An Experimental and Computational Study on the Reactivity and Regioselectivity for the Nitrosoarene Ene Reaction: Comparison with Triazolinedione and Singlet Oxygen

Waldemar Adam, Nils Bottke,* Bernd Engels, and Oliver Krebs

Contribution from the Institut für Organische Chemie, Universität Würzburg, Am Hubland, D-97074 Würzburg, Germany

Received December 27, 2000

Abstract: The regioselectivities and the reactivities (relative rates) for the ene reaction of the enophile 4-nitronitrosobenzene (ArNO) with an extensive set of regiochemically defined acyclic and cyclic olefins have been determined. These experimental data establish that the ArNO enophile attacks the olefinic substrate along the novel *skew* trajectory, with preferred hydrogen abstraction at the corner (*twix* regioselectivity). This is in contrast to the isoelectronic species singlet oxygen ($^1O_2$), which abstracts at the higher substituted side of the double-bond (*cis* effect), and triazolindione (TAD), which undergoes the ene reaction at the more crowded end (*gem* effect). Ab initio computations (B3LYP/6-31+g*) for the ene reaction of the ArNO with 2-methyl-2-butene reveal that the steric effects between the aryl group of the enophile and the substituents of the olefin dictate the *skew* trajectory. These computations identify the aziridine *N*-oxide (**AI**) as a bona fide intermediate in this ene reaction, whose formation is usually rate-determining and, thus, irreversible along the *skew* trajectory (*twix* selectivity). The reversible generation of the **AI** becomes feasible when conformational constraints outweigh steric effects, as manifested by enhanced *twin* regioselectivity.

Introduction

Although the nitroso ene reaction already was discovered in 1965,[1] this potentially valuable preparative method for the allylic amination of olefins has received relatively little attention compared to the well-established isoelectronic singlet-oxygen ($^1O_2$)[2] and triazolinedione (TAD)[3] enophiles. Presumably the low persistence of the initially formed hydroxylamines toward in situ oxidation, disproportionation, and elimination by the nitroso enophile has curbed the interest to apply this ene reaction for synthetic purposes. These primary ene products are converted into nitroxides, nitrones, imines, amines, and azoxy compounds,[4] which not only substantially lower the yield of the hydroxylamines, but encumber their isolation. Nevertheless, electron-withdrawing groups at the nitroso functionality not only increase the enophilic reactivity, but also afford relatively persistent hydroxylamine products toward further transformation. Therefore, most subsequent work on the nitroso ene reaction has employed electron-poor enophiles, e.g., pentafluoronitrosobenzene,[5] α-chloro nitroso,[6] and acyl nitroso[7] compounds, to minimize such problems.

The mechanistic features of the nitroso ene reaction are expected to be similar to the related $^1O_2$ and TAD enophiles.[8] For these two enophiles, extensive studies on the reactivity and regioselectivities have provided a detailed picture of the pertinent transition states and intermediates. Their reactions with regioselectively labeled trisubstituted olefins have established the preferred trajectories of the enophilic attack (Figure 1). $^1O_2$ favors hydrogen abstraction on the more substituted side of the olefin (*cis* effect),[9] while TAD prefers the more substituted end (*gem* effect).[3] Mechanistically significant, we have recently discovered the new *skew* trajectory for the 4-nitronitrosobenzene (ArNO) enophile (Figure 1). Thus, acyclic[10] and cyclic trisubstituted olefins[11] react regioselectively at the substituent located on the more substituted side and more substituted end, the so-called *twix* site.[12]

One of the few in-depth mechanistic investigations of the nitroso ene reaction was performed by Greene et al. in the early

* Address correspondence to this author. E-mail: adam@chemie.uni-wuerzburg.de. Fax: +49-931-8884756.

(1) Banks, R. E.; Barlow, M. G.; Haszeldine, R. N. *J. Chem. Soc.* **1965**, 4714−4718.

(2) (a) Orfanopoulos, M.; Stratakis, M. *Tetrahedron* **2000**, *56*, 1595−1615. (b) Clennan, E. L. *Tetrahedron* **2000**, *56*, 9151−9179.

(3) (a) Ohashi, S.; Leong, K.; Matyjaszewski, K.; Butler, G. B. *J. Org. Chem.* **1980**, *45*, 3467−3471. (b) Singleton, D. A.; Hang, C. *J. Am. Chem. Soc.* **1999**, *121*, 11885−11893. (c) Adam, W.; Schwarm, M. *J. Org. Chem.* **1988**, *53*, 3129−3130.

(4) (a) Johannsen, M.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 1689−1808. (b) Knight, G. T.; Pepper, B. *Tetrahedron* **1971**, *27*, 6201−6207.

(5) Banks, R. E.; Haszeldine, R. N.; Miller, P. J. *Tetrahedron Lett.* **1970**, *50*, 4417−4418.

(6) Braun, H.; Felber, H.; Kreβe, G.; Ritter, A.; Schmidtchen, F. P.; Schneider, A. *Tetrahedron* **1991**, *47*, 3313−3328.

(7) (a) Kirby, G. W. *Chem. Soc. Rev.* **1977**, 1−25. (b) Corrie, J. E. T.; Kirby, G. W.; Mackinnon, J. W. M. *J. Chem. Soc., Perkin. Trans. 1* **1985**, 883−886. (c) Kirby, G. W.; McGuigan, H.; McLean, D. J. *J. Chem. Soc., Perkin Trans. 1* **1985**, 1961−1966. (d) Quadrelli, P.; Mella, M.; Caramella, P. *Tetrahedron Lett.* **1998**, *39*, 3233−3236. (e) Quadrelli, P.; Campari, G.; Mella, M.; Caramella, P. *Tetrahedron Lett.* **1998**, *39*, 3233−3236. (f) Adam, W.; Bottke, N.; Krebs, O.; Saha-Möller, C. R. *Eur. J. Org. Chem.* **1999**, 1963−1965.

(8) (a) Stephenson, L. M.; Grdina, M. J.; Orfanopoulos, M. *Acc. Chem. Res.* **1980**, *13*, 419−425. (b) Cheng, C. C.; Seymour, C. A.; Petty, M. A.; Greene, F. D.; Blount, J. F. *J. Org. Chem.* **1984**, *49*, 2910−2916. (c) Orfanopoulos, M.; Foote, C. S.; Smonou, I. *Tetrahedron Lett.* **1987**, *28*, 15−18.

(9) (a) Orfanopoulos, M.; Grdina, M. J.; Stephenson, L. M. *J. Am. Chem. Soc.* **1979**, *101*, 1, 275−276. (b) Schulte-Elte, K. H.; Muller, B. L.; Rautenstrauch, B. *Helv. Chim. Acta* **1978**, *61*, 2777−2783. (c) Stratakis, M.; Orfanopoulos, M.; Chen, J. S.; Foote, C. S. *Tetrahedron Lett.* **1996**, *37*, 4105−4108.

(10) Adam, W.; Bottke, N.; Krebs, O. *J. Am. Chem. Soc.* **2000**, *122*, 6791−6792.

(11) Adam, W.; Bottke, N.; Krebs, O. *Org. Lett.* **2000**, *2*, 3293−3296.

10.1021/ja004356m CCC: $20.00
Published on Web 05/15/2001

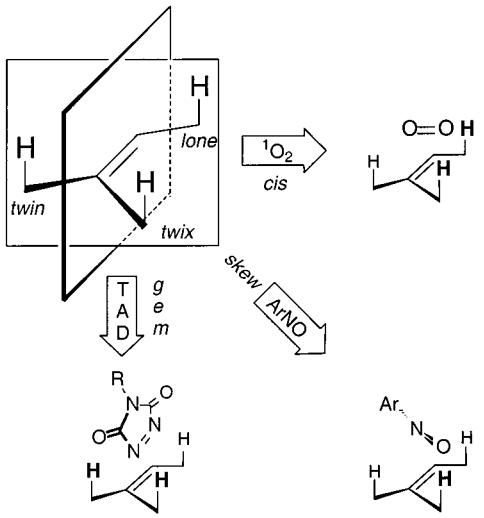


Figure 1. Regioselectivities in the ene reaction of trisubstituted olefins for the enophiles singlet oxygen ($^1O_2$), triazolinedione (TAD), and nitrosoarene (ArNO); the respective *cis*, *gem*, and *skew* hydrogen abstractions are shown.

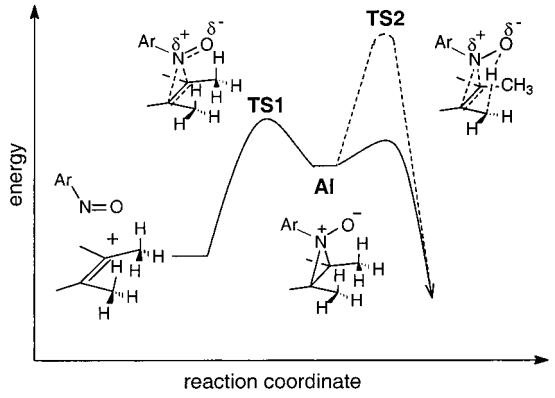


Figure 2. Energy profile of the nitrosoarene−ene reaction with tetramethylethylene; the solid trajectory represents *irreversible* and the dashed *reversible* formation of the aziridine-*N*-oxide intermediate (**AI**).

eighties.[13] In this study, the reactivities and product studies of regioselectively deuterated tetramethylethenes (TME) with pentafluoronitrosobenzene were assessed. From the observed isotope effects, this ene reaction was proposed to proceed in two steps, with the aziridine *N*-oxide as intermediate (Figure 2). The first step constitutes the slow step in the enophilic attack on the olefin, which is followed by fast abstraction of an allylic hydrogen atom in the second step. The absence of an intermolecular isotope effect between d_0- and d_{12}-TME substantiates that the latter product-forming step is not rate-determining, i.e., the solid trajectory in Figure 2 applies and the process is *irreversible*.

In our preliminary reports,[10,11] we have shown that for appropriate substrates, in which steric and conformational constraints compete, the nitrosoarene ene reaction may be *reversible*, i.e., that the dashed trajectory in Figure 2 operates. Herewith we supply the full details on this mechanistic work, which encompasses product studies, reactivities, and regioselectivities on the ene reaction of an extensive set of regioselectively labeled acyclic and cyclic trisubstituted olefins with *p*-nitronitrosobenzene (ArNO), as well as ab inito computations on the reaction profile for 2-methyl-2-butene. All these experimental and theoretical data establish that the *skew* trajectory and, consequently, the *twix* regioselectivity are general characteristics for the nitrosoarene ene reaction, provided that steric control is not counteracted by conformational constraints. Should the latter apply, the formation of the aziridine-*N*-oxide intermediate may be reversible.

Results

Product Studies. The ene reaction of *p*-nitronitrosobenzene with the olefins **1**−**6** afforded the corresponding hydroxylamines **1a,b**−**6a,b**. The olefins were used in excess, to suppress further oxidation of the primary ene products by the enophile.[14] The observed product ratios, which were determined by ^{1}H NMR spectroscopy directly on the crude reaction mixture, are given in Table 1. All olefins, except *Z*-**6**, were converted predominantly to the *twix* product; some *twin* regioisomer was observed, but no *lone* product. The *twix*:*twin* ratios for the cyclic and acyclic substrates vary from a moderate selectivity for *Z*-**1** (70:30, entry 2) to complete *twix* abstraction for *E*-**1**, **4**, and *E*-**6** (>95:5, entries 1, 6, and 9). Only *Z*-**1**-methylcyclooctene (*Z*-**6**) does not comply with the *twix* regioselectivity, since the *twin* product was obtained in moderate selectivity.

Compared to the isoelectronic enophiles singlet oxygen ($^1O_2$) and triazolinedione (TAD), *p*-nitronitrosobenzene (ArNO) gives the most regioselective ene reaction (Figure 3). For all three enophiles, the *E*-configured[15] *twix* product of the *Z*-**1** alkene is formed exclusively. In the case of the *E*-**1** diastereomer, only PTAD abstracts at the *twin* position, to afford again exclusively the *E*-configured ene product. The mechanistically important general fact about the regioselectivities of these three enophiles is that ArNO gives mainly the *twix* product (*skew* effect), $^1O_2$ abstracts primarily at the higher substituted side of the double bond (*cis* effect)[9] to result *in twix* and *lone* regioisomers, and TAD reacts at the more substituted end of the double bond (*gem* effect)[3] to give the *twix* and *twin* products (Figure 1). A pertinent exception is the *trans*-cyclooctene *E*-**6**, which leads essentially completely to the *twix* regioisomer for all three enophiles.

The reactivity of allylically functionalized olefins versus simple alkenes was tested in terms of intramolecular double-bond regioselectivities for the geraniol substrates and nerol **7**−**9**. The data of the product studies are summarized in Table 2. At conversions less than 50%, the regioisomeric ene products **7a**−**9a** and **7b**−**9b** were formed in high yields. The allylic alcohols geraniol (*E*-**7**) and nerol (*Z*-**7**) afforded a minor amount of the 2,3-adduct **7b** (entries 1 and 4), while the geraniol derivatives *E*-**8** and *E*-**9** selectively reacted at the 6,7 double bond, to afford only the regioisomers **8a** and **9a** (entries 2 and 3). It is conspicuous that the allylically oxy-functionalized 2,3 double bond is significantly less reactive than the unfunctionalized 6,7 double bond, although both are trisubstituted. Nevertheless, the free hydroxy group in geraniol (*E*-**7**) and nerol (*Z*-**7**) promotes some abstraction at the functionalized 2,3 site (hydroxy-group directivity[14]), which is completely suppressed by capping the

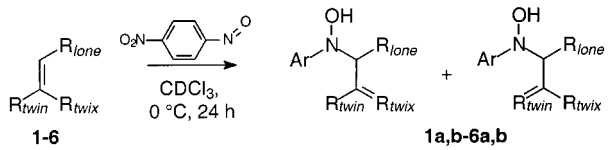
(12) The regiochemical differentiation of the three alkyl groups in trisubstituted olefins has to date not been well defined. For this reason and the ease of referral in the text, we suggest the following codification (see Figure 1): Attention is focused on the central alkyl substitutent, which is defined as the *twixt* group (R_{twix}, for simplification the last "t" has been dropped); "twixt" comes from old English and means "between", i.e., R_{twix} is between a geminal and vicinal alkyl group. The other geminal substitutent is then designated as the *twin* group (R_{twin}), and the remaining vicinal substituent as the *lone* one (R_{lone}).

(13) (a) Seymour, C. A.; Greene F. D. *J. Org. Chem.* **1982**, *47*, 5226−5227. (b) Greene, F. D. In *Stereochemistry and Reactivity of Systems Containing π-Electrons*; Watson, W. H., Ed.; Verlag Chemie Int.: Deersfield Beach, FL, 1983; pp 197−240.

(14) Adam, W.; Bottke, N. *J. Am. Chem. Soc.* **2000**, *122*, 9846−9847.

(15) *E*-configuration for the ArNO ene product was determined by a 2D-NOESY experiment.

Table 1. Regioselectivities (*twix*:*twin*) in the Ene Reaction of *p*-Nitronitrosonezene with a Variety of Olefinic Substrates



1-6 1a,b-6a,b

	olefin (equiv)		R_{twin}	R_{lone}	R_{twix}	convn[a,b] [%]	mb[a,c] [%]	regioselectivity[a] *twix*		*twin*	
1	*E*-**1**	(2.0)	C_2H_5	CH_3	CH_3	69	80	>95	(**1a**)	<5	(**1b**)
2	*Z*-**1**	(2.0)	CH_3	CH_3	C_2H_5	43	87	70	(**1b**)[d]	30	(**1a**)
3	*E*-**2**	(1.5)	CD_3	CH_3	CH_3	71	83	88	(**2a**)	12	(**2b**)
4	*Z*-**2**	(1.5)	CH_3	CH_3	CD_3	72	77	81	(**2b**)	19	(**2a**)
5	**3**	(2.0)	CH_3	$-(CH_2)_3-$		48	88	82	(**3a**)	18	(**3b**)
6	**4**	(2.0)	CH_3	$-(CH_2)_4-$		44	82	>95	(**4a**)	<5	(**4b**)
7	**5**	(2.0)	CH_3	$-(CH_2)_5-$		70	85	91	(**5a**)	9	(**5b**)
8	*Z*-**6**	(2.0)	CH_3	$-(CH_2)_6-$		52	88	31	(**6a**)	69	(**6b**)
9	*E*-**6**	(1.0)	$-(CH_2)_6-$		CH_3	>95	75	>95	(**6b**)	< 5	(**6a**)

[a] Determined by ^{1}H NMR spectroscopy, error ±5% of the stated value. [b] Based on 100% conversion of olefin. [c] Mass balance. [d] The product is *E* configured, which was determined by NOE spectroscopy.

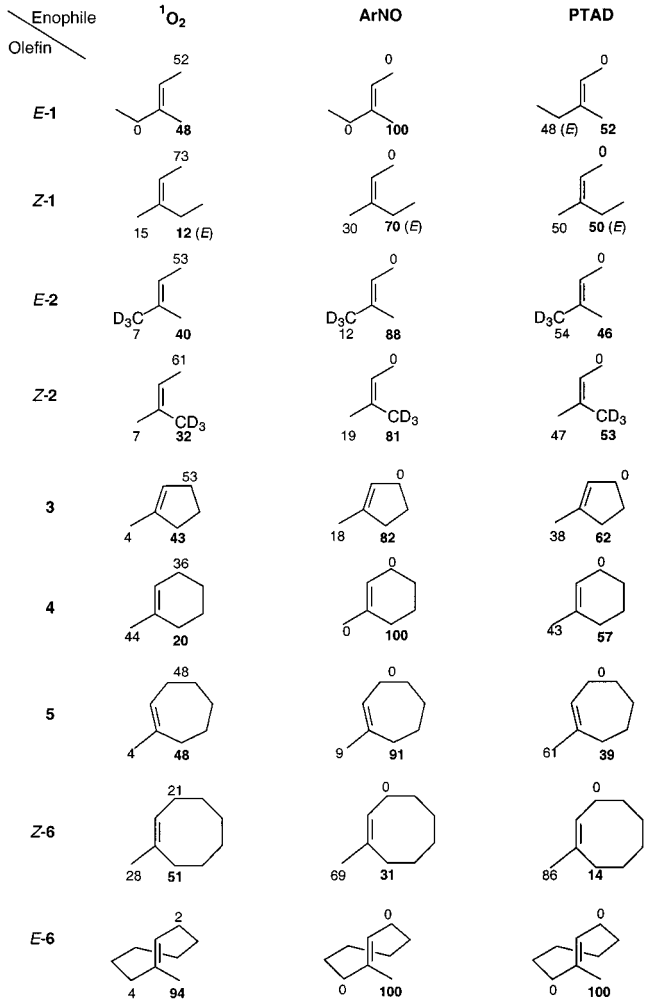
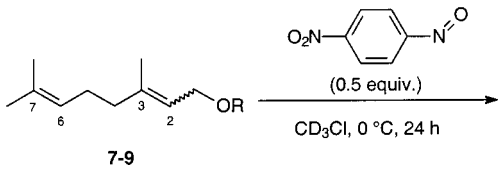


Figure 3. Regioselectivities in the ene reaction of the enophiles singlet oxygen, nitrosoarene, and PTAD with acyclic and cyclic olefins

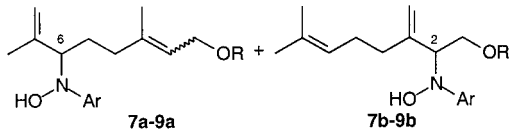
alcohol functionality by methylation (ether *E*-**8**) or acetylation (ester *E*-**8**). It is noteworthy that for nerol (*Z*-**7**) the observed 2,3-adduct **7b** derives from predominant *twin* abstraction rather than the usual *twix* reactivity, as observed for the geraniol (*E*-**7**).

Kinetic Studies. To determine experimentally the influence of the substitution pattern on the reactivity of the double bond,

Table 2. Product Data for the Ene Reaction of *p*-Nitronitrosobenzene with Geraniol (*E*-**7**), Its Derivatives **8** and **9**, and Nerol (*Z*-**7**)



7-9



7a-9a **7b-9b**

entry	olefin	R	convn[a,b] [%]	mb[a,b] [%]	regioselectivity[b] 6,7		:	2,3	
1	*E*-**7**	H	39	92	77	(**7a**)	:	23	(**7b**)[c]
2	*E*-**8**	Me	41	88	>95	(**8a**)	:	<5	(**8b**)
3	*E*-**9**	Ac	44	88	>95	(**9a**)	:	<5	(**9b**)
4	*Z*-**7**	H	27	>95	90	(**7a**)[d]	:	10	(**7b**)[e]

[a] Conversion and mass balance (mb) relative to the olefin. [b] Determined by ^{1}H NMR spectroscopy, error ±5% of the stated value. [c] Corresponds to *twix* abstraction. [d] Only the ***Z*** isomer was detected. [e] Corresponds to *twin* abstraction.

we measured the relative reaction rates by means of intermolecular competition experiments of the acyclic and cyclic alkenes in Table 1, as well as a variety of *lone*-substituted 2-methyl-2-butenes. The parent 2-methyl-2-butene was used as reference substrate ($k_{rel} = 1.00$). Table 3 contains the relative rates of the nitrosoarene ene reactions and, as far as available for comparison, also the relative rates for singlet oxygen[16] and phenyltriazolinedione (PTAD).[8b,17] 1-Methylcyclopentene (**3**) and 1-methylcycloheptene (**5**) have not been included in Table 3; the former is too unreactive to obtain reliable relative rate data through the competition experimentand the latter [k_{rel}(ArNO) = 0.41, $k_{rel}(^1O_2) = 1.00$, and k_{rel}(PTAD) not determined] provides no further mechanistic insight.

The data in Table 3 disclose that the nitroso ene reactivity differs significantly for substitution at the *twix*, *twin*, and *lone*

(16) (a) Monroe, B. M. *J. Am. Chem. Soc.* **1981**, *103*, 7253−7256. (b) Monroe, B. M. *J. Phys. Chem.* **1978**, *82*, 15−18.

(17) Ohashi, S.; Butler, G. B. *J. Org. Chem.* **1980**, *45*, 3472−3476.

Table 3. Relative Rate Constants (k_{rel}) for the Ene Reaction of the Enophiles Singlet Oxygen, PTAD, and *p*-Nitronitrosobenzene with Trisubstituted Olefins

entry	olefin		ArNO	$^1O_2$	PTAD
1		**2**	1.00[a]	1.00[a]	1.00[a]
2		*E*-**1**	0.47	0.85	-[b]
3			1.41	0.83	0.02
4			0.53	-[b]	-[b]
5			0.32	-[b]	-[b]
6			0.47	-[b]	-[b]
7			0.07	-[b]	-[b]
8			0.08	-[b]	-[b]
9		*Z*-**1**	0.34	0.65	-[b]
10		**4**	0.02	0.16	0.08
11		*Z*-**6**	0.32	0.23	-[b]
12		*E*-**6**	> 170	-[b]	-[b]

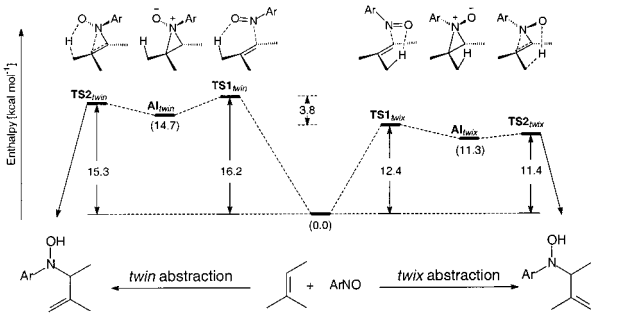
[a] Reference substrate with $k_{rel} = 1.00$. [b] Not determined.

positions. An ethyl group at the *twix* or the *twin* position lowers the relative rates of hydrogen abstraction (entries 2 and 9), while an ethyl group at the *lone* site even accelerates the reaction rate (entry 3). Only bulky substituents such as the tolyl group (entry 4), and more effectively the *tert*-butyl group (entry 5), decrease the reactivity. In comparison, the substituent effect for the singlet-oxygen ene reaction is less pronounced: a *twix* ethyl group (entry 9) lowers the relative rate more than *lone* and *twin* substitution (entries 2 and 3). For PTAD, the available data are too fragmentary to make any generalizations, but an ethyl group at the *lone* site lowers the ene reactivity dramatically (entry 3).

For the *lone*-functionalized olefins 3-methyl-2-buten-1-ol and its methyl ether and acetate derivatives, the effect on the reactivity is more pronounced. While for the allylic alcohol the relative rate is about half that of 2-methyl-2-butene (entry 1), its ether and ester derivatives are less than one tenth as reactive (entries 7 and 8). Unfortunately, no kinetic data are available for $^1O_2$ and PTAD with these olefins.

For the cyclic substrates, the nitrosoarene ene reactivity shows a strong dependence on ring size. The *cis*-configured cycloalkenes are less reactive than the acyclic 2-methyl-2-butene (entries 10 and 11). Most impressive is the very low ene reactivity of the *cis*-configured 1-methylcyclohexene (entry 10) and the very high reactivity of the *trans*-configured *E*-1-methylcyclooctene (entry 12). For the latter, only a lower limit of >170 could be estimated, because its reaction rate with ArNO was too fast to determine accurately.

Computational Studies. Ab initio molecular orbital calculations were performed with the GAUSSIAN 98 system of programs.[18] The Becke three-parameter hybrid functional,[19,20] combined with the Lee, Yang, and Parr (LYP) correlation functional,[21] denoted B3LYP,[22] was employed in the density-functional-theory (DFT) calculations. The geometries were optimized,[23] initially with the 6-31g* and then with the 6-31+g* basis set. The stationary points on the potential energy surfaces were characterized by calculation of the vibrational frequencies at the B3LYP/6-31+g* level. Test calculations by employing unrestricted wave functions proved the restricted ones to be stable.



	TS1 ΔH	TS1 ΔS	TS1 ν	AI ΔH	TS2 ΔH	TS2 ΔS	TS2 ν	ene product ΔH
twix	12.4	-50.6	-193.7	11.3	11.4	-2.9	-847.5	-9.2
twin	16.2	-48.2	-319.3	14.7	15.3	-1.9	-784.7	-9.2[a]
lone[b]	12.4	-50.6	-193.7	11.3	18.2	-6.2	-822.7	-2.4

a) The *twix* and *twin* ene products are rotamers. b) The *lone* pathway go through the same **TS1** and **AI** as the *twix*.

Figure 4. The computed (B3LYP/6-31+g*) energy profile with the enthalpies ΔH (kcal/mol), entropies (cal/(mol·K)), and frequencies υ (cm^{-1}) for the transition states **TS1** and **TS2**, the intermediates **AI**, and the ene products of the ene reaction between *p*-nitronitrosobenzol and 2-methyl-2-butene.

The energy profile of the ene reaction between 2-methyl-2-butene (**2**) and *p*-nitronitrosobenzene was computed (B3LYP/6-31+g*) by assuming a two-step mechanism with a three-centered intermediate. We located the two energy minima for the aziridine-*N*-oxide intermediates $\mathbf{AI}_{twix}$ and $\mathbf{AI}_{twin}$ as well as the five transition structures $\mathbf{TS1}_{twix}$, $\mathbf{TS1}_{twin}$, $\mathbf{TS2}_{twix}$, $\mathbf{TS2}_{twin}$, and $\mathbf{TS2}_{lone}$ (Figures 4 and 5). The initial approach of the enophile toward the olefin was found to occur by a side-on attack (*skew* effect) of the nitroso functionality. For the unsymmetric substrate, this leads to two different trajectories, which are represented by the two diastereomeric reaction pathways for *twix* and *twin* abstraction along **TS1** → **AI** → **TS2**. In both trajectories, the first step determines the rate (12.4 kcal/

(18) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Baboul, A. G.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A.; *Gaussian 98*, Revision A.7; Gaussian, Inc.: Pittsburgh, PA, 1998.
(19) Becke, A. D. *Phys. Rev. A* **1988**, *39*, 3098−3100.
(20) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648−5652.
(21) Lee, G.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785−789.
(22) Stephens, P. J.; Devlin, F. J.; Chabalowski, C. F.; Frisch, M. J. *J. Phys. Chem.* **1994**, *98*, 11623−11627.
(23) (a) Schlegel, H. B. *J. Comput. Chem.* **1982**, *3*, 214−218. (b) Schlegel, H. B. *Adv. Chem. Phys.* **1987**, *67*, 249−286. (c) Schlegel, H. B. In *Modern Electronic Structure Theory*; Yarkony, D. R., Ed.; World Scientific: Singapore, 1995; p 459.

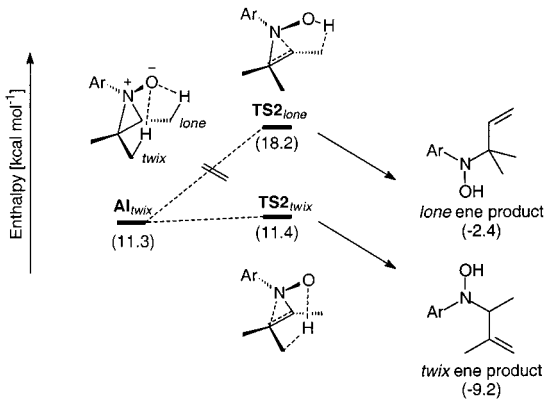


Figure 5. Computed (B3LYP/6-31+g*) enthalpies of the **AI**$_{twix}$ intermediate and transition states **TS2**$_{twix}$ and **TS2**$_{lone}$ for the ene reaction of nitrosoarenes with trisubstituted alkenes.

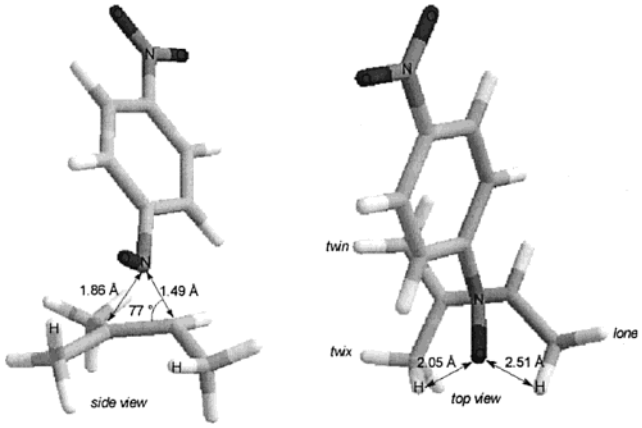


Figure 6. Side- and top-view projections of the computed (B3LYP/6-31+g*) transition structure **TS1**$_{twix}$ for the ene reaction between *p*-nitronitrosobenzene and 2-methyl-2-butene.

mol for **TS1**$_{twix}$ versus 11.4 kcal/mol for **TS2**$_{twix}$, cf. Figure 4), but the calculated energy-value differences fall within a narrow range of ≤1.1 kcal/mol. Most important, the calculations reveal that **TS1**$_{twix}$ is favored by 3.8 kcal/mol over **TS1**$_{twin}$; therefore, they predict the *twix* abstraction to be the major pathway.

Although experimentally not as yet observed, we also computed the hypothetical hydrogen-atom abstraction from the *lone* position of the olefin. By starting from the aziridine-*N*-oxide **AI**$_{twix}$, the **TS2**$_{lone}$ represents the transition structure for the *lone* ene product and is 6.8 kcal/mol higher in energy than the favored competing transition state **TS2**$_{twix}$ (Figure 5). From the experimental and computational results it may be concluded that **TS1**$_{twix}$ represents the preferred transition structure of the nitrosoarene ene reaction and provides a rationalization for the dominant *twix* abstraction (Figure 6). The nitroso enophile attacks the double bond along the *skew* trajectory side-on at the less substituted carbon atom (C−N = 1.49 Å). The bulky aryl group lies on the side with the *twin* substituent, while the small oxygen atom points in the direction of the *twix* and *lone* substituents. The *N*-oxide functionality is closer to the *twix* (O−H$_{twix}$ = 2.05 Å) than the *lone* (O−H$_{lone}$ = 2.51 Å) hydrogen atom.

Discussion

The above results provide compelling evidence that the regioselectivities in the ene reactions of *p*-nitronitrosobenzene with trisubstituted olefins are governed by a combination of steric repulsions and conformational constraints. Both effects act on the reaction at different stages of the two-step mechanism (Figure 2), of which the first one is the kinetic step and the second the product-forming one.

In the initial attack of the enophile, the nitrosoarene approaches the olefin side-on with the large aryl substituent on the less substituted side of the trisubstituted double bond (Figure 1). In this first step, the *skew* trajectory is favored for steric reasons and terminates in the irreversible formation of the *twix* aziridine-*N*-oxide intermediate. Therefore, for 2-methyl-2-butene (**2**), the reactivity and the *twix* preference is determined in this first step, because the activation barrier for the second, the hydrogen abstracting step, is lower in energy. When the *twix* position is substituted, then conformational constraints hinder hydrogen abstraction and increase the energy barrier of the second step. For *Z*-1-methylcyclooctene (*Z*-**6**), the conformational impediment may obstruct *twix* abstraction to such an extent that the aziridine-*N*-oxide intermediate is formed reversibly (the second step higher in energy, see Figure 2) and *twin* abstraction becomes competitive.

The following features about the nitrosoarene ene reaction are based on the computational and experimental facts collected in Figure 4 and Tables 1−3, and shall now be scrutinized in terms of the two-step mechanism (Figures 2 and 4):

(a) Steric interactions between the ArNO enophile and the substrate impose the skew trajectory. The computational model mediates a detailed picture of the pertinent mechanism (cf. Figure 4). The ene reaction proceeds on two different pathways, one leading to the *twix* (*skew* trajectory), the other to the *twin* product. The key step in both pathways is the irreversible formation of the aziridine-*N*-oxide intermediates **AI**$_{twix}$ and **AI**$_{twin}$ through the rate-determining transition states **TS1**$_{twix}$ and **TS1**$_{twin}$. Thus, once these intermediates have been formed, they convert to the corresponding ene products and the *twix:twin* ratio is decided in the initial attack (first step). Therefore, the energy gap between **TS1**$_{twix}$ and **TS1**$_{twin}$ determines the regioselectivity.

A closer look at the transition structure **TS1**$_{twix}$ reveals why the *skew* trajectory is favored for the 2-methyl-2-butene (Figure 6). The steric imposition of the two sides are significantly different for the trisubstituted double bond. In this arrangement, the small oxygen fits between the two methyl groups on the more substituted side, while the bulky aryl group lies on the less substituted side. Furthermore, to minimize the steric interactions, the aryl ring is twisted and pushed away from the *twin* methyl group (see side view) such that the nitroso oxygen atom is closer to the *twix* position (see top view) and *twix* abstraction is favored (*skew* effect).

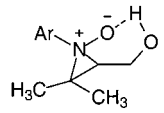
In the diastereomeric *twin* transition state **TS1**$_{twin}$, the small nitroso oxygen atom must point toward the singly substituted side of the double bond and as a consequence, the aryl group is forced to interact with the two methyl groups on the more substituted side. This sterically more demanding *twin* attack is disfavored by 3.8 kcal/mol in energy compared to the *twix* attack (Figure 4). Although this calculated energy difference (gas phase) appears to be overestimated, because the theoretical *twix:twin* product ratio would be >99:1 versus the experimental ratio of 85:15 (average value of the two deuterated 2-methyl-2-butenes *E,Z*-**2**, Figure 3), our computations (Figure 4) are in accord with the favored *skew* trajectory.

The lack of *lone* abstraction may also be satisfactorily explained by our computations (Figure 5). Such hypothetical *lone* abstraction would have to compete with *twix* abstraction *after* the **AI**$_{twix}$ intermediary is formed, that is, in the second product-determining step. Again, the relative energies of the **TS2**$_{twix}$ and **TS2**$_{lone}$ structures are controlled by steric factors.

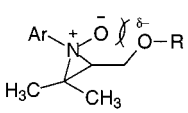
During the *lone* hydrogen abstraction, an unfavorable steric repulsion builds up between the *twin* methyl group of the substrate and the aryl substituent of the enophile, while for the preferred *twix* abstraction the aryl group is directed toward the small olefinic hydrogen atom. The energy difference between these two options has been computed to amount to 6.8 kcal/mol (Figure 5) and, consequently, exclusively *twix* abstraction is observed. Additionally, the preferred formation of the *twix* product follows also from opening of the more substituted C−N bond in the **AI**$_{twix}$ intermediate, which is expectedly weaker.

(b) Steric interactions between the enophile and the substituents in acyclic substrates control the reactivity. The relative reaction rate differs significantly depending on whether the substituent is located at the *lone*, *twin*, or *twix* position (Table 3). In this context, Figure 6 reveals that for **TS1**$_{twix}$ the twix and *lone* substituents are more remote from the sterically demanding aryl group of the enophile than the *twin* substituent. Therefore, the *twin* position is more prone to steric hindrance. By increasing the methyl group to the ethyl group, substrate *E*-**1** reacts only half as fast as 2-methyl-2-butene **2**, the reference compound (entries 1 and 2). On the opposite side, the nitroso oxygen atom is closer to the *twix* (2.05 Å) than to the *lone* (2.51 Å) position. Thus, it is expected that *lone* substitution should only affect slightly the reactivity; in fact, a *lone* ethyl group (entry 3) even accelerates the reaction by ca. 50% compared to the reference substrate (entry 1), probably by increasing the nucleophilicity of the double bond (+*I* effect). However, a decrease of the rate is evident for the bulky *p*-tolyl (entry 4) and *tert*-butyl (entry 5) groups. These substituents are large enough to reduce the space for a proper alignment of the enophile even in the less hindered **TS1**$_{twix}$. For a **TS1**$_{twin}$ arrangement, the steric interactions should be even more pronounced, but the deuterium-labeled substrate was not available to differentiate between the *twix* and *twin* reactivity.

(c) Hydrogen bonding between the substrate and the enophile increases the reactivity. The reactivity of 3-methyl-2-butene-1-ol, in which the *lone* position is a hydroxymethyl group, is reduced to 50% compared to the reference substrate **2** (entries 1 and 6). Since no steric effects are at work [as stated in point *b*, the *lone* ethyl substrate reacts even three times faster (entry 3) and should be comparable in steric demand to a hydroxymethyl group], presumably the lower reactivity is due to the decreased nucleophilicity of the π bond by the inductive effect (−*I*) of the hydroxy group. Nevertheless, compared to its methyl ether and acetate derivatives (entries 7 and 8), the allylic alcohol (entry 6) reacts about five times faster with the nitrosoarene. This substantial rate enhancement for the allylic alcohol may be accounted for in terms of hydrogen bonding, as shown in structure **A**. The dipolar aziridine-*N*-oxide is stabilized by



A

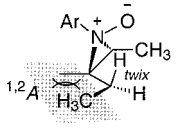


B

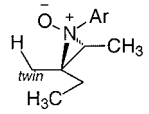
hydrogen bonding between the hydroxy functionality and the nitroso oxygen atom. In the methyl ether and acetate derivatives, the hydroxy functionality is capped and, therefore, such stabilization by hydrogen bonding is not possible (structure **B**). On the contrary, these intermediates are even destabilized by electronic repulsion between the negatively charged nitroso oxygen atom and the allylic oxygen functionality. Such hydrogen-bonding effects have been amply demonstrated to operate in the control of diastereoselectivity for the singlet-oxygen ene reaction.[24]

A similar situation is exhibited by the product studies (Table 2) for geraniol (*E*-**7**), its derivatives **8** and **9**, and nerol (*Z*-**7**), which reflect intramolecular double-bond reactivities. The attack of the nitrosoarene enophile takes place predominantly at the unfunctionalized 6,7 double bond for all substrates; however, when hydrogen bonding operates as in geraniol (*E*-**7**) and nerol (*Z*-**7**), significant amounts of the 2,3 adducts are formed (entries 1 and 4). Again, in the methyl ether **8** and acetate **9**, the hydroxy group is capped and the ene reaction takes place exclusively at the unfunctionalized 6,7 double bond (entries 2 and 3).

(d) Conformational constraints influence the reactivity. From the computed **TS1**$_{twix}$ transition structure (Figure 6), we anticipate only a moderate influence of *twix* substitution on the reactivity. Along the *skew* trajectory, the small oxygen atom of the nitroso functionality points closer to the *twix* than to the *lone* position due to the steric repulsion between the large aryl group and the *twin* substituent. Nevertheless, the relative rate of *Z*-**1** with a *twix* ethyl group is only one-third that of the reference compound **2** (Table 3, entries 1 and 9). Analogous to the singlet oxygenation of *Z*-**1**,[9] this lower reactivity for ArNO may be rationalized in terms of 1,2-allylic ($^{1,2}A$) strain, which builds up during the abstraction of the coplanar allylic hydrogen at the *twix* ethyl group (**AI-1**$_{twix}$). We would expect that the



AI-1$_{twix}$



AI-1$_{twin}$

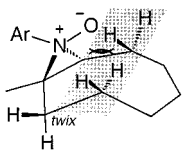
activation barrier for **TS2**$_{twix}$ increases, and as observed, the reactivity should drop. However, the hydrogen-abstracting second step should have no influence on the reactivity unless the activation barrier for **TS2**$_{twix}$ exceeds that of **TS1**$_{twix}$ (Figure 6). This has far-reaching consequences on the mechanism of the nitrosoarene ene reaction in that the initially proposed irreversible formation of the aziridine-*N*-oxide intermediate must become reversible for such substrates. This reversibility also explains the fact that for geraniol (*E*-**7**) more 2,3 adduct is formed than for nerol (*Z*-**7**), see Table 2 (entries 1 and 4). During the hydrogen abstraction at the 2,3 double bond in nerol (Z-**7**), $^{1,2}A$ strain builds up with the bulky *twix* substituent (C_6H_{11}) and a coplanar alignment of the allylic hydrogen is encumbered. The activation barrier for **TS2**$_{twix}$ exceeds even that of **TS1**$_{twin}$ in Figure 4 and only the *twin* product is observed.

These conformational constraints are also manifested in cycloalkenes. The ease of hydrogen abstraction from a methylene group of the ring depends on how well the hydrogen atom is aligned and what steric interactions prevail. A comparison of the relative rates of cyclohexene **4** with the enophiles $^1O_2$, ArNO, and PTAD indicates a much lower ene reactivity than the acyclic reference substrate **2** (Table 3, entries 1 and 10); in fact, this substrate displays the lowest relative rate of all the cases examined and reveals that some effective retardation is at work (we shall return to this point in the next section).

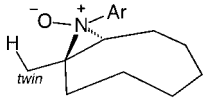
Cyclooctene *Z*-**6** reacts only moderately slower than **2** (entries 1 and 11). In the *skew* trajectory, the enophile attacks from the less hindered side of the double bond and, therefore, any steric effects of the ring on the more substituted side of the double bond should be nominal and not lower appreciably the reactivity.

(24) Adam, W.; Wirth, T. *Acc. Chem. Res.* **1999**, *32*, 703−710.

Instead, the significant difference in the reactivity may be rationalized in terms of conformational constraints in the hydrogen abstraction. Thus, the lower reactivity of ArNO with cyclooctene *Z*-**6** may be attributed to the build-up of a sterically



AI-6$_{twix}$



AI-6$_{twin}$

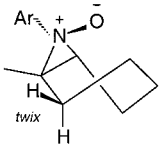
destabilizing 1,5-transannular interaction (**AI-6**$_{twix}$) during the abstraction of the coplanar *twix* hydrogen atom. This disfavors the *twix* abstraction within the ring and decreases the reactivity; consequently, an exalted *twin* abstraction with ArNO is observed, which applies also to $^1O_2$ and PTAD. In contrast, the *E*-**6** diastereomer, which is neither conformationally nor sterically hindered and contains ca. 17.9 kcal/mol ring strain,[25] reacts over 170 times faster with ArNO (entry 12) than the reference substrate **2** and, in fact, is by far the most reactive of all the cases studied.

(e) Regioselectivities display a competition between steric hindrance and conformational constraint. In the nitrosoarene ene reaction, the *skew* trajectory is favored for steric reasons, but we have seen that conformational effects may lessen the preferred *twix* abstraction and the formation of the aziridine-*N*-oxide intermediate becomes reversible (Figure 2). Such reversibility will lower the reactivity and allow otherwise less likely regioisomeric ene products to be formed competitively or even predominantly.

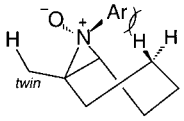
Relative rates only express reactivity factors, but the regioselectivities of stereochemically defined substrates allow the assessment of the contribution of steric as well as conformational effects. For example, in the acyclic substrate *Z*-**1**, the $^{1,2}A$ strain counteracts the *skew* effect and the amount of *twix* abstraction is decreased to 70% from 85%; the latter is the average for *E*-**2** and *Z*-**2** (Figure 3). For the *E*-**1** diastereomer, $^{1,2}A$ strain hinders the *twin* abstraction, so that both steric and conformational effects reinforce each other and provide exclusive *twix* regioselecivity.

The transannular conformational constraints in the cyclooctene Z-**6** (see structure **AI-6**$_{twix}$) lead to enhanced *twin* abstraction from the external methyl group for all three enophiles (Figure 3), that is, for singlet oxygen (28%), ArNO (69%), and PTAD (86%). This is to be contrasted with the *E*-**6** diastereomer, which gives essentially exclusively *twix* ene product (Figure 2). As stated already in the case of the reactivity (see point *d*), steric and conformational factors are absent for this highly exposed substrate; however, it should be stressed that this substrate constitutes a special case in view of its unique geometry.

Another special case concerns the already mentioned cyclohexene **4**, whose much lower reactivity for all three enophiles (Table 3, entry 10) clearly reveals that these ene reactions are severely impeded (see point *d*). In the case of singlet oxygen, for which steric effects are negligible, only conformational constraints are responsible for the increased *twin* abstraction (Figure 3). On the contrary, the nitrosoarene is exclusively *twix*-selective (>95), which must be due to the bulky aryl group of the ArNO enophile. The trajectory for *twin* abstraction is sterically severely hindered by the steric interaction of the nitroso aryl group with the ring skeleton, as displayed in the intermediate **AI-4**$_{twin}$. This encumbered *twin* approach of the bulky ArNO



AI-4$_{twix}$



AI-4$_{twin}$

enophile forces the *skew* trajectory to be pursued, but the *twix* hydrogen atom is conformationally poorly aligned for abstraction, as is evident in the **AI-4**$_{twix}$ structure. Like for the cyclooctene *Z*-**6**, the steric and conformational effects counteract each other, but in contrast to *Z*-**6**, the *twin* approach is so severely hindered in the cyclohexene **4** that *twix* abstraction is the exclusive pathway despite the unfavorable conformational arrangement. Competition between steric and conformational effects appears to control the regioselectivity and reactivity of the nitrosoarene ene reaction.

Conclusion

The 4-nitronitrosobenzene enophile undergoes the ene reaction with stereochemically defined, trisubstituted olefins in high *twix* selectivity along the *skew* trajectory. This novel *skew* effect rests on the present experimental and computational results. The competition between the steric hindrance in the attack of the enophile and conformational constraints during the hydrogen abstraction determines the regioselectivity as well as reactivity. When *twix* regioselectivity prevails, the aziridine-*N*-oxide intermediate is usually formed irreversibly along the *skew* trajectory; in contrast, when *twin* regioselectivity dominates, the enophile approaches from the more substituted side of the double bond, which may be the consequence of reversible generation of the aziridine *N*-oxide due to conformational constraints for *twix* abstraction. It should be of mechanistic interest to examine unsymmetric tetrasubstituted olefins, for which the *skew* effect should not apply. Moreover, the synthetic potential of this ene reaction should be emphasized. In principle, this methodology makes allylic amines accessible from olefins, provided appropriate nitroso enophiles are developed, that can allow the release of the free amino functionality from the resulting allylic hydroxylamines.

Acknowledgment. For financial support we thank the Deutsche Forschungsgemeinschaft (Schwerpunktprogramm: "Peroxidchemie") and the Fonds der Chemischen Industrie (doctoral fellowship for N.B.). This work is dedicated to Prof. Dr. Dr. h.c. mult. S. Hünig on the occasion of his 80th birthday, whose continued support and encouragement is much appreciated.

Supporting Information Available: Complete experimental procedures (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA004356M

(25) Allinger, N. L.; Sprague, J. T. *J. Am. Chem. Soc.* **1972**, *94*, 5734−5747.