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Stereoselection in 5-*exo* Radical Cyclizations of Polysubstituted 2-Oxahex-5-enyl Radicals: A Systematic Study of the Combination Substituent Effect[#]

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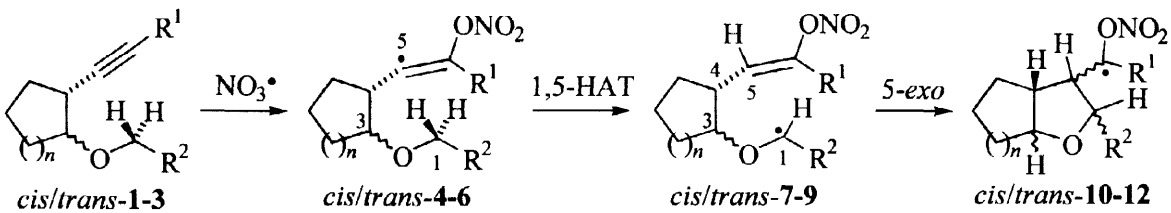
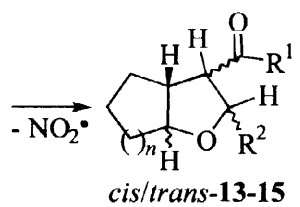
Abstract: The nitrate radical induced oxidative cyclization of the alkynyl ethers *cis/trans*-**1-3** proceeds with high diastereroselectivity and leads to the annellated tetrahydrofurans *cis/trans*-**13-15**. The stereoselectivity in this reaction sequence is likely determined in the 5-*exo* radical cyclization step of the intermediate polysubstituted 2-oxahex-5-enyl radicals *cis/trans*-**7-9**. The respective transition state geometries of these cyclizations are discussed within the framework of the Beckwith-Houk model. A dependence of the stereoselection on the configuration and size of the fused cycloalkyl ring as well as on the stability of the 2-oxahex-5-enyl radicals *cis/trans*-**7-9** is observed.

Keywords: Radicals and radical reactions; Diastereoselection; Transition states; Cyclization.

Introduction

Recently, we have shown that the annellated tetrahydrofurans *cis/trans*-**13-15** were obtained with generally excellent diastereoselectivity by intermolecular addition of electrogenerated nitrate radicals ($NO_3^•$) to the C≡C triple bond in the 3,4-cycloalkyl fused alkynyl ethers *cis/trans*-**1-3**.[1,2] After initial formation of the vinyl radicals *cis/trans*-**4-6** the reaction likely proceeds via an intramolecular rate determining 1,5-hydrogen atom transfer (1,5-HAT), subsequent 5-*exo* radical cyclization of the 2-oxahex-5-enyl radicals *cis/trans*-**7-9** to the newly formed C=C double bond and final loss of nitrogen dioxide ($NO_2^•$) in the cyclized radicals *cis/trans*-**10-12** (Scheme 1).





cis/trans-	*n*	substituents
1, 4, 7, 10, 13	1	**a, b*, c*, d***
2, 5, 8, 11, 14	2	**b, e**
3, 6, 9, 12, 15	3	**b**

* Only *cis*.

	R^1	R^2
a	*n*-Bu	Me
b	*n*-Bu	Et
c	*n*-Bu	OMe
d	*n*-Bu	CN
e	Me	Me

Scheme 1

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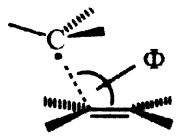
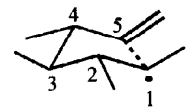
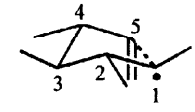
Because of the fragmentation of the latter radicals into $NO_2^{\bullet}$, which is comparably unreactive with respect to $NO_3^{\bullet}$, and the stable carbonyl compounds *cis/trans*-**13-15** this sequence may be considered as a self-terminating radical cyclization cascade.[3]

Many examples have demonstrated that 5-*exo* radical cyclizations of hex-5-enyl radicals often proceed with high stereoselectivity.[4] From ab initio calculations it was concluded that the transition state structure of radical additions to π-systems is dissymmetric with the angle of attack ($\Phi \approx 107°$) being close to the value for an sp^3 carbon.[5,6] In most cases the stereoselection in these radical cyclizations can be explained with a model invented by Beckwith et al. and Houk et al.[4-7] This model is based on the assumption that the preferred transition state structure in 5-*exo* radical cyclizations should be chair-like with the substituents arranged pseudo equatorial (structure **A**). Chair-like transition state structures with axial substituents (not shown) or boat-like transition states (structure **B**), respectively, are generally of minor importance.





A
chair-like
transition state



B
boat-like
transition state

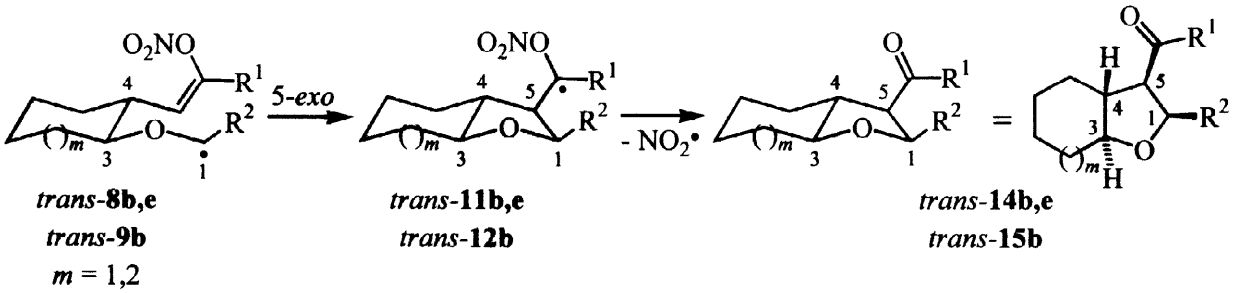
Thus, in the reaction sequence outlined in Scheme 1 it is reasonable to suggest that the stereochemistry in the annellated tetrahydrofurans *cis/trans*-**13-15** should be determined in the 5-*exo* cyclization step of the 2-oxahex-5-enyl radicals *cis/trans*-**7-9**. To our knowledge, a systematic study of the combination substituent effect on the stereoselection of 5-*exo* radical cyclizations of such 3,4-cycloalkyl fused, 1-substituted 2-oxahex-5-enyl radicals was not reported yet.

Results

In this work the stereoselection in 5-*exo* radical cyclizations of the 2-oxahex-5-enyl radicals *cis/trans*-7-9 was investigated. By reacting $NO_3^{\bullet}$ with the different alkynyl ethers *cis/trans*-1-3 shown in Scheme 1 the 2-oxahex-5-enyl radicals *cis/trans*-7-9 were obtained as intermediates. The stereochemistry of the ring fusion, the size of the cycloalkyl ring and also the substitution pattern R^1 and R^2 at the side chains were systematically varied. With this method a broad study of different parameters influencing the stereoselection could be achieved.

a) *trans*-3,4-Cycloalkyl fusion:

In the reaction of the *trans*-3,4-cycloalkyl fused alkynyl ethers *trans*-**2b,e** and *trans*-**3b**, respectively, with $NO_3^{\bullet}$ a prediction of the stereochemical outcome in the cyclized products on the basis of the Beckwith-Houk model could be easily made (Scheme 2). Since all substituents work in concert a pseudo equatorial arrangement in the 5-*exo* cyclization transition state of the 2-oxahex-5-enyl radicals *trans*-**8b,e** and *trans*-**9b** (analog to transition structure **A**, see above) should lead to the cyclized products *trans*-**14b,e** and *trans*-**15b**, respectively, with the alkyl substituents at C(1), C(3) and C(5) being *cis*. These diastereoisomers were indeed exclusively formed in these reactions.[1]

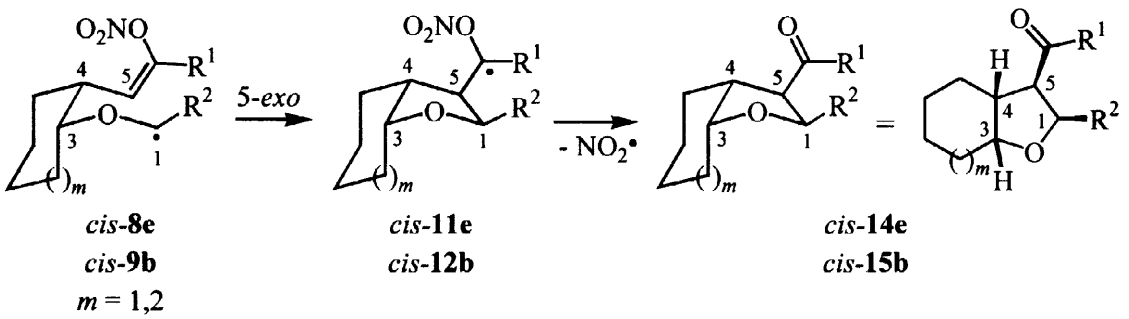


Scheme 2

b) *cis*-3,4-Cycloalkyl fusion:

The situation in the case of the *cis* compounds *cis*-**1-3** turned out to be significantly more complex. Due to the *cis* fusion of the cycloalkyl ring in the respective 2-oxahex-5-enyl radicals *cis*-**7-9** the C(3) and C(4) substituent work in opposition. In these systems we observed not only a dependence of the transition state geometry of the 5-*exo* radical cyclization on the size of the fused ring but also on the steric and electronic properties of the R^2 substituent.

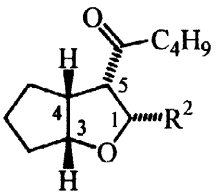
In the reaction of $NO_3^•$ with alkynyl ethers fused with a comparatively large cycloalkyl ring e.g. the *cis* disubstituted cyclohexyl system *cis*-**2e** or the cycloheptyl system *cis*-**3b** (see Scheme 1) only the diastereoisomers *cis*-**14e** and *cis*-**15b**, respectively, were obtained (Scheme 3).[1] In these products the substituents at C(1) and C(5) are both *cis* but oriented *anti* to the fused cycloalkyl ring. The stereoselection in this reaction could be explained according to the Beckwith-Houk model by assuming a chair-like transition state for the 5-*exo* cyclization of the 2-oxahex-5-enyl radicals *cis*-**8e** and *cis*-**9b**, respectively, in which the substituents at C(1) and C(4) are both arranged pseudo equatorial, but the C(3) substituent, by force, axial.



Scheme 3

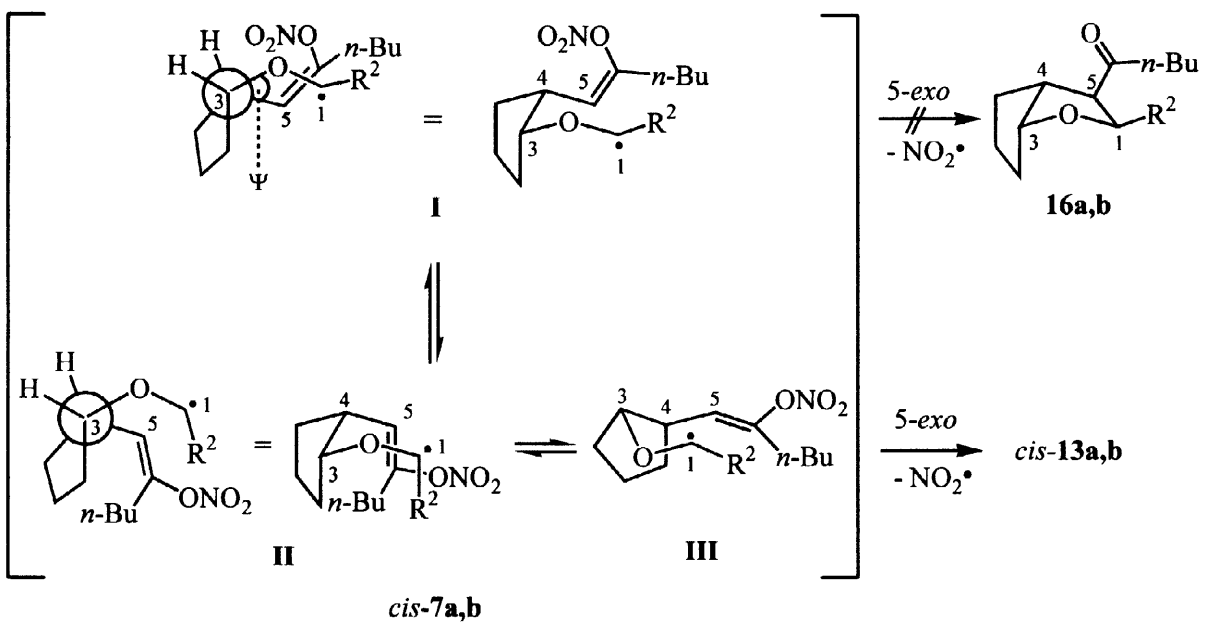
In the case of competing C(3) and C(4) substituents it is known that the stereoselection in 5-*exo* radical cyclizations is generally dictated by the C(4) substituent.[4] This is due to the fact that a pseudo equatorial position of the C(4) substituent in the cyclization transition state leads to a nearly eclipsed arrangement of the C(4)-H bond and the C=C double bond thus resulting in minimum energy of the allylic C(4)-C(5) bond.[4] Therefore, our observation of a dominant C(4) substituent dictating the stereoselection in the 5-*exo* cyclization of the 2-oxahex-5-enyl radicals *cis*-**8e** and *cis*-**9b**, respectively, strongly supports the literature data.

In contrast, the stereoselection in the $NO_3^{\bullet}$ induced radical cyclization of the *cis*-3,4-cyclopentyl fused alkynyl ethers *cis*-**1a** and *cis*-**1b**, respectively (see Scheme 1), was intirely different. In these reactions, the annellated tetrahydrofurans *cis*-**13a,b** were obtained in which the alkyl substituents and the fused cyclopentyl ring are located on the same side of the heterocyclic ring.[1] This result is remarkable, since the steric interactions between the four substituents at the tetrahydrofuran subunit should be significant in *cis*-**13a,b**.



cis-**13a,b**

A tentative explanation for this unexpected finding may be given by taking the higher rigidity of the fused cyclopentyl ring into account. By comparison with the cyclohexyl or cycloheptyl ring in the homologue radicals *cis*-**8e** and *cis*-**9b**, respectively, the reduced flexibiliy in the 2-oxahex-5-enyl radicals *cis*-**7a,b** causes a decrease of the dihedral angle Ψ between O-C(3)-C(4)-C(5) (Scheme 4). Thus, in a chair-like transition structure for the radical cyclization of *cis*-**7a,b**, according to the Beckwith-Houk model with every but the C(3) substituent arranged pseudo equatorial, the unpaired electron is lying directly above the center of the C=C double bond (conformation **I**, for clarity also shown in the Newman projection). A dissymmetric radical attack at C(5) of the C=C double bond which would lead to the annellated tetrahydrofurans **16a,b** possessing a similar stereochemistry as *cis*-**14e** and *cis*-**15b** (see Scheme 3) is not possible in this conformation.

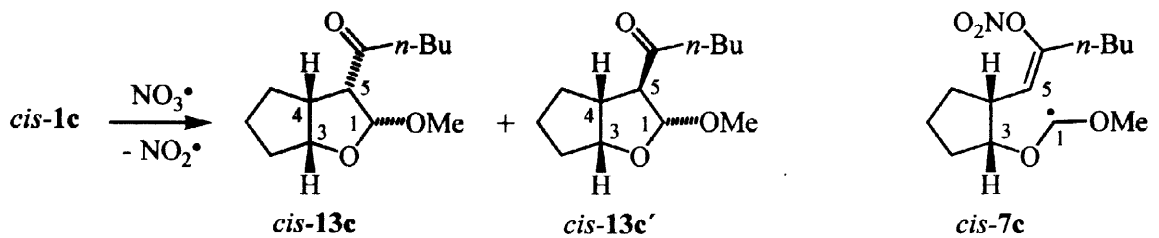


Scheme 4

On the other hand, a boat-like conformation **II** with only the C(4) substituent in a pseudo equatorial position would not only geometrically allow a dissymmetric radical addition at C(5) of the π system but could also explain the sterochemical outcome in the reaction products *cis*-**13a,b**. However, conformation **II** is expected to be energetically disfavored due to strong 1,3 diaxial interactions.

By flipping the boat-like conformation **II** into a chair and inverting the axial into pseudo equatorial substituents (and vice versa), conformation **III** can be obtained with only the C(4) substituent arranged axial. In **III**, the energy release due to decreasing 1,3-diaxial interactions should compensate the increased energy caused by eclipsing the C(4) substituent and the C=C double bond. Therefore, differing from the previous knowledge,[4] we assume that the stereoselection in the 5-*exo* cyclization of 2-oxahex-5-enyl radicals which are fused with the small and rigid cyclopentyl ring, as in *cis*-**7a,b**, is dictated by a pseudo equatorial arrangement of the C(3) substituent and not by the substituent at C(4).

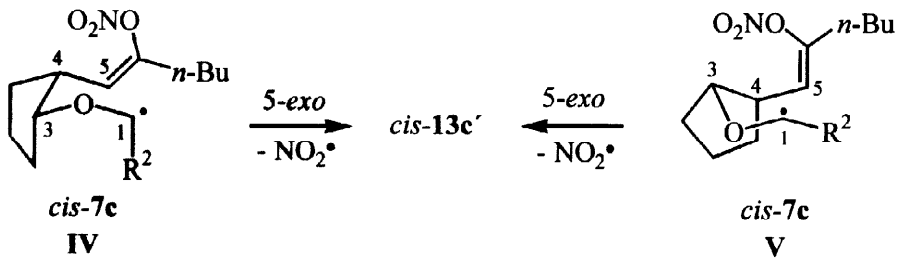
However, in addition to these steric effects we have indications that the stereoselection in 5-*exo* radical cyclizations is also significantly influenced by the stability of the 2-oxahex-5-enyl radicals. The NO_3• induced cyclization of the methoxy substituted alkynyl ether *cis*-**1c** possessing a *cis*-fused cyclopentyl ring (see Scheme 1) was the only reaction where formation of diastereoisomers was observed. Besides the major compound *cis*-**13c**, which may be formed via 5-*exo* radical cyclization of the 2-oxahex-5-enyl radical *cis*-**7c** from a conformation analog to structure **III** with a dictating C(3) substituent (R^2 = OMe; see Scheme 4), *cis*-**13c′** was obtained as minor diastereoisomer (*cis*-**13c** : *cis*-**13c′** = 2.4 : 1).[1] In *cis*-**13c′** the stereocenter at C(5) was inverted with respect to *cis*-**13c** thus resulting in a *trans* arrangement of the substituents at C(1) and C(5).[8]



cis-**13c** : *cis*-**13c′** = 2.4 : 1

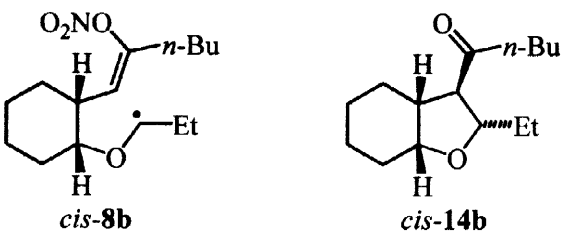
From literature it is known that 1-heteroatom substituted hex-5-enyl radicals often cyclize with a low level of *cis* stereoselectivity.[4,9-11] In the reaction of NO_3• with the alkynyl ether *cis*-**1c** the reason for competing transition state geometries which results in diastereoisomer formation may be caused by the bis-donor stabilization of the intermediate 2-oxahex-5-enyl radical *cis*-**7c** caused by two adjacent oxygen atoms. With respect to the cyclizations of the 2-oxahex-5-enyl radicals described in Scheme 2-4, the 5-*exo* radical cyclization of *cis*-**7c** is less exothermic thus resulting in a comparably late transition state in which the new bond is already formed to a significant degree. Therefore, with the methoxy group in a pseudo equatorial position like in conformation **III** (R^2 = OMe; see Scheme 4), a considerable energy penalty for eclipsing the C(1) substituent and the C=C double bond in the transition state should result.

Two different transition state geometries leading to the minor diastereoisomer *cis*-**13c′** may be discussed: 5-*exo* cyclization of the 2-oxahex-5-enyl radical *cis*-**7c** from either a chair-like conformation with the C(4) substituent pseudo equatorial (conformation **IV**) or from the inverted conformation **V** [C(3) substituent pseudo equatorial] may both be possible (Scheme 5). With respect to conformation **IV**, 1,3 diaxial interactions are avoided in conformation **V**. However, in the latter radical conformation the *anti* position of the C(4) substituent and the C=C double bond should also be energetically unfavored. Therefore, without ab initio calculations a probable transition state geometry may not be assigned in this case.

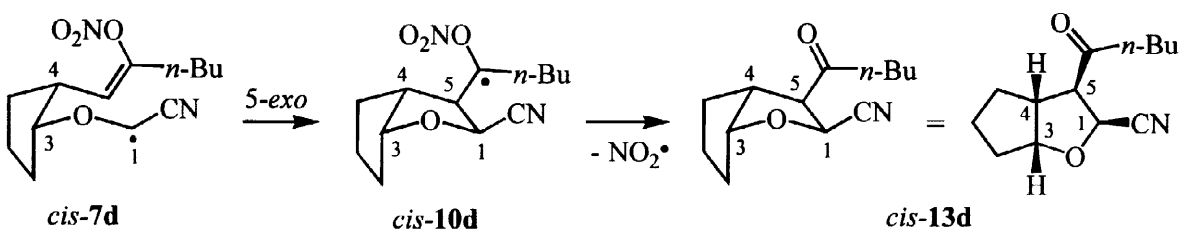


Scheme 5

A similar *trans* substitution at the newly formed bond was also observed in the annellated tetrahydrofuran *cis*-**14b**. This compound was obtained as single diastereoisomer by treating the *cis*-3,4-cyclohexyl fused alkynyl ether *cis*-**2b** with $NO_3^•$ (see Scheme 1).[1] Unlike the methoxy substituted 2-oxahex-5-enyl radical *cis*-**7c**, the unpaired electron in *cis*-**8b** is not bis-donor stabilized by a second oxygen atom. We have no obvious explanation for this unexpected behaviour yet.



The $NO_3^•$ induced radical cyclization of the cyano substituted alkynyl ether *cis*-**1d** (see Scheme 1) proceeded with high diastereoselectivity to yield the annellated tetrahydrofuran *cis*-**13d** as single diastereoisomer with the substituents at C(1) and C(5) both arranged *cis* but *anti* to the fused cyclopentyl ring (Scheme 6).[1] Therefore, the stereochemistry in *cis*-**13d** was identical to that observed in the annellated tetrahydrofurans *cis*-**14e** and *cis*-**15b**, respectively (see Scheme 3). Hence, the stereoselection in the 5-*exo* cyclization of the 2-oxahex-5-enyl radical *cis*-**7d** may be explained in an analogue way according to the Beckwith-Houk model by assuming a chair-like transition state with the C(4) substituent arranged pseudo equatorial.



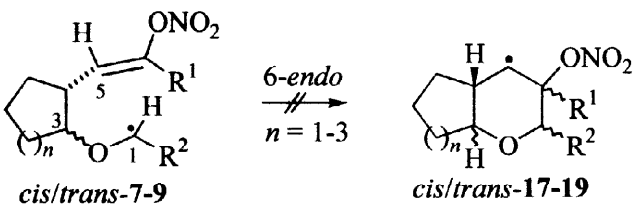
Scheme 6

Because of the stabilization of the unpaired electron in *cis*-**7d** due to capto-dative substitution, which is larger than the stabilization caused by bis-donor substitution (as in *cis*-**7c**),[6] the 5-*exo* cyclization of the 2-oxahex-5-enyl radical *cis*-**7d** to *cis*-**10d** likely is the least exothermic of all radical cyclizations under investigation.

Therefore, a late transition state is also expected in which an axial arrangement of the cyano substituent should be preferred to avoid eclipsing with the C=C double bond. Despite of that, the observed *cis* substitution at the newly formed bond in the annellated tetrahydrofuran ***cis*-13d** may be explained by the comparably low steric demand for the linear cyano group which should not cause any significant steric hindrance with the C=C double bond in the transition state of the radical cyclization. In addition, an axial position of the cyano substituent would be energetically disfavored due to strong 1,3-diaxial interactions.

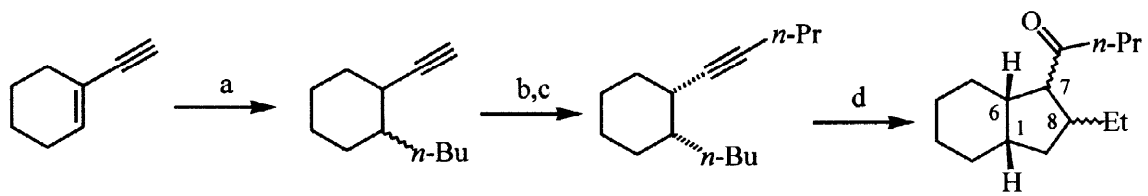
The reason for the obvious inconsistency between the transition state geometries which were assigned for the 5-*exo* cyclization leading to ***cis*-13a-c** on the one hand (Scheme 4) and to ***cis*-13d** on the other hand (Scheme 6) is not clear. Since a cyclopentyl ring is fused with the 2-oxahex-5-enyl chain in all of these cases, this finding suggests that also the stability of the 2-oxahex-5-enyl radicals has a significant influence on the transition state geometry of the cyclization. Stablization effects due to electronic interactions are not considered in the Beckwith-Houk model. For a proper understanding of the influence of electronic factors on the transition states, ab initio calculations seem therefore to be indispensable. These calculations should also take a possible additional stabilization caused by the nitrate substituent at the C=C double bond through its unpaired electrons into account.

Stabilization of hex-5-enyl radicals generelly leads to an increased reversibility of the 5-*exo* radical cyclization and to a preferred formation of the thermodynamically more stable 6-*endo* cyclization products.[4,6] So far, we have no indication for formation of tetrahydropyranes by the $NO_3^{\bullet}$ induced radical cyclization of the alkynyl ethers ***cis/trans*-1-3** through a 6-*endo* pathway. Besides the fact that no $NO_2^{\bullet}$ cleavage would be possible in the secondary radicals ***cis/trans*-17-19** obtained after a 6-*endo* radical cyclization, these radicals are expected to be energetically disfavored with respect to the tertiary radicals ***cis/trans*-10-12** (see Scheme 1). The latter radicals are, in addition, also stabilized by an adjacent oxygen atom from the nitrate substituent.



cis/trans-**7-9** *cis/trans*-**17-19**

To analyze the influence of the oxygen atom in the hex-5-enyl chain on the stereoselectivity of the 5-*exo* cyclizations described so far, the *cis*-3,4-cyclohexyl fused, oxygen-free alkyne ***cis*-22** was synthesized from the enyne **20**[12] in two steps (see Experimental).



20 *cis/trans*-**21** 4:1 *cis*-**22** 1,6-*cis*-**23a** 1,6-*cis*-**23b** [§] 2:1

a: *n*-BuLi, 32%; b: Chromatographical separation; c: *n*-PrBr, *n*-BuLi, 68%; d: $NO_3^{\bullet}$, 9%.

[§] The stereochemistry at C-7 and C-8 could not be established.

Interestingly, the radical cyclization of *cis*-**22** induced by addition of $NO_3^\bullet$ to the C≡C triple bond leads to formation of a 2:1 diastereomeric mixture of 1,6-*cis*-**23a** and 1,6-*cis*-**23b** in 9% total yield.[13,14] Since both diasteroisomers could not be separated by column chromatography the respective stereochemistry at C(7) and C(8) in these compounds could not be assigned.

Conclusion

These results show that the stereoselection in the polysubstituted 2-oxahex-5-enyl radicals *cis/trans*-**7-9** is very complex. The stereoselection is dependent not only on the stereochemistry of the ring fusion but also on the size of the cycloalkyl ring as well as on the stability of the 2-oxahex-5-enyl radicals *cis/trans*-**7-9**.

Since all substituents work in concert in the reaction of $NO_3^\bullet$ with the *trans*-3,4-cycloalkyl fused alkynyl ethers *trans*-**2b,e** and *trans*-**3b**, the observed stereochemistry in the reaction products *trans*-**14b,e** and *trans*-**15b**, respectively, could be successfully explained by application of the Beckwith-Houk model.

With substituents working in opposition, as shown in the reactions of the *cis*-3,4-cycloalkyl fused alkynyl ethers *cis*-**1-3**, the stereoselection in the 5-*exo* radical cyclization is significantly more complex. However, in the case of alkynyl ethers fused with a relatively large cycloalkyl ring (e.g. a cyclohexyl or a cycloheptyl ring in *cis*-**2e** and *cis*-**3b**, respectively) the stereoselection is dictated according to the Beckwith-Houk model by a pseudo equatorial C(4) substituent. In contrast, in the case of the more rigid cyclopentyl ring (as in *cis*-**1a,b**) a dictation by a pseudo equatorial C(3) substituent is proposed for geometrical reasons.

The additional influence of electronic factors on the transition state geometry of the 5-*exo* radical cyclization becomes obvious by comparing the non-diastereoselective $NO_3^\bullet$ induced cyclization of the oxygen-free alkyne *cis*-**22** with the diastereoselective reaction of the alkynyl ethers *cis/trans*-**1-3** (except the reaction of the methoxy substituted compound *cis*-**1c**). These results show that the radical stabilization by the α-oxygen in the hex-5-enyl chain of the radicals *cis/trans*-**7-9** leads to a clear preference of one transition state geometry. Bis-donor or capto-dative stabilization of the hex-5-enyl radical results in dramatic changes of the transition state geometry which cannot be explained with the Beckwith-Houk model.

In any case, for a proper understanding of the stereoselection in cyclizations involving stabilized radicals, additional ab inito calculations are necessary.

Acknowledgment

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Experimental

*General information, preparation of the alkynyl ethers cis/trans-**1-3** and $NO_3^\bullet$ induced cyclization to cis/trans-**13-15**:* see ref.[1].

(±)-*cis*-Butyl-2-(pent-1-ynyl)-cyclohexane (*cis*-22)

*a) (±)-cis- and- trans-Butyl-2-ethynyl cyclohexane (cis-**21**, trans-**21**):* Under nitrogen 4.75 g (44.3 mmol) 1-ethynyl cyclohexene (**20**)[12] were added dropwise at 40°C to a solution of 25 mL anhydrous diethyl ether and 87.0 mL (133 mmol) *n*-butyl lithium (1.6N in *n*-hexane). The mixture was stirred for 25 h at 35°C and then poured under cooling into a saturated aqueous ammonium chloride solution. After extraction with diethyl ether

the combined organic fractions were dried and concentrated in vacuo. The residue was distilled to yield 2.38 g (14.1 mmol, 32%) (lit.[15] 40%) of *cis/trans*-**21** as colorless liquid at 85-87°C/15 torr (lit.[15] 97°C/20 torr). The diastereomeric mixture could be separated by column chromatography (SiO_2, *n*-pentane).

Diastereomeric mixture: IR (film): $\tilde{\nu}$ = 3310 (ν ≡C-H), 2929, 2856 (ν C-H), 2111 cm^{-1} (ν C≡C). – MS (CI); *m/z* (%) = 165 (11) [M^++H], 151 (23), 149 (7), 135 (6), 121 (12), 107 (20). – *cis*-**21**: R_f (*n*-pentane) = 0.67. – ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 2.73 (1H, m, 1-H), 2.03 (1H, d, *J* = 2.5 Hz, 2′-H), 1.84 (1H, dddt, *J* = 1.6, 3.5, 3.5, 12.8 Hz, 3-H_A), 1.70 - 1.59 and 1.52 - 1.15 (14H, 2m, 1′′-H_2 - 3′′-H_2, 1-H, 3-H_B - 6-H_2), 0.90 ppm (3H, t, *J* = 7.0 Hz, 4′′-H_3). – ^{13}C NMR ($CDCl_3$, 125.8 MHz): δ = 85.7 (d, C-1′), 70.4 (d, C-2′), 39.8 (d, C-2), 34.2 (t), 32.0 (d, C-1), 31.4 (t), 29.1 (t), 28.5 (t), 26.0 (t), 22.9 (t), 22.0 (t), 14.1 ppm (q, C-4′′). – *trans*-**21**: R_f (*n*-pentane) = 0.52. – ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 2.06 (1H, d, *J* = 2.3 Hz, 2′-H), 2.02 - 1.93 (2H, m), 1.84 (1H, ddddd, *J* = 1.8, 3.5, 3.5, 3.5, 13.2 Hz), 1.79 (1H, m), 1.72 - 1.66 (2H, m), 1.44 - 1.12 (9H, m), 0.89 (1H, m), 0.90 ppm (3H, t, *J* = 7.0 Hz, 4′′-H_3). – ^{13}C NMR ($CDCl_3$, 125.8 MHz): δ = 88.5 (s, C-1′), 68.6 (d, C-2′), 41.9 (d, C-2), 35.5 (d, C-1), 34.2 (t), 33.3 (t), 31.0 (t), 28.7 (t), 25.8 (2t), 23.0 (t), 14.1 ppm (q, C-4′′).

*b) (±)-cis-Butyl-2-(pent-1-ynyl)-cyclohexane (cis-***22***):* Under nitrogen 1.00 g (6.13 mmol) *cis*-**21** were dissolved in 10 mL abs. THF and 8 mL 1,3-dimethyl tetrahydro-2(1H)-pyrimidinone. At -78°C 4.0 mL (6.40 mmol) *n*-butyl lithium (1.6N in *n*-hexane) were added, the mixture stirred for 45 min at this temperature after which 5.0 mL (55 mmol) *n*-propyl bromide were added. After stirring for 1.5 h at -78°C and 18 h at room temperature, the mixture was poured into 40 mL diethyl ether/water (1:1), separated and the aqueous phase extracted three times with diethyl ether. The combined organic fractions were dried, concentrated in vacuo, and the residue was purified by column chromatography (SiO_2, *n*-pentane) to yield 859 mg (4.17 mmol, 68%, R_f = 0.70) *cis*-**22** as colorless liquid.

IR (film): $\tilde{\nu}$ = 2958, 2928, 2855 cm^{-1} (ν C-H). – ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 2.67 (1H, m, 2-H), 2.16 (2H, dt, *J* = 2.3, 6.9 Hz, 3′-H_2), 1.78 (1H, ddddd, *J* = 1.8, 3.5, 3.5, 3.5, 12.6 Hz, 6-H_A), 1.66 - 1.13 (16H, m, 16H), 0.99 (3H, t, *J* = 7.4 Hz, 5′-H_3), 0.89 ppm (3H, t, *J* = 7.1 Hz, 4′′-H_3). – ^{13}C NMR ($CDCl_3$, 125.8 MHz): δ = 82.6 (s, C-1′), 81.2 (s, C-2′), 40.3 (d, C-2), 34.4 (t), 32.1 (d, C-1), 32.0 (t), 29.1 (t), 28.7 (t), 26.2 (t), 23.0 (t), 22.9 (t), 22.1 (t), 20.9 (t, C-3′), 14.1 (q, C-4′′), 13.5 ppm (q, C-5′). – MS (70 eV); *m/z* (%) = 206 (16) [M^+], 205 (43), 191 (24), 177 (24), 163 (49), 149 (40), 139 (11). – Due to the extremely high volatility of *cis*-**22** an elemental analysis could not be performed.

Diastereomeric mixture of 1,6-*cis*-8-ethyl-7-(1-oxobutyl)-bicyclo[4.3.0]nonanes (1,6-*cis*-23a and 1,6-*cis*-23b)

504 mg (2.45 mmol) *cis*-**22** and 451 mg (6.54 mmol) lithium nitrate were electrolyzed for 6.5 h in 40 ml acetonitrile/water/diethyl ether (5:1:2) at I = 200 mA and U = 2.0-2.4 V. The undivided cell was equipped with a platin net anode, a stainless stell cathode and a silver/silver chloride/(0.1M tetraethylammonium chloride in acetonitrile) as reference ($E_0 \approx$ SCE).[1] The reaction mixture was poured into brine and extracted with diethyl ether. The combined organic fractions were dried, concentrated in vacuo and purified by column chromatography [SiO_2, *n*-pentane/diethyl ether (25:1)]. Besides several by-products, which were not analyzed, 49 mg (0.22 mmol, 9%) of the diastereoisomeric bicylo[4.3.0]nonanes 1,6-*cis*-**23a** and 1,6-*cis*-**23b** were obtained as colorless oil (R_f = 0.33), which could not be further separated. By ^{13}C NMR a 2: 1 ratio of 1,6-*cis*-**23a** and 1,6-*cis*-**23b** was determined.

1,6-*cis*-**23a** (major diastereoisomer): ^{13}C NMR ($CDCl_3$, 125.8 MHz): δ = 221.1 (s, C-1′), 53.3 (d), 47.7 (d, C-7), 42.7 (d), 39.8 (d), 37.3 (t), 33.7 (t), 28.7 (t), 23.54 (t), 23.50 (t), 22.5 (t), 21.0 (t), 20.7 (t), 14.5 (q, C-2′′), 14.3 ppm (q, C-4′). – 1,6-*cis*-**23b** (minor diastereoisomer): ^{13}C NMR ($CDCl_3$, 125.8 MHz): δ = 224.3 (s, C-1′), 51.9 (d), 49.3 (d), 47.8 (d), 38.9 (d), 32.3 (t), 31.8 (t), 29.9 (t), 28.0 (t), 26.1 (t), 22.7 (t), 21.7 (t), 19.2 (t),

14.2 (q, C-2′′), 14.1 ppm (q, C-4′). – Diastereomeric mixture: IR (film): $\tilde{\nu}$ = 2957, 2928, 2859 (ν C-H), 1736 cm^{-1} (ν C=O). – MS (CI); *m/z* (%) = 223 (11) [M^++H]. – $C_{15}H_{26}O$: calcd. 222.19836; found 222.19830 (MS).

Refencens and Notes

[#] NO_3 radicals in synthesis, part 3; for part 2 see ref.[1].

[1] Wille, U.; Lietzau, L. *Tetrahedron*, **1999**, *55*, 10119-10134.

[2] The stereochemistry of the four stereogenic centers in the cyclized products *cis/trans*-**13-15** was determined by ^{1}H NMR from NOE measurements and coupling constants, see ref.[1].

[3] The *trans*-3,4-cyclopentyl fused alkynyl ether *trans*-**1a** could not be cyclized by reaction with NO_3•. In this compound both substituents point in nearly orthogonal directions and, due to their large distance, no intramolecular 1,5-HAT is possible (Scheme 1; see also ref.[1]).

[4] A compilation and detailed discussion is given in: Curran, D.P.; Porter, N.A.; Giese, B. *Stereochemistry of Radical Reactions*; VCH: Weinheim, New York, Basel, Cambridge, Tokyo, 1996.

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[8] A subsequent inversion at C(5) in *cis*-**13c** via an enolate intermediate through the work-up and isolation procedure of the reaction mixture (see Experimental and ref.[1]) to yield the thermodynamically more stable *cis*-**13c′** can be excluded: After stirring a 2.4 : 1 mixture of *cis*-**13c** and *cis*-**13c′** with SiO_2 in *n*-pentane/diethyl ether (3:1) at room temperature over night, no change of the ratio between both diastereoisomers was observed. However, an inversion of the stereogenic center at C(5) was possible by column chromatography using alumina (L. Lietzau, *Ph.D. Thesis*, University of Kiel, in preparation).

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[13] The low yield of 1,6-*cis*-**23a,b** in the NO_3• induced cyclization of *cis*-**22** was comparable to that obtained in the reaction of NO_3• with the respective oxygen containing compounds *cis*-**2b,e**. This was obviously due to a poor interaction between both substituents at the cyclohexyl ring (see also ref.[1,3]).

[14] Formation of 1,6-*cis*-**23a** and 1,6-*cis*-**23b** may proceed through a similar mechanism as proposed in Scheme 1 for the alkynyl ethers *cis/trans*-**1-3** with the oxygen atom in the hex-5-enyl chain being replaced by a methylene group.

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