placed hydroxy group can direct the attack of $^1O_2$ to the side of minimum steric congestion in the [4 + 2] cycloaddition (peri strain in the case of the chiral naphthyl alcohols **1**). Presumably, nucleophilic association of the HO functionality with the electrophilic $^1O_2$ is responsible for this steering effect. When large groups such as the *tert*-butyl group are placed at the chirality center, kinetic control directs the entry of the singlet oxygen from the HO-coordinated side; but due to the facile reversion of the latter, the diastereoselectivity can be completely inverted under thermodynamically controlled conditions.

Acknowledgment. Generous financial support by the Deutsche Forschungsgemeinschaft (SFB 347 "Selektive Reaktionen Metallaktivierter Moleküle") and the Fonds der Chemischen Industrie is gratefully appreciated.

(8) The electrophilic singlet oxygen dienophile is expected to coordinate through nucleophilic association with the hydroxy group rather than by hydrogen bonding. However, a referee pointed out the likelihood of significant charge separation along the reaction coordinate, and consequently the transition state leading to the *R,S,R* product would be expected to be stabilized through hydrogen bonding of the hydroxy group with the negatively charged oxygen atom in the polarized transition state.

(9) From the present data we cannot exclude the possibility that steric effects of the substituents on the stereogenic center control the direction of singlet oxygen attack, which would dictate the same stereochemical outcome. Such an explanation, however, does not reconcile the observed solvent effect (cf. entries 3 and 4 in Table I).