Table I. NMR Viscosity Determination

sample	T, °C	F_c, Hz	ν_{NMR},[c] cSt	ν_{Ubb},[d] cSt
EG[a]	23	32.62 ± 0.2	14.85	14.57 ± 0.09
EG/D_2O (80:20 v/v)	23.5–23.8	17.55 ± 0.26	7.98	7.84 ± 0.10
EG/CH_3CN (80:20v:v)	23.0 ± 0.5[b]	11.21 ± 0.25	5.10	5.16 ± 0.01
Carbowax 600/ Me_2SO (20% w/w)	34.0 ± 0.5[b]	15.23 ± 0.25 15.27 ± 0.25	6.93 6.95	6.94 ± 0.12

[a] EG = ethylene glycol. [b] Actual temperature calculated with a C-13 thermometer insert (acetone-d_6/CCl_4; 1:1 v/v). Led, J. L.; Petersen, S. G. *J. Magn. Reson.* **1978**, *32*, 1. [c] $\nu_{NMR} = F_c/219.7$ (Stokes) for 5-mm o.d./NMR tube inside 10-mm tube. a = 0.247 65 cm, b = 0.450 85 cm, q = 0.5493, T_c = 5614.5. [d] Viscosity measured with Ubbelohde viscometer.

where k is an arbitrary constant. The intercept of this linear plot gives F_c. Substitution of F_c into eq 2 gives the kinematic viscosity of the liquid. The results obtained for several test liquids are shown in Table I. Viscosities determined by using a conventional Ubbelohde viscometer and the NMR values agree within 2%. The experiment is independent of the choice of nucleus. Both homonuclear and heteronuclear measurements are feasible provided peak separation is larger than the gradient width. Individual components in a mixture give the same viscosity as the fluid flow is governed by the bulk viscosity (cf. Carbowax 600/Me_2SO mixture).

An implication of the current work is that an NMR image of coherent linear flow should be detectable in a rotating magnetic field.

Acknowledgment. The generous financial support of Eli Lilly & Co. is gratefully acknowledged. M. Vera was supported by a Committee on Institutional Cooperation (CIC) Minority fellowship. The continued instrumental expertise of Dr. R. Santini is gratefully acknowledged.

Supplementary Material Available: NMR image of TVF in ethylene glycol as a function of axial field gradient strength and a table of a, b, d, q, T, F_c/ν, and ν values (3 pages). Ordering information is given on any current masthead page.

Intramolecular [4 + 2] Cycloadditions of Nitroalkenes with Olefins[†]

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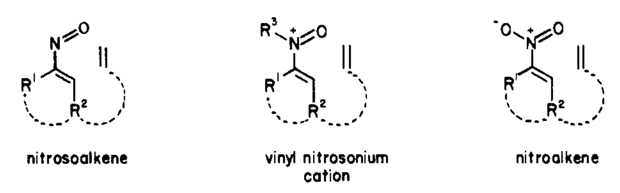
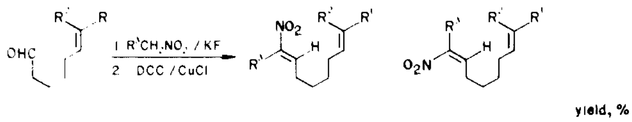
As part of a program aimed at the development of general methods of construction of polycyclic ring systems, we have been investigating the intramolecular cycloadditions of various heterodienes with olefins.[2] Our efforts have focused on the N=O family of heterodienes shown in Chart I. We have recently reported successful cycloadditions with nitrosoalkenes[3,4] and vinylnitrosonium cations.[4b] In this paper *we wish to report that nitroalkenes also serve admirably as 4π components in highly stereoselective cycloadditions with unactivated alkenes.*[5]

Chart I



Scheme I



(*E*)-**1**, $R^1 = CH_3$; R^2 = H (*E*,*E*)-**2**, $R^1 = CH_3$; $R^2 = R_3$ = H 79

(*Z*)-**1**, R^1 = H; $R^2 = CH_3$ (*E*,*Z*)-**2**, $R^1 = R^3$ = H; $R^2 = CH_3$ 96

(*E*,*E*)-**3**, $R^1 = R^3 = CH_3$; $R^2 = H^3$ 89

(*Z*,*E*)-**3**, $R^1 = R^3 = CH_3$; R^2 = H

Scheme II

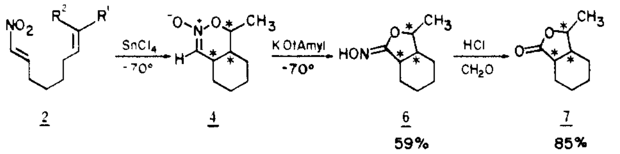
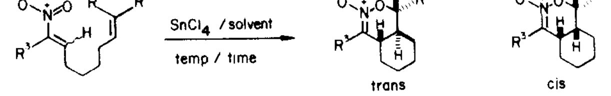


Table I. Cycloadditions of Nitroalkenes **2** and **3**[a,b]



4, R^3 = H
5, $R^3 = CH_3$

substrate	solvent	temp, °C	time, h	trans	cis	yield,[c] %
(*E*,*E*)-**2**	CH_2Cl_2	−70	2.25	52	48	59
(*E*,*Z*)-**2**	CH_2Cl_2	−70	2.25	75	25	68
(*E*,*E*)-**3**[d]	toluene	−29 → 0	3	>98	<2	80[e]
(*Z*,*E*)-**3**[f]	toluene	−78	7	<2	>98	63

[a] Nitroalkene was 0.04 M and 1.0–1.6 equiv of $SnCl_4$ were used. Best yields were obtained with fresh nitroalkene. [b] Cis/trans product ratios were determined by ^1H NMR and GC as described in the text for **4** and **5**. [c] Yields for isolated, purified nitronates. [d] >98% *E* by ^1H NMR. [e] 11% of i was isolated in this run. [f] >98% *Z* by ^1H NMR.

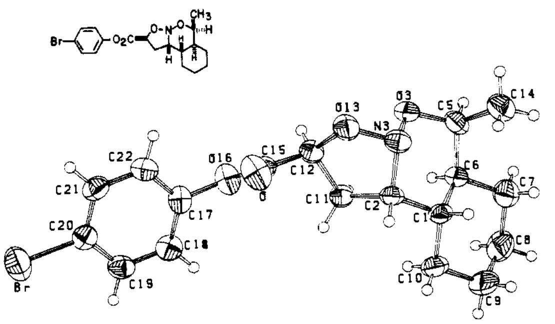


Figure 1. ORTEP plot of double cycloadduct (35% probability).

[†] Dedicated to Professor Dr. Albert Eschenmoser on the occasion of his 60th birthday.

(1) (a) Fellow of the Alfred P. Sloan Foundation (1985–1987), NSF Presidential Young Investigator (1985–1990). (b) Taken in part from: Dappen, M. S. Ph.D. Thesis, University of Illinois, Urbana, 1985. (c) NSF Graduate Fellow, 1984–1987.

(2) For reviews of heterodiene [4 + 2] cycloadditions, see: (a) Desimoni, G.; Tacconi, G. *Chem. Rev.* **1975**, *75*, 651. (b) Schmidt, R. R. *Angew. Chem., Int. Ed. Engl.* **1973**, *12*, 212. For intramolecular [4 + 2] cycloadditions, see: Ciganek, E. *Org. React.* **1984**, *32*, 1.

(3) Denmark, S. E.; Dappen, M. S.; Sternberg, J. A. *J. Org. Chem.* **1984**, *49*, 4741.

(4) (a) Denmark, S. E.; Dappen, M. S.; Sternberg, J. A. "Abstracts of Papers", 187th American Chemical Society Meeting, St. Louis, MO, April 1984; American Chemical Society: Washington, DC, 1984; ORGN 45. (b) Denmark, S. E.; Cramer, C. J. "Abstracts of Papers", 189th American Chemical Society Meeting, Miami, FL, April 1985; American Chemical Society: Washington, DC, 1985; ORGN 151.

The substrates for this study were prepared by modified Henry reaction[6] of nitromethane or nitroethane with the appropriate aldehyde (*E*)-**1**[7,8] or (*Z*)-**1**[7,9] (Scheme I). The labile nitro aldols were dehydrated according to Seebach[11] to afford the nitroalkenes in good overall yields. The disubstituted nitroalkenes **2** (R^3 = H)[7] were formed exclusively in the *E* configuration while the trisubstituted nitroalkenes **3** (R^3 = CH_3)[7] were produced as an *E*/*Z* mixture of variable composition, generally ca. 60:40 *E*/*Z*. The isomers were separated by MPLC[12] for mechanistic experiments. However, on a preparative scale, we developed a simple method to isomerize the mixture to (*E*,*E*)-**3** (>98% *E*,*E*, 91% recovery)[13] using TMEDA.[14]

The results of cyclization reactions are collected in Table I. Survey experiments with (*E*,*E*)-**2** identified $SnCl_4$ as the optimal catalyst.[15] Extensive optimization was done only for (*E*,*E*)-**3** (entry 3), where a byproduct was observed in minor amounts.[16] The yields given are for isolated, purified nitronates, although, in the case of **4**, better yields were obtained by the direct transformations described below. Both **4** and **5** were surprisingly stable.[17] The facility of these reactions is noteworthy in light of related intermolecular reactions of silyl enol ethers reported recently.[5i–k]

To evaluate the stereoselectivity of the cycloaddition it proved expedient to transform the crude nitronate mixture **4** to the known lactones **7**[18] by the procedure outlined in Scheme II. Transformation of **4** to **6** presumably involves fragmentation to a nitrile oxide followed by immediate collapse.[19] A combination of ^1H NMR and capillary GC analysis of the lactone mixtures allowed the following conclusions: (1) the olefin geometry in **2** is preserved for both *E* and *Z* isomers and (2) the folding of the side chain exo (to trans) or endo (to cis) is unselective (1:1) for (*E*,*E*)-**2** (entry 1) and moderately selective (3:1) for (*E*,*Z*)-**2** (entry 2). However, we were delighted to discover that both trisubstituted nitroalkenes (*E*,*E*)-**3** and (*Z*,*E*)-**3** cyclized *completely stereoselectively* by exclusive exo folding of the side chain to produce *trans*-**5**[7] and *cis*-**5**,[7] respectively.[21] Thus, the reactions are completely stereochemically coupled, if not concerted, and allow for the production of any of the four possible diastereomeric nitronates by appropriate selection of double-bond geometries. This stands in contrast to the intermolecular reactions of nitroolefins with enamines which are independent of olefin geometry.[5g]

In exploring the synthetic potential for nitronates **4** and **5** we have investigated their behavior as dipoles in [3 + 2] cycloadditions.[22] Treatment of nitronates **4** and **5** with methyl and 4-bromophenyl acrylate produced cycloadducts[7] in good overall yields (66–86%). The full stereostructure of the double cycloadducts[23] was assured by an X-ray crystal-structure determination[24,25] (Figure 1). The preference for exo orientation of the ester group has been established in these reactions by Tartakovskii[26] and Carrie.[27] Further, the high selectivity of α-face attack by the acrylate can be interpreted in terms of the kinetic anomeric effect.[27b,28]

Further studies are under way on allylic stereodynamics of the side chain, double-intramolecular cycloadditions, and synthetic transformations of **4** and **5**.

Acknowledgment. We gratefully acknowledge financial support for this project provided by the National Institutes of Health (PHS GM-30938), Eli Lilly, and the Upjohn Co. This work was supported in part by the University of Illinois Regional Instrumentation Facility (NSF CHE-79-16100) and Mass Spectrometry Laboratory (NH GM 27029).

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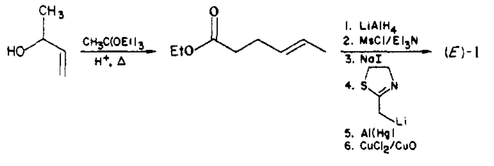
[5] The reactions of nitroalkenes with electron-rich olefins have been studied in detail. However, it is likely that these reactions are mechanistically distinct involving Michael additions to form betaines followed by collapse to formal [4 + 2] adducts. See discussion in ref 5f,g. Enamines: (a) Colonna, F. P.; Valentin, E.; Pitacco, G.; Risaliti, A. *Tetrahedron* **1973**, *29*, 3011. (b) Valentin, E.; Pitacco, G.; Risaliti, A. *Ibid.* **1974**, *30*, 2471. (c) Calligaris, M.; Manzini, G.; Pitacco, G.; Valentin, E. *Ibid.* **1975**, *31*, 1501. (d) Daneo, S.; Pitacco, G.; Risaliti, A.; Valentin, E. *Ibid.* **1982**, *38*, 1499. (e) Barbarella, A.; Pitacco, G.; Russo, C.; Valentin, E. *Tetrahedron Lett.* **1983**, 1621. (f) Seebach, D.; Golinski, J. *Helv. Chim. Acta* **1981**, *64*, 1413. (g) Seebach, D.; Beck, A. K.; Golinski, J.; Hay, J. N.; Laube, T. *Ibid.* **1985**, *68*, 162. (h) Blarer, S.; Seebach, D. *Chem. Ber.* **1983**, *116*, 2086. Silyl enol ethers: (i) Miyashita, M.; Kumazawa, T.; Yoshikoshi, A. *J. Am. Chem. Soc.* **1976**, *98*, 4679. (j) Miyashita, M.; Yanami, T.; Kumazawa, T.; Yoshikoshi, A. *Ibid.* **1984**, *106*, 2149. (k) Seebach, D.; Brook, M. A. *Helv. Chim. Acta* **1985**, *68*, 319. Silyl ketene acetals: (l) Miyashita, M.; Kumazawa, T.; Yoshikoshi, A. *Chem. Lett.* **1980**, 1043. Enolates: (m) Haner, R.; Laube, T.; Seebach, D. *Chimia* **1984**, *38*, 255. Allylsilanes: (n) Ochiai, M.; Arimoto, M.; Fujita, E. *Tetrahedron Lett.* **1981**, 1115.

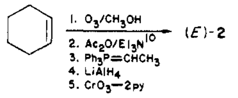
[6] (a) Wollenberg, R. H.; Miller, S. J. *Tetrahedron Lett.* **1978**, 3219. (b) Pakenden, H. G.; von Schickh, O.; Segnitz, A. In "Houben-Weyl: Methoden der Organischen Chemie"; Mueller, E., Ed.; Georg Theime Verlag: Stuttgart, 1971; Band 10/1, p 250.

[7] All new compounds have been characterized by ^1H NMR (200 or 360 MHz), IR, mass spectroscopy, and combustion analysis (±0.4%).

[8] (*E*)-**1** was prepared in seven steps from 3-buten-2-ol in 29% overall yield. The olefin was >96% *E* by GC analysis (5% TCEP, 12 ft × 1/8 in.).



[9] (*Z*)-**1** was prepared in five steps from cyclohexene in 27% overall yield. The olefin was 87:13 *Z*/*E* by GC analysis (5% TCEP, 12 ft × 1/8 in.).



[10] Claus, R. E.; Schreiber, S. L. *Org. Synth.* **1985**, *64*, 150. We thank Prof. Schreiber for a preprint of this procedure.

[11] Knochel, P.; Seebach, D. *Synthesis* **1982**, 1017.

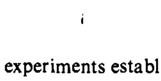
[12] Silica gel (G-type) 10:1 hexane/benzene, 5 mL/min monitored at 280 nm, t_R (*Z*,*E*)-**3**, 280 min, t_R (*E*,*E*)-**3**, 425 min.

[13] Geometrical purity by HPLC analysis silica gel (5 μm). 10:1 hexane/benzene, 1 mL/min monitored at 270 nm. The vinyl H-C(3) is also diagnostic: (*E*,*E*)-**3**, δ 7.13; (*Z*,*E*)-**3**, δ 5.82.

[14] Conditions: 0.25 M in CH_2Cl_2, 5 mol % TMEDA, 20 °C, 8 h. Monitored by HPLC (vide supra).

[15] Other catalysts examined: $TiCl_4$, $AlCl_3$, $FeCl_3$, $(i\text{-PrO})_2TiCl_2$.

[16] The byproduct, i, was characterized by ^1H NMR, ^{13}C NMR, IR, and



i

mass spectrometry. Control experiments established i as a primary product.

[17] The simple parent nitronates are very unstable, cf.: Chlenov, I. E.; Morozova, N. S.; Khudak, V. I.; Tarkakovskii, V. A. *Izv. Akad. Nauk. SSSR, Ser. Khim.* (*Engl. Transl.*) **1970**, 2492.

[18] Fujiwara, Y.; Kimoto, S.; Okamoto, M. *Chem. Pharm. Bull. Jpn.* **1973**, *21*, 1166; **1975**, *23*, 1396.

[19] Many attempts at hydrolytic, oxidative, and reductive versions of the Nef[20] reaction failed.

[20] Review: Seebach, D.; Colvin, E. W.; Lehr, F.; Weller, T. *Chimia* **1979**, *33*, 1.

[21] The selectivity can be understood in terms of destabilizing nonbonded interactions between the R^3 group and the allylic methylene unique to the endo transition state. The stereoselectivity was assessed by ^1H NMR integration of the diagnostic H-C(4) methine resonances: *trans*-**5**, δ 4.12; *cis*-**5**, δ 4.64.

[22] For a review of [3 + 2] cycloadditions of nitronates, see: Tartakovskii, V. A. *Izv. Akad. Nauk. SSSR, Ser. Khim.* (*Engl. Transl.*) **1984**, 147.

[23] For a recent example of a tandem Diels–Alder/nitrone cycloaddition, see: Kozikowski, A. P.; Hiragu, K.; Springer, J. P.; Wang, B. C.; Xu, Z.-B. *J. Am. Chem. Soc.* **1984**, *106*, 441.

[24] We thank Scott R. Wilson, Department of Chemistry, University of Illinois, for the structure determination.

[25] The full details of the double cycloaddition and structure determination will be presented elsewhere.

[26] (a) Shitkin, V. M.; Khudak, V. I.; Chlenov, I. E.; Tartkovskii, V. A. *Izv. Akad. Nauk. SSSR, Ser. Khim.* (*Engl. Transl.*) **1974**, 1836. (b) Shitkin, V. M.; Chlenov, I. E.; Tartkovskii, V. A. *Ibid.* **1977**, 187.

[27] (a) Gree, R.; Tonnard, F.; Carrie, R. *Tetrahedron* **1976**, *32*, 675. (b) Gree, R.; Carrie, R. *Ibid.* **1976**, *32*, 683. (c) Gree, R.; Carrie, R. *J. Heterocycl. Chem.* **1977**, *14*, 965.

[28] (a) Petrizilka, M.; Felix, D.; Eschenmoser, A. *Helv. Chim. Acta* **1973**, *57*, 2950. (b) Vasella, A. *Ibid.* **1977**, *60*, 1273.