π-Facial Diastereoselectivity in the [4+2] Cycloaddition of Singlet Oxygen as a Mechanistic Probe

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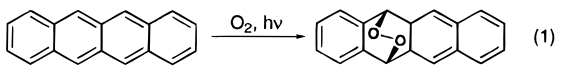
The first singlet oxygen reaction[1] was discovered as early as in 1867 by Fritzsche,[2] who noted the reversible formation of a crystalline material when a solution of naphthacene (**1**) was exposed to light (eq 1). This



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reaction is relevant to the present Account since it involves the [4+2] cycloaddition of singlet oxygen.[3,4] Expectedly, at that time neither the structure of the product nor the nature of the process as a self-sensitized singlet oxygen [4+2] cycloaddition was recognized. The pioneering work by Dufraisse,[5] Windaus,[6] and Kautsky[7] again raised interest in photooxidation reactions in the 1920s, but the next decades were characterized by controversies[1,8] over the identity of the species involved in the photosensitized oxidations. Once the intermediacy of singlet oxygen was unequivocally established,[9] now generally known as type II photooxidation, the various types of singlet oxygen reactions ([4+2],[10] ene,[11,12] [2+2],[13] and sulfoxidation[14]) gained increasing importance in synthetic chemistry.[15] Simultaneously, mechanistic studies addressed the query of *concerted versus nonconcerted* reactivity and the detection and structural characterization of possible reaction intermediates.[10,12ab,16]

Mechanisms of the Singlet Oxygen [4+2] Cycloaddition

In view of the formal analogy to the classical Diels−Alder reaction,[17] for the *superdienophile*[18] singlet oxygen a synchronous (Scheme 1, pathway A) or asynchronous (Scheme 1, pathway B) reaction mechanism was assumed for many years.[16b,d,19] However, recent kinetic studies[20] have made evident that such endoperoxidations may occur stepwise. Open-chain[21] (Scheme 1, pathway C) or perepoxide-like[22] (Scheme 1, pathway D) dipoles were postulated as intermediates. Modern computational methods do not differentiate between these proposed reaction mechanisms,[22b,23] not even for the simplest model reaction, namely, 1,3-butadiene with singlet oxygen,

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Michael Prein, born in Germany in 1967, commenced his chemistry studies in 1987 at the University of Würzburg and joined Professor Adam's research group in 1992 (Diplom 1992, Dr. rer. nat. 1995). In October 1995 he joined Prof. Padwa's research group at Emory University as a NATO postdoctoral fellow. During his graduate work, which forms the basis of this Account, he was concerned with stereocontrol in the singlet oxygen [4+2] cycloaddition.

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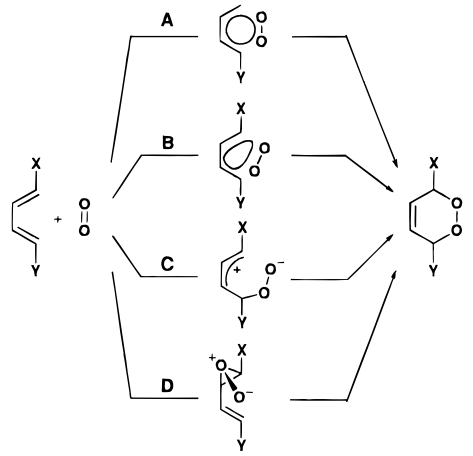
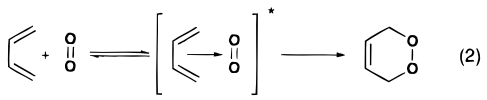
Scheme 1. Possible Reaction Mechanisms for the Singlet Oxygen [4+2] Cycloaddition



for which high-level calculations were conducted.[24] Moreover, the excited nature of singlet oxygen[25] (ca. 23 kcal/mol excess energy for its Δ_g state, the usually reactive form) must be emphasized, for which physical quenching may compete effectively with chemical reactions.[26,27] In view of this happenstance, it is expected that the course of the cycloaddition is highly sensitive to the substrate structure and the reaction conditions.[28,29] Thus, the pathways in Scheme 1 merely represent characteristic points on a continuous, substrate-dependable spectrum of possible reaction mechanisms.[10b]

As expected for excited states,[30] the initial encounter between the electronically excited singlet oxygen and the substrate leads to exciplex formation (eq 2). The


(2)

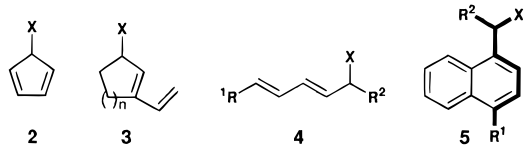
intermediacy of such electronically excited charge transfer complexes has been previously established[16c,d,20,31] and accounts for most mechanistic features. Thus, as a function of the substrate structure, the exciplex may have zwitterionic and/or diradical character. Furthermore, this loosely structured species matches the experimental findings that many singlet oxygen [4+2] cycloadditions, even for stepwise processes, occur stereospecifically.[10,32] We consider it both appropriate and convenient to use the exciplex concept[31] for the mechanistic description of the [4+2] cycloaddition.

Stereochemistry in the [4+2] Cycloaddition

The classical studies of Rigaudy[32b] and Rio[32a] demonstrated that the [4+2] cycloaddition of singlet oxygen occurs as a suprafacial process. Only if the dienic system cannot readily adopt a *cisoid* conformation, e.g., for (*Z*,*E*)-hexa-2,4-diene,[21b,31a] will singlet oxygen-induced isomerization and, consequently, loss of stereochemical information occur. The π-facial selectivity of singlet oxygen attack toward chiral or plane-nonsymmetric dienes has not been studied systematically prior to our efforts. The previous examples of diastereoselective endoperoxidations of polycyclic substrates[17a,33,34] show straightforward steric stereocontrol; i.e., the singlet oxygen attack on the α face is sterically shielded by angular substituents for most of these substrates.[33,34]

Inspired by our recent breakthrough in the diastereoselective Schenck ene reaction of singlet oxygen,[35] we decided to investigate the stereochemistry of substrate-controlled singlet oxygen [4+2] cycloadditions in a systematic fashion. Knowledge of the directing propensities of functional groups in singlet oxygen [4+2] cycloadditions is desirable for preparative purposes. Furthermore, the use of stereochemical probes should provide valuable information on the reaction mechanism and the electronic and geometrical properties of the intermediates involved. With its small size, high symmetry ($D_{\infty h}$), and pronounced reactivity, singlet oxygen may serve as a sensitive model dienophile to probe stereochemical effects in the Diels–Alder reaction.

During the last few years we have conducted singlet oxygen [4+2] cycloadditions with the diene types **2**–**5**.



Our results establish these dienic substrates as an informative set of substrates for the elucidation of the mechanism of the singlet oxygen [4+2] cycloaddition. Both cyclic **2**[36–38] and semicyclic dienes **3**[39] have been

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previously studied in the π-facial selective Diels−Alder reaction with carbon dienophiles.[40] Since the directing substituent X is located within a ring system, its conformation is more or less fixed, and any steric or electronic interaction with the incoming dienophile can operate only on one of the two π faces. In contrast, for the chiral acyclic dienes **4**, the conformational flexibility of the stereogenic unit[41] creates additional complexities in rationalizing experimental diastereoselectivities,[42] and the energy discrimination of different rotamers[43] through allylic strain[44] comes into play. The chiral naphthalenes **5**,[10] which do not usually react with conventional dienophiles by the Diels−Alder reaction, are closely related to acyclic dienes **4** in regard to stereocontrol since also here the chiral substituent can adopt a variety of conformational arrangements.

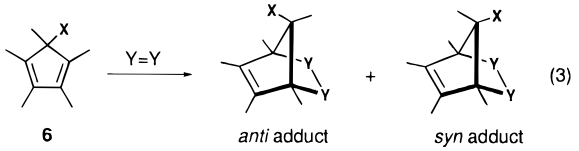
Cyclic Dienes

The 5-substituted, plane-nonsymmetric cyclopentadienes are the most prominent representatives for this substrate class, and numerous experimental results have accumulated over the years on the π-facial selectivity of Diels−Alder reactions.[36] This wealth of data provided the opportunity to scrutinize the singlet oxygen findings within the framework of other dienophiles. In view of the appreciable thermal lability of the parent cyclopentadiene endoperoxide[45] and to avoid complications due to 1,5-hydrogen shifts, we chose the pentamethyl derivatives **6** as substrates.[46] The substrates **6a**−**e** have been previously studied in the Diels−Alder reaction with maleic anhydride (MA) by Fallis,[36d] and therefore, the direct comparison with literature results is informative (eq 3, Table 1). We also performed the [4+2] cycloaddition with the highly reactive nitrogen dienophile *N*-methyl-1,2,4-triazolinedione (MTAD), the dienophile which best mimics the chemical behavior of singlet oxygen.[47]

Table 1. π-Facial Selectivities in [4+2] Cycloadditions of 5-Substituted Cyclopentadienes[a]

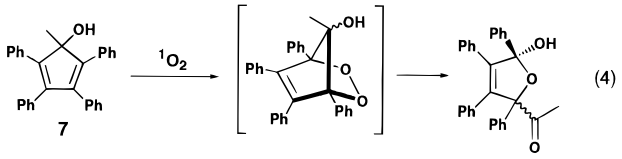
compd no.	X	MA *anti:syn*	MTAD *anti:syn*	$^1O_2$ *anti:syn*
6a	H	20:80[b]	25:75	20:80
6b	SMe	90:10[b]	95:5	≥90:10
6c	SOMe	≥95:5[b]	≥95:5	≥95:5
6d	SO_2Me	≥95:5[b]	≥95:5	≥95:5
6e	OH	≤5:95[b,c]	≤5:95	*d*
6f	iPr	≥95:5	≥95:5	≥95:5
6g	Et	≥95:5	≥95:5	≥90:10
6h	CHO	≥95:5	≥95:5	≥95:5
6i	CH_2OH	≥95:5[c]	≥95:5	≥95:5

[a] The dr values were determined by ^{1}H-NMR analysis of the appropriate signals. The yield of cycloadducts was ≥80% in all cases. [b] Taken from ref 37d. [c] NPM adduct. [d] An unidentified product mixture was obtained.



(3)

The [4+2] cycloaddition mode of singlet oxygen clearly prevails,[46] and high yields of endoperoxides are obtained despite the fact that the substrates contain numerous allylic hydrogen atoms, which are prone to ene reactions. Even for the thioether **6b**, the facile sulfoxidation process[14] was suppressed in favor of the cycloaddition, and the resulting endoperoxide was observed at low temperature.[48] Only for the alcohol **6e**, which has been described as a labile compound itself,[36d] a complex product mixture was obtained under the photooxygenation conditions. The attempt to employ alcohol **7** (eq 4) as a substitute proved



(4)

unsuccessful, since a facile subsequent rearrangement[49] masked the stereochemical information about the preferred dienophile attack. Therefore, the question of the directing propensity of the allylic hydroxy group on singlet oxygen remains unsolved for these substrates at the moment.

In order to assess the importance of steric control, we also employed the cyclopentadienes **6f**−**i** (Table 1) in the [4+2] cycloaddition with various dienophiles.[36f,50] The use of carbon-bonded substituents should minimize stereoelectronic effects[36d,e,37d−f] and help to evaluate the importance of steric bias. Indeed, for all dienophiles and also the small singlet oxygen molecule, these dienes gave very high sterically controlled *anti* diastereoselectivities. These results demonstrate

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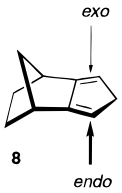
that it is not necessary to invoke deep-seated stereoelectronic effects to rationalize the reported π-facial selectivities for many cyclopentadienes. This pertains also to the previously investigated substrates **6a**−**e**. However, the relevance of the rare cases for which a contrasteric attack was observed[36a,e,37d] is accentuated.

Within the error limits, all dienophiles showed the same sterically controlled high diastereoselectivities at least for the electron-rich, pentamethylated cyclopentadienes. In contrast, the classical studies of Paquette on the dienophilic capture of isodicyclopentadiene derivatives,[18,51] e.g., diene **8**, revealed that



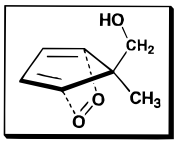
8

endo/exo ≥ 90 : 10 for NPM, methyl acrylate, 1,4-benzoquinone
endo/exo = 73 : 27 for $^1O_2$

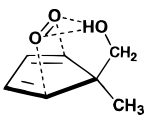
NPM = *N*-phenylmaleimide

singlet oxygen possesses a reduced discriminatory aptitude for *endo/exo* attack compared to other dienophiles.[52] The high *endo* selectivities for various dienophiles are believed to derive from stereoelectronic control for these substrates,[37b,c,53] and the reduced sensitivity of singlet oxygen was rationalized in terms of reversible exciplex formation.[38,51] In a more general sense, these findings support recent considerations by Inagaki[37f] that for cyclopentadienes there exists an *inverted reactivity*−*selectivity* pattern; i.e., highly alkylated and, therefore, more reactive derivatives such as **6** will in many instances show higher selectivities than their electron-poor counterparts **8**.

It is important to note that for the alcohol **6i** there exists no evidence for stabilization of the transition state *syn*-**6i**‡ or the intermediary exciplex through hydrogen bonding with the incoming singlet oxygen.[36c] Instead, the sterically controlled attack (transition state *anti*-**6i**‡) prevails, even for as small a difference

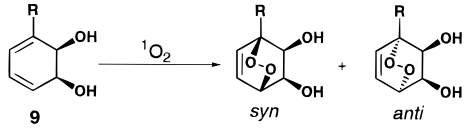


anti-**6i**‡



syn-**6i**‡

in steric bias as for the hydroxymethyl *versus* methyl groups.[50] The lack of a *syn*-directing effect of hydroxy groups[54] also becomes evident in the photooxygenation of *cis*-1,2-dihydroxycyclohexadienes **9** (eq 5),[55] for which only moderate sterically controlled *anti* selectivities were observed. This behavior is in strong contrast to what we will see later for the open-chain alcohols.



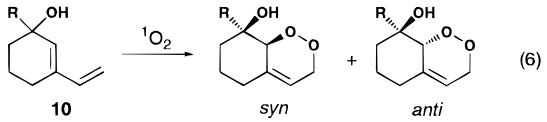
9 (5)

R=H: 26 : 74
R=Me: 38 : 62

Semicyclic Dienes

This type of chiral diene, in which the directing substituent and one of the reactive double bonds is incorporated into a cyclic structure, has been studied only in a few substrate-controlled Diels−Alder reactions.[39] Since the steering functionality is no longer located symmetrically with respect to the double bonds as in the case of 5-substituted cyclopentadienes, steric effects should be diminished for a symmetrical, concerted approach of the dienophile. Furthermore, stereoelectronic factors should also be less important than for cyclic dienes primarily because the adjacent double bond should be affected.

Only a few examples of this informative substrate class have been employed in the singlet oxygen [4+2] cycloaddition. Irrespective of whether the hydroxy group resides next to C-1[56] or C-2[57] of the diene moiety (eq 6), moderate sterically controlled π-facial selectivi-



10 (6)

R=H: 43 : 57
R=Me: 70 : 30

ties are observed. The results lie within the range of conventional carbon dienophiles (NPM, dimethyl acetylenedicarboxylate),[39d] and therefore, on the basis of this very limited set of data, singlet oxygen represents no special case in the [4+2] cycloaddition to semicyclic dienes.

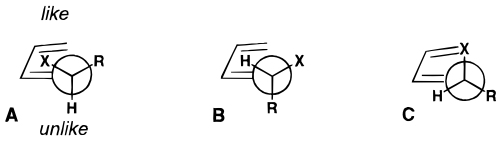
Nevertheless, these results are of mechanistic significance. For typical carbon dienophiles, the steric control in dienol **10** in the symmetrical concerted transition state is thought to arise from nonbonding repulsion between the functional groups in the six-membered ring and the incoming dienophile.[39c,d] The small singlet oxygen molecule, however, does not occupy the space proximate to the hydroxy group in the symmetrical approach, and consequently, steric interactions and the diastereoselectivity should be decreased. Therefore, one has either to envisage a highly unsymmetrical attack of singlet oxygen toward these semicyclic dienes or to invoke additional stereoelectronic effects in the stereocontrol to rationalize the identical π-facial selectivities for the different types of dienophiles.

Regardless of these mechanistic queries, it is evident that the approach of singlet oxygen toward semicyclic dienes is primarily sterically controlled, although the effect of steric bias is clearly reduced compared to that in the symmetrical cyclopentadienes. Therefore, the application of such substrates in stereoselective synthesis with singlet oxygen does not seem promising.

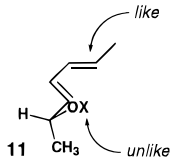
(51) Paquette, L. A.; Carr, R. V. C.; Arnold, E.; Clardy, J. *J. Org. Chem.* **1980**, *45*, 4907−4913.
(52) For related results, cf. (a) Paquette, L. A.; Bellamy, F.; Böhm, M. C.; Gleiter, R. *J. Org. Chem.* **1980**, *45*, 4913−4921. (b) Landheer, I.; Ginsburg, D. *Tetrahedron* **1981**, *37*, 133−142. (c) Mehta, G.; Uma, R.; Pramanik, A.; Chandrasekhar, J.; Nethaji, M. *J. Chem. Soc., Chem. Commun.* **1995**, 677−678.
(53) Ginsburg, D. *Tetrahedron* **1983**, *39*, 2095−2135.
(54) For hydroperoxy groups, cf. Seçen, H.; Salamanci, E.; Sütbeyaz, Y.; Balci, M. *Synlett* **1993**, 609−610.
(55) (a) Carless, H. A. J.; Oak, O. Z. *Tetrahedron Lett.* **1989**, *30*, 1719−1722. (b) Carless, H. A. J.; Billinge, J. R.; Oak, O. Z. *Tetrahedron Lett.* **1989**, *30*, 3113−3116.
(56) Adam, W.; Prein, M. Unpublished results.
(57) For 1-vinyl-2-cyclohexenol, cf. Herz, W.; Juo, R.-R. *J. Org. Chem.* **1985**, *50*, 618−627.

Acyclic Dienes

The stereocontrolling factors of acyclic, chiral dienes show an appreciably higher level of complexity than for their cyclic or semicyclic counterparts. The enhanced flexibility of these substrates obliges a detailed consideration of the conformational features.[41] Depending on the preferred arrangement of the stereogenic unit in the transition state, steering effects of the substituent can operate on either of the two π faces. In the absence of appreciable allylic strain,[44] the π-facial selectivity of electrophilic attack is primarily determined by stereoelectronic effects.[58] These factors are weak, and a critical dependence of both sense and extent of π-facial selectivity on the respective reaction partners should be expected and is observed. Cases of *unlike*-selective reaction, e.g., in the [3+2] cycloaddition[58c] of chiral allylic alcohol derivatives, were rationalized in terms of a preference for conformation **A** (*inside* effect),[58a−c] while Franck discussed his *like* selectivities in the Diels−Alder reaction in terms of the transition states **B** and **C**.[42c]



The reaction of singlet oxygen with the (*E,E*)-heptadienol **11a** and the two derivatives **11b,c** as

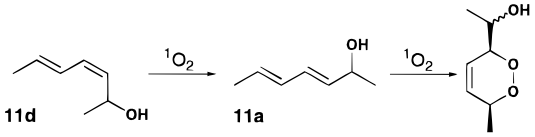


Nr	X	NPM [42c]	MTAD	$^1O_2$
11a	H	63 : 37 (*l*)	37 : 63 (*u*) [42c]	**54 : 46**
11b	Me	83 : 17 (*l*)	30 : 70 (*u*)	**32 : 68 (*u*)**
11c	$SiMe_3$	88 : 12 (*l*)	15 : 85 (*u*)	**31 : 69 (*u*)**

model compounds showed only low to moderate diastereoselectivities in the endoperoxide formation.[46] The preferred π face for the singlet oxygen attack could only be assigned by spectral correlation with the MTAD adducts, for which the stereochemistry was also not unequivocally assigned.[42c] The data clearly demonstrate that both sense and extent of the π-facial selectivity in the [4+2] cycloaddition will critically depend on the dienophile employed for acyclic substrates without allylic strain. Furthermore, the present results imply a reduced sensitivity of singlet oxygen toward stereoelectronic control, a behavior that can be accounted for by the high reactivity of this dienophile. Thus, singlet oxygen captures the various rotamers of the substrate, all of which are populated in the ground state,[41] and the diastereoselectivity decreases.

(58) (a) Paddon-Row, M. N.; Rondan, N. G.; Houk, K. N. *J. Am. Chem. Soc.* **1982**, *104*, 7162−7166. (b) Houk, K. N. *Pure Appl. Chem.* **1983**, *55*, 277−282. (c) Houk, K. N.; Moses, R. S.; Wu, Y.-D.; Rondan, N. G.; Jäger, V.; Schohe, R.; Fronczek, F. R. *J. Am. Chem. Soc.* **1984**, *106*, 3880−3882. (d) Fleming, I.; Lewis, J. L. *J. Chem. Soc., Chem. Commun.* **1985**, 149−151. (e) McGarvey, G. J.; Williams, J. M. *J. Am. Chem. Soc.* **1985**, *107*, 1435−1437. (f) Kaila, N.; Franck, R. W.; Dannenberg, J. J. *J. Org. Chem.* **1989**, *54*, 4206−4212.

In view of this happenstance, it was clearly desirable to design acyclic substrates with 1,3-allylic strain, for which stereocontrol does not depend on conformational preferences in the transition state through stereoelectronic effects. This requirement is met by the (*Z,E*)-heptadienol **11d** (eq 7) for which the *Z* geometry of

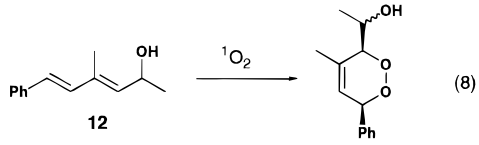


(7)

d.r. 55 : 45

the C3−C4 double bond provides the necessary 1,3-allylic strain. Unfortunately, the photooxygenation did not provide the desired *trans*-endoperoxides in a suprafacial process due to the inaccessibility of a *cisoid* conformation. Instead, as for (*Z,E*)-hexa-2,4-diene,[21b,31a] a singlet oxygen-induced *cis−trans* isomerization to dienol **11a** and subsequent endoperoxidation were observed.[59] Consequently, the photooxygenation of the diastereomers **11a,d** gave the same products with identical diastereoselectivities. Also in this case, the use of stereochemical probes provides valuable mechanistic insight. Were the endoperoxidation of the (*Z,E*)-dienol **11d** to occur by the direct collapse of any intermediate without preceding isomerization, a change of the diastereoselectivity should have been expected compared to that of dienol **11a**.

Another attempt at hydroxy-directed stereocontrol in acyclic substrates was undertaken in the photooxygenation of dienol **12** (eq 8). The presence of a *cis*



(8)

< 20%, d.r. ?

substituent renders the *inside* position the preferred conformation in the ground and transition state for the smallest substituent, i.e., the hydrogen atom.[43] For these preferred rotamers, the directing hydroxy group is placed on the *like* face of the reactive diene moiety, and any steric or electronic interaction with the incoming dienophile can operate only on this particular π face. Unfortunately, for the dienol **12**, which had proven its utility in highly diastereoselective Diels−Alder reactions with other dienophiles,[42h] with singlet oxygen the ene reaction of the trisubstituted double bond prevailed (ca. 80%).[46] Therefore, the determination of diastereoselectivities in the [4+2] mode was precluded.

In summary, due to the described drawbacks in the photooxygenation of the dienols **11d** and **12**, at the present time it is not possible to define the stereochemical perspectives of the hydroxy-directed [4+2] cycloaddition of singlet oxygen with chiral acyclic dienes. To circumvent the side reactions (mainly the ene process), which plague the photooxygenation of acyclic dienes, we turned our attention to aromatic substrates, in particular chiral napthalenes, which undergo clean endoperoxidation.

(59) Adam, W.; Wirth, T. Unpublished results.

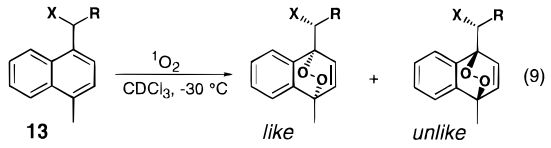
Table 2. Substituent Effects in the Photooxygenation of Chiral Naphthlene Derivatives[a]

entry	compd no.	X	R	*t* (h)	convn[b] (%)	yield[b] (%)	dr[b] *like:unlike*
1	**13a**	OH	Me	4	≥95	≥95	85:15
2	**13b**	OH	Et	6	≥95	≥95	88:12
3	**13c**	OH	tBu	2.5	30	≥95	87:13
4	**13d**	CH_2OH	Me	5	≥95	≥95	90:10
5	**13e**	tBu	Me	6	30	95	34:66[c]
6	**13f**	OMe	Me	7	87	>95	66:34[c]
7	**13g**	$OSiMe_3$	Me	7	≥95	>95	58:42
8	**13h**	OAc	Me	14	37	95	55:45
9	**13i**	CN	Me	6	40	≥95	51:49[d]
10	**13j**	CHO	Me	16	48	ca. 90	60:40[d]
11	**13k**	COOH	Me	4	90	≥95	21:79
12	**13l**	COOMe	Me	6	≥95	≥95	22:78
13	**13m**	Cl	Me	12	95	≥95	13:87[c]
14	**13n**	Br	Me	4	≥95	≥95	5:95[c]
15	**13o**	$SiMe_3$	Me	3.5	≥95	95	5:95

[a] The photooxygenations were carried out at −30 °C in $CDCl_3$ with tetraphenylporphine (TPP) as sensitizer. [b] Determined by ^{1}H-NMR analysis of appropriate signals. [c] The relative stereochemistry was assigned in accordance with the singlet oxygen ene reaction (cf ref 35). [d] The relative stereochemistry was not assigned.

Chiral Arenes

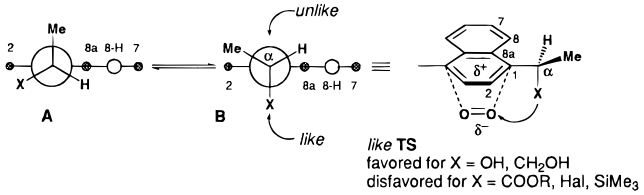
The chiral naphthalene derivatives **13** contain a conformationally flexible stereogenic unit and *peri* steric strain due to the 8-H atom. Furthermore, their accessibility and clean conversion to the corresponding endoperoxides (eq 9)[60] allow the screening of the stereocontrolling properties of a variety of substituents. The experimental results are summarized in Table 2.



Remarkable is the *like*-directing effect of the hydroxy group both in the benzylic (entries 1−3)[61] and in the homobenzylic positions (entry 4).[62] That steric bias is not particularly effective for stereocontrol can be seen in the photooxygenation of the *tert*-butyl-substituted hydrocarbon **13e** (entry 5)[63] and the negligible influence of the aliphatic substituent R on the high π-facial selectivity in the derivatives **13a**−**c** (entries 1−3).[61] While protection of the free hydroxy group in derivatives **13f**−**h** (entries 6−8) or the utilization of nitriles[62] or aldehydes[62] (entries 9 and 10) both slow the reaction rate and lead to low stereocontrol, *unlike*-selective singlet oxygen attack was achieved by employing a carbonyl (entries 11 and 12),[62] halogen (entries 13 and 14),[63] or silyl (entry 15)[63] substituent.

On the basis of these stereochemical results, we propose the integrated mechanistic picture in Scheme 2.[61−63] The preferred conformations **A** and **B** bear the small hydrogen substituent proximate to the *peri* hydrogen, which provides the necessary steric strain[64] both in the ground and in the transition states. Thus, the extent and sense of stereocontrol for singlet oxygen

Scheme 2. Reaction Mechanism of the Singlet Oxygen [4+2] Cycloaddition with Chiral Naphthalene Derivatives



attack is a function of steric and electronic interactions. Highly *like*-selective reactions should be expected when X is small compared to R and/or when X undergoes attractive interactions with the incoming singlet oxygen. Evidently, these requisites are not met by the methoxy, acetoxy, siloxy, cyano or formyl substituent (Table 2, entries 6−10), since their selectivities are low. In contrast, the small hydroxy substituent (entries 1−3) leads to remarkably high *like* selectivities in the present as well as in related cases.[61] The synergistic action of steric bias and electronic effects, namely, hydrogen bonding between the negatively polarized singlet oxygen and the hydroxyl proton, accounts for this pronounced steering effect. The contribution of electronic features is substantiated by large solvent effects, i.e., loss of stereoselectivity in polar solvents,[61] and the fact that for the homobenzylic alcohol **13d** a contrasteric *like* approach of singlet oxygen is observed.[62]

The charge transfer from the arene to singlet oxygen during exciplex formation also provides a rationale for the *unlike* selectivities for X = COOR and Hal. Thus, electrostatic repulsion on the *like* face between the negatively charged singlet oxygen and the electronegative heteroatom substituent, as was also proposed in the singlet oxygen ene reaction,[35c] renders the *unlike* attack more favorable. Superimposed on these simple steric and electronic effects could also operate stereoelectronic features, which may influence the diastereoselectivities. Thus, although the two decisive conformers **A** and **B** possess similar *peri* strain, they should lead to a different extent of stereocontrol. A higher population of the **B** conformer should give more *unlike* product, since the perpendicular X substituent represents a more severe obstacle to singlet oxygen attack than in **A**. Stereoelectronic effects, i.e., preference for conformer **B** by hyperconjugation in the transition state, might promote *unlike* control for the

(60) (a) Wasserman, H. H.; Larsen, D. L. *J. Chem. Soc., Chem. Commun.* **1972**, 253−254. (b) van den Heuvel, C. J. M.; Steinberg, H.; de Boer, Th. J. *Recl. Trav. Chim. Pays-Bas* **1980**, *99*, 109−117.

(61) (a) Adam, W.; Prein, M. *J. Am. Chem. Soc.* **1993**, *115*, 3766−3767. (b) Adam, W.; Peters, E. M.; Peters, K.; Prein, M.; von Schnering, H. G. *J. Am. Chem. Soc.* **1995**, *117*, 6686−6690.

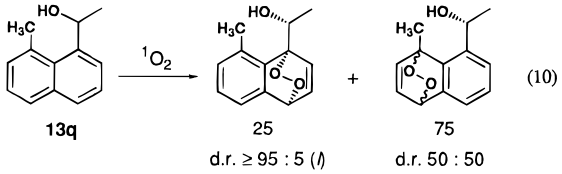
(62) Adam, W.; Prein, M. *Tetrahedron* **1995**, *51*, 12583−12590.

(63) Adam, W.; Prein, M. *Tetrahedron Lett.* **1994**, *35*, 4331−4334.

(64) This conformational preference in the ground state was confirmed by AM1 calculations.

higher row elements (X = Cl, Br, SiMe3[65]), but to date the available experimental and theoretical data are too limited for a definitive interpretation.

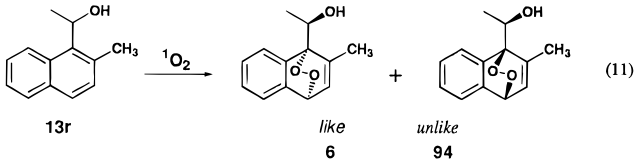
With the data of Table 2 at hand, the mechanistic picture was corroborated by varying the steric strain through the proper choice of chiral naphthyl alcohols. An increase in *peri* strain, as in the 1,8-disubstituted alcohol **13q**, led to the expected higher degree of *like* attack of singlet oxygen (eq 10);[61b] i.e., the preference



(10)

for the rotamers **A** and **B** through steric strain is further promoted. The regioselectivity of singlet oxygen attack on alcohol **13q** demonstrates that for this substrate the attractive interaction through hydrogen bonding does not override the deactivating effect of the inductively electron-withdrawing benzylic heteroatom substituent.[66] Therefore, cycloaddition to the electron-richer methyl-substituted benzene moiety is favored to afford the 5,8-endoperoxides. The lack of diastereoselectivity in the formation of the 5,8-endoperoxide (diastereomeric ratio (dr) 50:50) validates the proposed mechanism of hydroxy-directed stereocontrol. Thus, strict geometry requirements for effective hydrogen bonding between singlet oxygen and the hydroxy functionality (Scheme 2) are essential for high stereocontrol.

Further support for the proposed interplay between conformational adjustment through steric strain and hydrogen bonding with singlet oxygen can be seen in the photooxygenation of the 1,2-disubstituted naphthyl alcohol **13r** (eq 11).[61] The addition of an *ortho* substituent renders the conformations **A** and **B** unfavorable and places the hydroxy functionality on the *unlike* face of the substrate.[64] Consequently, the major product results from *unlike* attack, which clearly demonstrates that *ortho* strain overrides the effect of *peri* strain in this substrate. The higher extent of stereocontrol for 1,2-disubstituted naphthalene



(11)

derivatives[61b] was accounted for in terms of an unsymmetrical singlet oxygen attack on the electron-rich double bond proximate to the directing stereogenic center.

The present results on the diastereoselective photooxygenation of chiral naphthalene derivatives demonstrate that the π-facial selectivity of singlet oxygen attack can be efficiently controlled by strategically placed substituents at stereogenic sites in combination with strain-controlled conformational preferences. It should be worthwhile to test whether functional groups such as chloro, bromo, or carboxylate, whose directing propensity in the [4+2] cycloaddition has been probed for the first time ever in our singlet oxygen studies, will show similar directing effects in the Diels–Alder reaction with carbon and nitrogen dienophiles.

The Exciplex as a Mechanistically Unifying Intermediate

To gain a unifying view of the reaction mechanism of singlet oxygen reactions, it is important to blend the present stereochemical results for the *[4+2] cycloaddition* with those of other reaction modes, particularly the *Schenck ene reaction*. The hydroxy group-directing effect for open-chain systems seems to be of broad scope, as can be seen from numerous *like*-selective ene reactions of chiral, allylic alcohols[35a,c] and also from the diastereoselective oxygenation of chiral phenol derivatives.[67] This parallelism between the singlet oxygen ene reaction and the [4+2] cycloaddition can be extended over a wide range of substituents, as shown in the comparison in Table 3. Both extent and sense of stereocontrol show an amazing degree of correspondence between the model systems examined. Logically, this raises the question of common structural and electronic properties of intermediates in both reaction modes of singlet oxygen.[28] The plausible contenders for the hydroxy-stabilized species are exemplified for the [4+2] cycloaddition mode in Figure 1.

While the observed electronic effects render a strictly synchronous, concerted transition state of the reaction (Figure 1a) or the intermediacy of nonpolarized diradicals (Figure 1b) unlikely, it is much more difficult to differentiate between the remaining options. The perepoxide structure (Figure 1c) has again been accepted during the last few years for the ene reaction.[68] However, what seems important to realize is that the available kinetic data speak only for a perepoxide-like geometry of the singlet oxygen approach and not that a *bona fide* 1,2-dipole actually intervenes.[69] In fact, for the [4+2] cycloaddition, the strained perepoxide structure (Figure 1c) would be expected to be inferior to the delocalized 1,4-dipole (Figure 1d). Both struc-

(65) Fleming, I. *Pure Appl. Chem.* **1988**, *60*, 71–78.

(66) It was pointed out by a reviewer that the observed regioselectivity in the photooxygenation of the **13q** substrate contradicts the mechanistic concept of the hydroxy-directing effect because an attractive interaction between the hydroxy group and the incoming singlet oxygen dienophile should manifest itself in an increased reaction rate such that the preferred endoperoxidation should occur at the hydroxyethyl- rather than the observed methyl-substituted ring. However, it should be kept in mind that the reactivity of singlet oxygen is characterized by a high sensitivity to steric and electronic effects of the reacting π system. For example, it is well documented (cf. refs 10 and 17a) that *any* allylic oxygen substituent markedly decreases the rate of singlet oxygen reactions through its inductive effect. The hydroxyethyl-substituted naphthalene ring will, therefore, possess a significantly lower reactivity than the alkylated one, and the hydroxy group, although decisive in dictating the diastereoselectivity, is incapable of counteracting the inherent lower reactivity of the hydroxyethyl-substituted benzene ring despite the rate-accelerating association through hydrogen bounding. Moreover, the validity of the proposed mechanistic concept of hydrogen bonding is substantiated in the reactivity trends observed for several α-oxygen-substituted substrates (Table 2). Thus, inspection of the data makes evident that the methoxy and acetoxy derivatives react more slowly than the naphthyl alcohols, as expected on account of their lack of hydrogen bonding; consequently, the more reactive substrates are also the more diastereoselective ones. Similar trends are documented in the stereoselective Schenck ene reaction (ref 35). Finally, the acylation of allylic alcohols may quite generally even completely suppress their reaction with singlet oxygen (ref 17a), which is in line with the proposed attractive interaction through hydrogen bonding.

(67) Prein, M.; Adam, W.; Maurer, M.; Peters, E. M.; Peters, K.; von Schnering, H. *Chem. Eur. J.* **1995**, *1*, 89–94.

(68) Frimer, A. A.; Stephenson, L. M. In *Singlet Oxygen*; Frimer, A. A., Ed.; CRC Press: Boca Raton, FL, 1985; Vol. 2, p 67.

Table 3. Diastereoselectivities for the Ene and [4+2] Modes of Singlet Oxygen

ene[a] *like*:*unlike*	X	[4+2] *like*:*unlike*
93:7[b]	OH	85:15
70:30[b]	OAc	56:44
72:28[b]	OMe	66:34
55:45[c]	CH_2OH	90:10
10:90[b]	Cl	13:87
10:90[b]	Br	5:95
20:80[c]	COOH	21:79
22:78[c]	COOMe	22:78

[a] Reference 35c. [b] R = Me. [c] R = H.

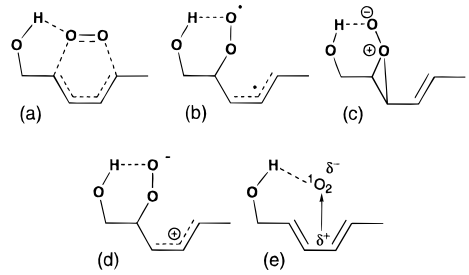


Figure 1. Hydroxy-stabilized transition states and intermediates.

tures account for the stabilization through hydrogen bonding, but in order to collapse to the product, they would have to undergo relatively complex conformational reorganization. Furthermore, for such dipolar species solvent trapping and loss of *syn* selectivity with respect to the diene should be expected, which is generally not observed.[10,16,17]

We propose that a stabilized exciplex (Figure 1e) describes best and in a unifying manner the mechanism for the various reaction modes of singlet oxygen. Clearly, this exciplex description intentionally leaves open such features as the extent of charge transfer and the geometrical properties. Nonetheless, this is exactly what makes this model so attractive as a unifying mechanistic concept in rationalizing the kinetic and stereochemical results of singlet oxygen reactions.

Extent of Charge Transfer

What still needs to be addressed is why certain compound classes, e.g., the cyclopentadienes **6**, show a considerable lower sensitivity toward electronic stabilization of the exciplex through hydrogen bonding than the chiral naphthalene derivatives.[70] A striking example is the hydroxymethyl group, which directs singlet oxygen attack contrasterically to the *like* face in the chiral arene **13d**,[62] while for the cyclic analog

(69) The reported trapping experiments do not necessarily prove the intermediacy of perepoxides in the ene reaction since substrates have been employed which do not undergo ene reactions (e.g., Schaap, A. P.; Recher, S. C.; Faler, G. R.; Villasenor, S. R. *J. Am. Chem. Soc.* **1983**, *105*, 1691−1693); moreover, also open-chain zwitterions or exciplexes (ref 21c) may be trapped to form identical products (cf. Jefford, C. W. *Chem. Soc. Rev.* **1993**, 59−66).

(70) A diminished directing effect of the hydroxy group in cyclic systems was also observed in the singlet oxygen ene reaction; cf. ref 35c.

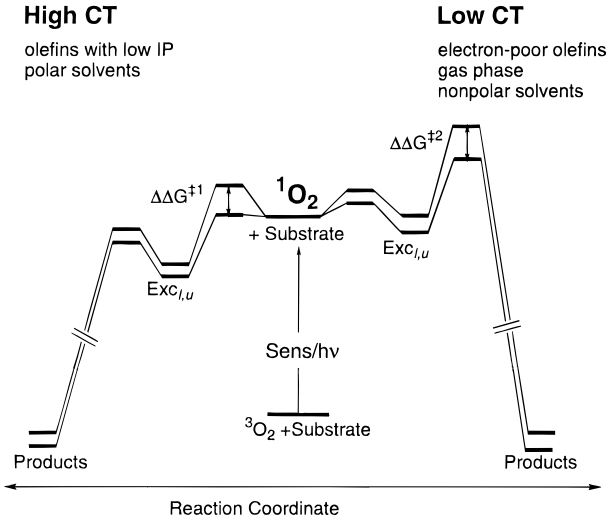


Figure 2. Composite reaction coordinates for the high (left) and low (right) charge transfer cases in photooxygenation.

6i steric effects operate exclusively and lead to the *anti* product.[50]

At this point a closer inspection of the possible reaction coordinates is instructive. The present stereochemical results substantiate the theoretical analysis of singlet oxygen reactions proposed by Yamaguchi, who emphasized the importance of charge transfer in singlet oxygen reactions.[28] These computations reveal that the extent of charge transfer in singlet oxygen reactions is a function of the olefin structure and the reaction medium. One can discriminate two distinct kinetic situations for the stepwise process, which are exemplified for the photooxygenation of chiral substrates in Figure 2.

In the case of substrates and conditions for which *low charge transfer* applies, the second step is rate-determining with exciplex formation reversible (Figure 2, right side). In contrast, in the case of *high charge transfer*, the first step becomes rate-determining and the exciplex formation is no longer completely reversible (Figure 2, left side), i.e., exciplex generation becomes rate-determining, and the product formation is fast. Indeed, the *high charge transfer* case pertains to the *fast* and the *low charge transfer* one to the *slow* photooxygenations, with orders of magnitude differences in reactivity.

On the basis of detailed kinetic studies for a variety of substrates, Gorman[31b,71] and Foote[72] independently proposed similar limiting cases in terms of the exciplex concept. The shape of the reaction profile, i.e., *high versus low charge transfer*, will affect the stereocontrol in diastereoselective singlet oxygen reactions. Any stabilization in one of the two diastereomeric exciplexes $Exc_{l,u}$ is expected to be expressed in $\Delta\Delta G^{\ddagger,2}$. This energy difference $\Delta\Delta G^{\ddagger,2}$ will be reflected in the product ratio only if the product-forming second step is rate-determining and exciplex generation (first step) necessarily reversible, i.e., the case of *low charge transfer* (Figure 2, right side). In other words, when exciplex formation proceeds with a substantial degree of reversibility, such a charge transfer complex has

(71) (a) Gorman, A. A.; Gould, I. R.; Hamblett, I. *J. Am. Chem. Soc.* **1982**, *104*, 7098−7104. (b) Gorman, A. A.; Gould, I. R.; Hamblett, I.; Standen, M. C. *J. Am. Chem. Soc.* **1984**, *106*, 6956−6959.

(72) Orfanopoulos, M.; Smonou, I.; Foote, C. S. *J. Am. Chem. Soc.* **1990**, *112*, 3607−3614.

available the necessary time to select favored encounters through electronic stabilization and, hence, controls the product ratio. The present stereochemical results in the naphthalene series suggest that for these substrates the *low charge transfer* case is applicable. As observed, such endoperoxidations are sensitive toward electronic effects at the exciplex stage, most prominently hydrogen bonding.

For the alternative *high charge transfer* case (Figure 2, left side), the first step ($\Delta\Delta G^{\ddagger,1}$) determines the π-facial selectivity, and consequently, hydroxy stabilization in the irreversible exciplex[73] is no longer effective. Instead, steric effects will become decisive or even entropic factors may operate, since it is well documented that exciplex formation constitutes a typical entropy-controlled process.[31b,71,74]

Substrates which belong in this category are the electron-rich pentamethylcyclopentadienes **6** of the present study. They are prone to high charge transfer during photooxygenations,[28] which is reflected in the increased reaction rate ($>10^9$) compared to that of the chiral naphthalene derivatives (ca. 10^4-10^5).[27] This dramatic difference in the reactivity between these two substrate classes leads to the seemingly paradoxical situation that, with their high propensity for charge-separated intermediates, the electron-rich cyclopentadienes show only a poor response toward electronic stabilization of the exciplex through hydrogen bonding. Thus, in the diastereoselective endoperoxidation there exists a subtle balance between the extent of charge transfer and the efficacy of stabilizing electronic effects. While a certain degree of polarization is essential for efficient π-facial stereocontrol through hydrogen bonding or electrostatic repulsion, the charge transfer must not exceed the point at which the exciplex generation (first step) becomes rate-determining and stereocontrol through stabilization of the exciplex becomes ineffective.[75]

In summary, the present stereochemical studies should stimulate interest in the application of stereoselective [4+2] cycloadditions in organic synthesis. Moreover, they have unquestionably contributed some new aspects to a better understanding of the mechanistic complexities of the singlet oxygen [4+2] cycloaddition. Thus, the π-facial selectivity of the singlet oxygen dienophile (also enophile) serves as a sensitive mechanistic probe to scrutinize the subtleties and intricacies of photooxygenation processes and, thereby, complements kinetic, spectral, and computational studies. The relative importance of steric and electronic factors in the stereocontrol depends both on the type of the substrate (cyclic *versus* acyclic) and on the reaction conditions (polar *versus* unpolar solvents). The present stereochemical studies constitute a new and interesting facet to understand the chemical behavior of the fascinating singlet oxygen molecule, whose challenging chemistry has by no means been exhausted yet.

(73) In the borderline situation, exciplex formation will be partially reversible; i.e., $\Delta\Delta G^{\ddagger,1}$ and $\Delta\Delta G^{\ddagger,2}$ will both influence the product ratio. For such a partitioning of reactive intermediates cf. Song, Z.; Beak, S. *J. Am. Chem. Soc.* **1990**, *112*, 8126−8134.

(74) Hurst, J. R.; Wilson, S. L.; Schuster, G. B. *Tetrahedron* **1985**, *41*, 2191−2197.

(75) The different extent of charge transfer also provides a satisfactory rationale for the solvent effects in the photooxygenation of chiral olefins and dienes. Polar solvents promote charge transfer (cf refs 28 and 29), and consequently, stabilization of the exciplex by intramolecular hydrogen bonding with the hydroxy group is ineffective and loss of stereocontrol is expected and observed.

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