per residue for one of the helical senses multiplied by the number of residues in the sequence. By this amplification mechanism, very small energy differences per residue can cooperatively lead to large differences in the ratio of right- and left-handed helical sequences and thereby to large optical rotations, as observed here.

Experiments are in progress to reveal the per deuterium energy difference favoring one helical sense.[20] Such information will be helpful to understanding the structural forces behind the conformational equilibrium isotope effect reported in this work. Diastereotopic carbon hydrogen stretching frequency differences could play a role,[15] and their contribution could be evaluated by spectroscopic experiments also in progress.

Acknowledgment. Work at the Polytechnic University was supported by the National Science Foundation (CHE-8615872) and by the Petroleum Research Fund administered by the American Chemical Society. We are grateful to these organizations and as well to Professors H. Morawetz (Polytechnic University) and S. Lifson (Weizmann Institute) for helpful discussions. We also thank Prof. W. Agosta for allowing use of the circular dichroism spectrometer at Rockefeller University (purchased with the support of the National Science Foundation). This paper is dedicated to our teacher Professor Kurt Mislow on the occasion of his 65th birthday.

---

(20) Professor S. Lifson of the Weizmann Institute has completed a statistical mechanical analysis (to be published) which is consistent with the cooperative effect proposed here and makes predictions of the relationship between the energy difference per deuterium favoring one helical sense and the temperature dependence of the optical rotation. He has also made the challenging suggestion that the energy difference per residue in **1** could arise, at least in part, from an electrostatic interaction between the dipole of the C-H(D) bond α to nitrogen and one of the carbonyl oxygens. In such an interaction which could be described as a C-H to oxygen hydrogen bond, deuterium will differ, however slightly, from hydrogen. See: Melander and Saunders in ref 15 above, pp 197-198. Katz, J. J.; Crespi, H. L. In *Isotope Effects in Chemical Reactions*; ACS Monograph 167; Van Nostrand Reinhold: New York, 1970; Chapter 5. This idea could find support in the following: Taylor, R.; Kennard, O. *J. Am. Chem. Soc.* **1982**, *104*, 5063 and references therein. See, also: Seiler, P.; Weisman, G. R.; Glendening, E. D.; Weinhold, F.; Johnson, Van B.; Dunitz, J. D. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1175.

Intermolecular Hetero-Diels-Alder Reactions of Enamino Ketones at High Pressure. The First Significant Pressure-Induced Diastereoselectivity in Organic Transformations[1]

Lutz F. Tietze,[*,†] Thomas Hübsch,[†] Edgar Voss,[†]
Michael Buback,[*,‡] and Winfried Tost[‡]

Institut für Organische Chemie and
Institut für Physikalische Chemie
of the Georg-August-Universität
D-3400 Göttingen, Federal Republic of Germany

Received January 4, 1988
Revised Manuscript Received April 13, 1988

Stereoselectivity[2] is today one of the main goals in the development of new synthetic methods in organic chemistry. It is therefore of great interest to explore the potential of applying high pressure to increase the diastereoselectivity of chemical transformations. The first attempts, however, to use this method for diastereoselective synthesis[3,4] were not very promising as the observed $\Delta\Delta V^{\neq}$ values did not exceed ±1 cm^3·mol^{-1}. Sera[5] found for the cycloaddition of various dienophiles and cyclopentadienes values of $\Delta V^{\neq}_{exo} - \Delta V^{\neq}_{endo}$ between 1.0 and −0.5 cm^3·mol^{-1}. We have now shown for the *hetero*-Diels-Alder reaction[6] of the enamino ketone **1** and ethyl vinyl ether (**2**)[7] that a significant increase of diastereoselectivity can be obtained by applying high pressure.

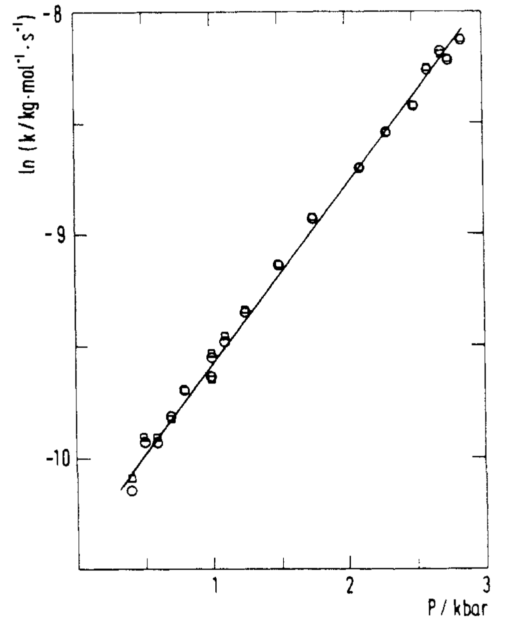
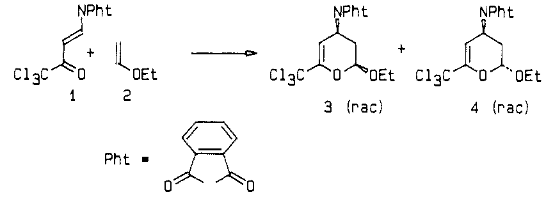


Figure 1. Pressure dependence of the rate coefficient k for the Diels-Alder reaction of **1** and **2** in CH_2Cl_2 solution at 90 °C: The symbols ○ and □ refer to kinetic analysis with two different regions in the spectrum of the C=O fundamentals of the educt **1** around 1740 cm^{-1}.



We assume that **1** reacts in the shown (*E*)-configuration giving the cis-adduct **3** via an endo orientation and the trans-adduct **4** via an exo orientation in the transition state. The reaction of **1** and **2** is of considerable interest as it allows an easy access to 3-amino sugars.[7,8] The kinetics of the cycloaddition of **1** and **2** in CH_2Cl_2 solution was directly measured under high pressure by Fourier transform infrared spectroscopy on the characteristic educt and product C=O stretching fundamentals. The reaction mixture was contained within a closed thin-walled Teflon bag which is transparent to IR light. The Teflon bag was positioned between the silicon windows of an optical cell for operation up to 3 kbar.[9] The cycloadditions were performed with the con-

---

[†] Institut für Organische Chemie.

[‡] Institut für Physikalische Chemie.

(1) Intra- and Intermolecular Hetero-Diels-Alder Reactions. 23. This work was generously supported by the Deutsche Forschungsgemeinschaft (SFB 93 "Photochemie mit Lasern") and by the Fonds der Chemischen Industrie. Part 22: Buback, M.; Tost, W.; Tietze, L. F.; Voss, E. *Chem. Ber.* **1988**, *121*, 781.

(2) (a) For selective reviews, see: *Selectivity-A Goal for Synthetic Efficiency*; Bartmann, W., Trost, B. M., Eds.; VCH Verlagsgesellschaft: Weinheim, 1984. (b) *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic: New York, 1983-1987.

(3) For recent excellent reviews, see: Asano, T.; le Noble, W. J. *Chem. Rev.* **1978**, *78*, 4. Matsumoto, K.; Sera, A. *Synthesis* **1985**, 999. Isaacs. N. S.; George, A. V. *Chem. Brit.* **1987**, 47. Eldik, R. van; Jonas, J. *High Pressure Chemistry and Biochemistry*; D. Reidel: Dordrecht, 1987. Jurczak, J. *J. Physica Status Solidi* [*Sectio*] *B* **1986**, *139/140*, 709.

(4) Dauben, W. G.; Gerdes, J. M.; Look, G. C. *Synthesis* **1986**, 532.

(5) Seguchi, K.; Sera, A.; Marayuma, K. *Tetrahedron Lett.* **1973**, *17*, 1585.

(6) Boger, D. L.; Weinreb, S. M. *Hetero-Diels Alder Methodology in Organic Synthesis*; Academic: New York, 1987. L. F. Tietze in ref 2a, p 299.

(7) Tietze, L. F.; Voss, E. *Tetrahedron Lett.* **1986**, *27*, 6181. See Also: Tietze, L. F.; Voss, E.; Harms, K.; Sheldrick, G. M. *Tetrahedron Lett.* **1985**, *26*, 5273.

(8) Lockhoff, O.; Aminoglycosid-Antibiotica in Ruschig, H. *Arzneimittel, Entwicklung-Wirkung-Darstellung*; VCH Verlagsgesellschaft: Weinheim, 1987.

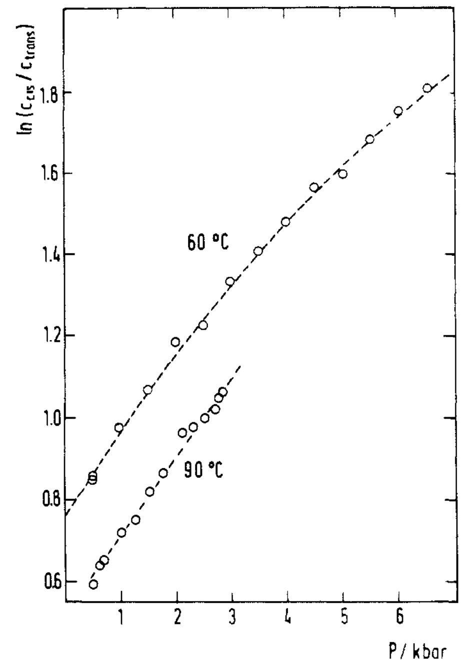


Figure 2. Pressure dependence of diastereoselectivity, in terms of ln (c_{cis}/c_{trans}), for the cycloaddition of **1** and **2** in CH_2Cl_2 solution at 60 and 90 °C.

centration of the ether **2** exceeding that of the *hetero* diene **1** by more than two orders of magnitude. The Kezdy–Swinbourne plot[10] for the pseudo-first-order reaction yields a straight line over the whole range up to complete conversion of the diene **1**. From the first-order rate coefficient and from the known amount of **2**, the second-order Diels–Alder rate coefficient k was obtained. The k values presented in Figure 1 for 90 °C as a function of pressure refer to a rate law with concentrations in terms of mole per kilogram of solution. The rate coefficient increases with pressure. For reactions at 90 °C with the vinyl ether **2** in a large excess concentration of 1 $mol{\cdot}kg^{-1}$, the half-life of **1** decreases from 6.2 h at ambient pressure to 34 min at 3 kbar. From the slope of the straight line fitted to the ln k vs P data in Figure 1, the overall activation volume found was $-\Delta V^{\ddagger} = 24.2 \pm 1.0$ $cm^3{\cdot}mol^{-1}$, which is very close to the value measured for a similar *hetero*-Diels–Alder reaction.[1] Both values are, however, relatively small in comparison to $-\Delta V^{\ddagger} > 30$ $cm^3{\cdot}mol^{-1}$ which is normally found for intermolecular Diels–Alder reactions.[3,4] An explanation for this discrepancy might be that the transition state in the reaction of **1** and **2** has a lower polarity compared to the ground state.[11]

Since the diastereomeric cycloadducts **3** and **4** could not be distinguished by IR spectra (C=O) under high pressure conditions, pressure-induced diastereoselectivity was investigated by HPLC analysis of the reaction mixture after complete conversion of **1**. For these studies cycloadditions were performed in a 7-kbar cell without windows. The logarithm of the concentration ratio of **3** and **4**, ln (c_{cis}/c_{trans}), plotted vs pressure at 60 and 90 °C is shown in Figure 2. For the 60 °C curve a slight deviation from linearity is observed. This corresponds to a pressure-dependent decrease of activation volume as found for many other reactions.[3] At 60 °C the ratio fo **3** and **4** changes from 2.15:1 up to 6.07:1 between ambient pressure and 6.5 kbar. From the slope of both isomers, for P approaching ambient pressure, the difference in activation volume between the reaction paths leading to diastereomers **3** and **4**, respectively, was found to be $-\Delta\Delta V^{\ddagger} = 5.8 \pm 0.5$ $cm^3{\cdot}mol^{-1}$. From $\Delta\Delta V^{\ddagger}$ the individual $\Delta V^{\ddagger}$ values for the endo and exo cycloadditions were found to be -26.0 ± 1.5 $cm^3{\cdot}mol^{-1}$ and -20.1 ± 1.5 $cm^3{\cdot}mol^{-1}$, respectively. The temperature dependence of diastereoselectivity in Figure 2 corresponds to a difference in activation energy of $-\Delta\Delta H^{\ddagger} = 8.1 \pm 2.4$ $kJ{\cdot}mol^{-1}$. It should be noted that the observed diastereoselectivity comes from kinetic control. Isomers **3** and **4** do not interconvert within typical reaction times, even at 90 °C and 6 kbar. From thermodynamics the trans product **4** is strongly favored. Isomerization of **3** with boron trifluoride etherate followed by crystallization allows an almost complete transformation of **3** into **4**.[7]

In the system studied our experiments show there is a twofold advantage of applying high pressure: (1) According to the remarkable large difference in activation volume, $\Delta\Delta V^{\ddagger}$, diastereoselectivity is enhanced toward high pressure at constant temperature. (2) From the experimental $\Delta\Delta H^{\ddagger}$ it can be deduced that diastereoselectivity also increases toward lower temperature. As $\Delta V^{\ddagger}$ is fairly large and negative, high pressure enables the cycloaddition to be run with reasonable rate even at and below 0 °C. High selectivity for **3** can therefore be achieved in transformations at high pressure and low temperature. Thus, **3** and **4** are formed at 90 °C and 1 bar only in a 1.67:1 ratio, whereas at 0.5 °C and 6 kbar at 13.6:1 ratio is obtained. The corresponding ln (c_{cis}/c_{trans}) values (cf. Figure 2) are 0.51 and 2.61, respectively.

---

(9) Tost, W. Thesis, Göttingen 1988.

(10) Kezdy, F. J.; Jaz, J.; Bruylants, A. *Bull. Soc. Chim. Belg.* **1958**, *67*, 687. Swinbourne, E. S. *J. Chem. Soc.* **1960**, 2371.

(11) le Noble, W. J.; Ojosipe, B. J. *J. Am. Chem. Soc.* **1975**, *97*, 5939.

Stereoselective Synthesis of Monosubstituted *cis*-Aryldiazenes, NH=NR†

Milton R. Smith, III, and Gregory L. Hillhouse*

Searle Chemistry Laboratory
Department of Chemistry, The University of Chicago
Chicago, Illinois 60637

Received February 8, 1988

Monosubstituted diazenes (NH=NR) are invoked as reactive intermediates in numerous important organic reactions including oxidations of arylhydrazines,[1] Wolff–Kishner reductions,[2] the McFadyen–Stevens conversion of carboxylic acids to aldehydes,[3] and reductive deaminations.[4] However, this elusive molecular class was not detected until 1965 when Kosower and Huang observed *trans*-phenyldiazene as the product of the decarboxylation of phenyldiazenecarboxylic acid.[5] Several monoalkyl- and monoaryldiazenes have since been prepared by various routes.[6-9] Diazenes possessing a hydrogen atom(s) attached to a diazenyl nitrogen differ from their disubstituted cousins (NR=NR) in two important ways: (1) diimine (NH=NH)[10] and NH=NR[11] are reactive, thermally unstable species, usually decomposing with extrusion of dinitrogen well below ambient temperature, in contrast to the relatively inert disubstituted derivatives (like azobenzene), and (2) although both cis and trans isomers of disubstituted diazenes are well-known,[12] only *trans*-NH=NH[13,14] and *trans*-

---

† Dedicated to our colleague Professor Gerhard L. Closs on the occasion of his 60th birthday.

(1) (a) Cram, D. J.; Bradshaw, J. D. *J. Am. Chem. Soc.* **1963**, *85*, 1108. (b) Huyser, E. S.; Wang, R. H. S. *J. Org. Chem.* **1968**, *33*, 2901.

(2) Szmant, H. H.; Roman, M. M. *J. Am. Chem. Soc.* **1966**, *88*, 4034.

(3) McFadyen, J. S.; Stevens, T. S. *J. Chem. Soc.* **1936**, 584.

(4) (a) Nickon, A.; Hill, A. S. *J. Am. Chem. Soc.* **1964**, *86*, 1152. (b) Bumgardner, C. L.; Martin, K. H.; Freeman, J. P. *Ibid.* **1963**, *85*, 97. (c) Doldouras, G. A.; Kollonitsch, J. *Ibid.* **1978**, *100*, 341.

(5) (a) Kosower, E. M.; Huang, P. C. *J. Am. Chem. Soc.* **1965**, *87*, 4646. (b) Kosower, E. M.; Huang, P. C. *Ibid.* **1968**, *90*, 2354. (c) Kosower, E. M.; Huang, P. C. *Ibid.* **1968**, *90*, 2362.

(6) Tsuji, T.; Kosower, E. M. *J. Am. Chem. Soc.* **1971**, *93*, 1992.

(7) McKenna, C. E.; Traylor, T. G. *J. Am. Chem. Soc.* **1971**, *93*, 2313.

(8) Evanochko, W. T.; Shevlin, P. B. *J. Am. Chem. Soc.* **1978**, *100*, 6428.

(9) Ackermann, M. N.; Ellenson, J. L.; Robinson, D. H. *J. Am. Chem. Soc.* **1968**, *90*, 7173.

(10) (a) Hünig, S.; Müller, H. R.; Thier, W. *Angew. Chem., Int. Ed. Engl.* **1965**, *4*, 271. (b) Miller, C. E. *J. Chem. Ed.* **1965**, *42*, 254.

(11) (a) Kosower, E. M. *Acc. Chem. Res.* **1971**, *6*, 193. (b) Kosower, E. M.; Huang, P. C. *J. Am. Chem. Soc.* **1968**, *90*, 2367.

(12) *The Chemistry of the Hydrazo, Azo and Azoxy Groups*; Patai, S., Ed.; Wiley: New York, 1975.

(13) Wiberg, N.; Bachhuber, H.; Fischer, G. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 829.

0002-7863/88/1510-4066$01.50/0