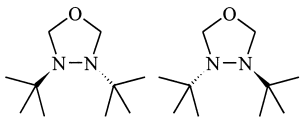
Pronounced Steric Hindrance for Nitrogen Inversion in 1,3,4-Oxadiazolidines**

Remir G. Kostyanovsky,* Gulnara K. Kadorkina, Vasilii R. Kostyanovsky, Volker Schurig,* and Oliver Trapp

In tertiary amines[1] and aziridines[2] the barrier for nitrogen inversion decreases as the size of the nitrogen substitutents increases; this occurs because the pyramidal ground state is destabilized by the steric interaction of the substituents. Therefore, triisopropylamine[3a,b] and diisopropyl-3-pentylamine[3c] are characterized by an almost planar configuration of the nitrogen atom in the ground state, a geometry that corresponds to the transition state of the inversion process. In contrast to this, the barrier for double nitrogen inversion in cyclic hydrazines rises with increasing the size of the nitrogen substituents[4] due to steric hindrance of the transition state.[5] If inversion occurs via a biplanar transition state in sterically hindered systems, for example double nitrogen inversion in diaziridines,[6] the transition state should be additionally destabilized by electronic interaction between the lone electron pairs of adjacent nitrogen atoms.

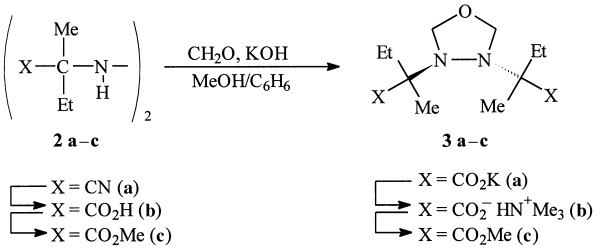
Indeed, as previously reported, high barriers for nitrogen inversion were found for compounds with bulky nitrogen substituents, for example, for 1,2-di-*tert*-butyldiazetidine the barrier for nitrogen inversion has been determined to be $\Delta G^{\neq} = 91.3\ \mathrm{kJ\,mol^{-1}}$ at 155 °C.[5] For 3,4-di-*tert*-butyl-1,3,4-oxadiazolidine (**1**)[5b,c,7] only a lower limit of $\Delta G^{\neq} > 99.6\ \mathrm{kJ\,mol^{-1}}$ at 130 °C could be deduced by NMR studies.[8]



(*R*,*R*)-**1** (*S*,*S*)-**1**

The true barrier for nitrogen inversion for 1,3,4-oxadiazolidine derivatives has now been determined through indirect evidence (by the introduction of chiral substituents on the nitrogen atoms and monitoring diastereomerization by NMR spectroscopy) and by direct evidence (enantiomerization by the stopped-flow multidimensional gas chromatographic method (sfMDGC)).

3,4-Bis(1′-methoxycarbonyl-1′-methylpropyl)-1,3,4-oxadiazolidine (**3c**) was synthesized as shown in Scheme 1. Compound **3c** contains four stereogenic centers (two at carbon atoms and two at nitrogen atoms) however, only 6 of the 16 possible stereoisomers are observed, because of the presence of constitutionally equivalent chiral substituents on the nitrogen atoms and the absence of *cis* isomers (Figure 1).



Scheme 1. Synthesis of **3c**.

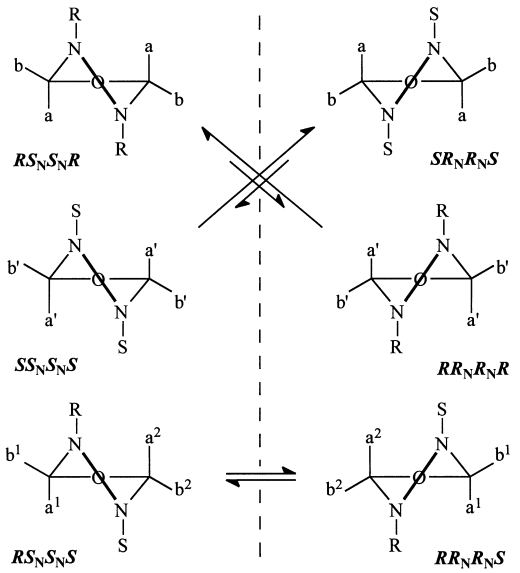


Figure 1. Stereoisomers of **3c**; substituents: R: *(R)*-C(Et)(Me)COOMe; S: (*S*)-C(Et)(Me)COOMe.

Two enantiomeric pairs exist for the major and minor diastereomers (RR_NR_NR)-**3c**/(SS_NS_NS)-**3c** and (RS_NS_NR)-**3c**/(SR_NR_NS)-**3c**, which are interconverted by nitrogen inversion until thermodynamic equilibrium is reached; for the third diastereomer there is one enantiomeric pair (RS_NS_NS)-**3c**/(SR_NR_NR)-**3c** which represents a quasi-*meso* form[9] (with respect to configurationally opposite N substituents) undergoing a degenerated inversion. Therefore, only three sets of signals for each of the three diastereomers are observed in the ^{1}H and ^{13}C NMR spectra of the synthetic mixture (Figure 2); in all the cases the signals from the protons and the carbon atoms of the ring do not overlap.

[*] Prof. R. G. Kostyanovsky, Dr. G. K. Kadorkina, V. R. Kostyanovsky
N.N. Semenov Institute of Chemical Physics
Russian Academy of Sciences
117977 Moscow (Russian Federation)
Fax: (+7) 095-938-2156/939-7417
E-mail: kost@center.chph.ras.ru
Prof. Dr. V. Schurig, Dipl.-Chem. O. Trapp
University of Tübingen
Institute of Organic Chemistry
72076 Tübingen (Germany)
Fax: (+49) 7071-29-5538
E-mail: volker.schurig@uni-tuebingen.de

[**] Asymmetric Nitrogen, Part 83. This work was supported by the Russian Foundation for Basic Research (RFBR) (grant No. 97-03-33021) and DFG-RFBR (grant No. 98-03-04119). O.T. thanks the Fonds der Chemischen Industrie for a doctorate scholarship. Part 82: D. A. Lenev, K. A. Lyssenko, R. G. Kostyanovsky, *Izv. Akad. Nauk. Ser. Khim.* **2000**, *N7* [*Russ. Chem. Bull.* **2000**, *49*, in press].

Supporting information for this article is available on the WWW under http://www.wiley-vch.de/home/angewandte/ or from the author.

  1433-7851/00/3916-2938 $ 17.50+.50/0

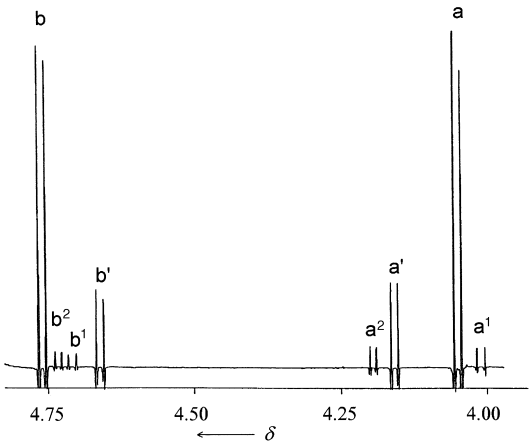


Figure 2. 400 MHz ^{1}H NMR spectrum of **3c** in CD_3OD showing the signals of the NCH_2O protons of the major, minor, and quasi-*meso* diastereomers of **3c** (for assignments see Figure 1).

In the quasi-*meso* diastereomer all four protons are nonequivalent and two AB systems with different ^2J spin–spin coupling constants are observed, whereas only one AB system is found for each of the major and minor diastereomers (Figure 2).

The kinetics of the diastereomerization process (in [D_6]benzene at 56.5 °C) for the major diastereomer of **3c** (Figure 3) gave the following parameters: $k_1^{inv} = 1.8 \times 10^{-5}\ s^{-1}$, $k_{-1}^{inv} = 6.6 \times 10^{-5}\ s^{-1}$, $\Delta G_1^{\neq} = 112.6 \pm 1.7\ kJ\,mol^{-1}$, $\Delta G_{-1}^{\neq} = 107.2 \pm 1.7\ kJ\,mol^{-1}$, which represents a very high barrier for nitrogen inversion for 1,3,4-oxadiazolidines.

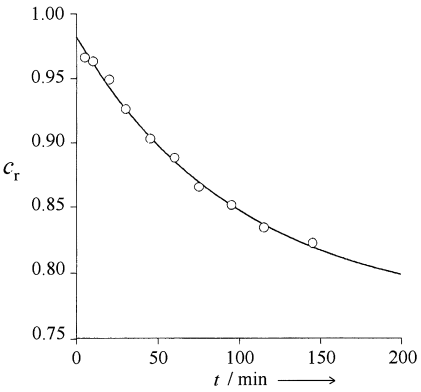


Figure 3. Kinetics of the diastereomerization process of the major diastereomer of **3c** in [D_6]benzene at 329.5 K, initial concentration $c_0 = 0.1\ mol\,L^{-1}$ (the relative concentration $c_r = c_{major}/c_0$ versus time t is plotted). The regression curve is calculated with the following equation: $c = c_\infty + (c_0 - c_\infty)e^{-2kt}$ ($k = 8.5 \times 10^{-5}\ s^{-1}$ where k is the sum of the rate constants of forward and back reaction calculated for one nitrogen atom).

An even higher barrier for nitrogen inversion $\Delta G^{\neq}$ was anticipated for 3,4-di-*tert*-butyl-1,3,4-oxadiazolidine[8b] (**1**) because the conformational energy of the methyl group is higher than that of CO_2Me (7.12 and 5.32 kJ mol^{-1}, respectively).[10] Thus, **1** was prepared and the enantiomers were separated by gas chromatography on a Chirasil-β-Dex column[11] (20 m × 250 μm internal diameter, film thickness 400 nm, 85 °C, 0.45 bar H_2, separation factor $\alpha = 1.17$).

To quantify the barrier for nitrogen inversion of **1** in the inert gas phase, the stopped-flow multidimensional gas chromatographic method (sfMDGC),[12] which was recently developed for the determination of very high inversion (enantiomerization) barriers, was applied (see Experimental Section). The sfMDGC experiment can easily be carried out at different temperatures (Table 1), which allows the activation parameters $\Delta H_{gas}^{\neq}$ and $\Delta S_{gas}^{\neq}$ to be determined. The barrier for nitrogen inversion ($\Delta G_{gas}^{\neq} = 131.8\ kJ\,mol^{-1}$ at 56.5 °C compared to $\Delta G_{gas}^{\neq} = 112.6\ kJ\,mol^{-1}$ for **3c**) for a pyramidal nitrogen atom in **1** is the highest value so far for a five-membered cyclic compound.

Table 1. Results of the sfMDGC experiment for **1**.

T [°C]	t [min]	A [%][a]	k^{gas} [s^{-1}]	$\Delta G_{gas}^{\neq}$ [kJ mol^{-1}]
126.2	20.8	98.6	1.12×10^{-5}	136.7 ± 0.8
139.2	28.4	95.7	2.60×10^{-5}	138.4 ± 0.8
150.8	21.0	91.7	7.23×10^{-5}	138.8 ± 0.9
160.2	24.3	81.0	1.65×10^{-4}	139.0 ± 1.3
170.0	22.5	79.7	1.94×10^{-4}	141.5 ± 0.1

[a] A = Major peak area.

The mean values of $\ln(k/T)$ were plotted as a function of T^{-1} in an Eyring diagram. The activation parameters of **1** were found by using a linear fit ($r = 0.98$), and are $\Delta H_{gas}^{\neq} = 101.1 \pm 0.2\ kJ\,mol^{-1}$ and $\Delta S_{gas}^{\neq} = -93\ J\,K^{-1}mol^{-1}$.

The experimental value of $\Delta H^{\neq}$ for **1** is considerably lower than that calculated for nitrogen inversion,[1a] and the high negative value of $\Delta S^{\neq}$ can be considered as evidence for a dissociative mechanism for the inversion process. Such a dissociative inversion mechanism has been proposed for several heterocycles: for *N*-chlorooxaziridines (calculated: $\Delta H^{\neq} = 185\ kJ\,mol^{-1}$, experimental: $\Delta H^{\neq} = 64.1\ kJ\,mol^{-1}$, $\Delta S^{\neq} = -182\ J\,K^{-1}mol^{-1}$),[13] *N*-chlorodiaziridines (calculated: $\Delta H^{\neq} = 143\ kJ\,mol^{-1}$, experimental: $\Delta H^{\neq} = 46.9\ kJ\,mol^{-1}$, $\Delta S^{\neq} = -176\ J\,K^{-1}mol^{-1}$),[14] and Tröger's Base (experimental: $\Delta H^{\neq} = 62.7\ kJ\,mol^{-1}$, $\Delta S^{\neq} = -168\ J\,K^{-1}mol^{-1}$).[12b] The increase in the negative entropy is characteristic for charge separation in heterolytic processes,[15] but not for homolytic processes.[16] Thus, we assume that nitrogen inversion in **1** proceeds via dissociation with the breaking of a CH_2–O bond and formation of a methyleneiminium ion. It is known that 1,3,4-oxadiazolidines react with amines as aminomethylating reagents with the breaking of this particular bond.[17]

Experimental Section

Synthetic procedures and spectroscopic data can be found in the Supporting Information.

The stopped-flow multidimensional gas chromatography (sfMDGC) was performed on a Siemens Sichromat 2 gas chromatograph equipped with two ovens, a pneumatically controlled six-port valve (Valco), a cooling trap for use with liquid nitrogen in oven 2, two flame-ionization detectors and a C-R 6A integrator (Shimadzu). The whole process is monitored by a control computer.

For the separation of enantiomers of **1** a fused silica column coated with Chirasil-β-Dex[11] (12.5 m × 0.25 mm internal diameter, 0.4 μm film thickness, 110 °C) in oven 1 was employed. Either the first or second eluted (pure) enantiomer was trapped on the reactor column, which was a

  1433-7851/00/3916-2939 $ 17.50+.50/0

deactivated fused silica column coated with dimethylpolysiloxane (1 m × 0.25 mm internal diameter, 0.002 μm film thickness). The reactor column was quickly heated to the temperature T and enantiomerization commenced. After the reaction time t the reactor column was rapidly cooled with liquid nitrogen and the new enantiomeric mixture was transferred onto the second separation column coated with Chirasil-β-Dex (12.5 m × 0.25 mm internal diameter, 0.4 μm film thickness, 110 °C), where the enantiomers were separated. The carrier gas used was helium. The experiment was repeated three times at each temperature. The rate constant k for inversion was calculated according to Equation (1) using the observed enantiomeric ratio (% *er*) of the major peak area, the temperature T, and the reaction time t.

$$k = \frac{1}{2t} \ln \frac{er+1}{er-1} \quad (1)$$

The mean values of $\ln(k/T)$ were plotted as a function of T^{-1} according to the Eyring equation. The activation parameters $\Delta H^{\neq}_{gas}$ and $\Delta S^{\neq}_{gas}$ were obtained from the gradient and the y intercept, respectively, of a linear fit. A statistical factor κ of 0.5 for a reversible inversion process was applied.

Received: March 31, 2000 [Z14931]

[1] a) C. H. Bushweller in *Acyclic Organonitrogen Stereodynamics* (Eds.: J. B. Lambert, Y. Takeuchi), VCH, New York, **1992**, p. 1; b) L. Lunazzi, D. Macciantelli, L. Grossi, *Tetrahedron* **1983**, *39*, 305.

[2] W. B. Jennings, D. R. Boyd in *Cyclic Organonitrogen Stereodynamics* (Eds.: J. B. Lambert, Y. Takeuchi), VCH, New York, **1992**, p. 105.

[3] a) H. Bock, I. Goebel, Z. Havlas, S. Liedle, H. Oberhammer, *Angew. Chem.* **1991**, *103*, 193; *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 187; b) R. Boese, D. Bläster, M. Yu. Antipin, V. Chaplinski, A. de Meijere, *Chem. Commun.* **1998**, 781; c) J. E. Anderson, D. Casarini, L. Lunazzi, *J. Org. Chem.* **1996**, *61*, 1290; d) T. C. Wong, L. R. Colazzo, S. Guziec, Jr., *Tetrahedron* **1995**, *51*, 649.

[4] a) J. E. Anderson, J.-M. Lehn, *J. Am. Chem. Soc.* **1967**, *89*, 81; b) G. V. Shustov, A. Yu. Shibaev, Yu. V. Puzanov, R. G. Kostyanovsky, *Izv. Akad. Nauk SSSR Ser. Khim.* **1988**, 1869; G. V. Shustov, A. Yu. Shibaev, Yu. V. Puzanov, R. G. Kostyanovsky, *Bull. Acad. Sci. USSR Div. Chem. Sci.* **1988**, *37*, 1671.

[5] a) J. H. Hall, W. S. Bigard, *J. Org. Chem.* **1978**, *43*, 2785; b) V. J. Baker, A. R. Katritzky, J.-P. Majoral, S. F. Nelsen, R. J. Hintz, *J. Chem. Soc. Chem. Commun.* **1974**, 823; c) V. J. Baker, A. R. Katritzky, J.-P. Majoral, *J. Chem. Soc. Perkin Trans. 2*, **1975**, 1191.

[6] S. F. Nelsen, P. A. Petillo, H. Hang, T. B. Frigo, D. A. Dougherty, M. Kaftory, *J. Org. Chem.* **1991**, *56*, 613.

[7] M. Förterer, P. Rademacher, *Chem. Ber.* **1980**, *113*, 221.

[8] a) R. G. Kostyanovsky, G. K. Kadorkina, V. N. Voznesensky, I. I. Chervin, M. Yu. Antipin, K. A. Lyssenko, E. V. Vorontzov, V. I. Bakhmutov, P. Rademacher, *Mendeleev Commun.* **1996**, 69; b) R. G. Kostyanovsky, P. Rademacher, Yu. I. El'natanov, G. K. Kadorkina, G. N. Nikiforov, I. I. Chervin, S. V. Usachov, V. R. Kostyanovsky, *Izv. Akad. Nauk Ser. Khim.* **1997**, 1346 [*Russ. Chem. Bull.* **1997**, *46*, 1291].

[9] Inversion of one nitrogen atom leads to a true *cis*-configurated *meso*-form.

[10] J. A. Hirsch in *Topics in Stereochemistry* (Eds.: N. L. Allinger, E. L. Eliel), Wiley, New York, **1967**.

[11] V. Schurig, D. Schmalzing, M. Schleimer, *Angew. Chem.* **1991**, *103*, 994; *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 987.

[12] a) V. Schurig, S. Reich, *Chirality* **1998**, *10*, 316; b) O. Trapp, V. Schurig, *J. Am. Chem. Soc.* **2000**, *122*, 1424; c) S. Reich, O. Trapp, V. Schurig, *J. Chromatogr.* **2000**, *892*, in press.

[13] G. V. Shustov, S. V. Varlamov, A. Yu. Shibaev, Yu. V. Puzanov, R. G. Kostyanovsky, *Izv. Akad. Nauk SSSR Ser. Khim.* **1989**, 1816.

[14] G. V. Shustov, S. N. Denisenko, A. Yu. Shibaev, Yu. V. Puzanov, R. G. Kostyanovsky, *Khim. Physica* **1989**, *8*, 366.

[15] a) A. A. Frost, R. G. Pearson, *Kinetics Mechanism, 2nd ed.*, Wiley, New York, **1961**, p. 135; b) H. Hermann, R. Huisgen, H. Mader, *J. Am. Chem. Soc.* **1971**, *93*, 1779; c) E. W. Yankee, F. D. Bader, N. E. Howe, D. J. Cram, *J. Am. Chem. Soc.* **1973**, *95*, 4210; d) O. Gonzales, D. E. Gallis, De Lanson R. Crist, *J. Org. Chem.* **1986**, *51*, 3266.

[16] a) H.-D. Beckhaus, G. Hellmann, C. Rüchardt, *Chem. Ber.* **1978**, *111*, 72; b) A. Haas, K. Schlosser, S. Steenken, *J. Am. Chem. Soc.* **1979**, *101*, 6282; c) K. Schlosser, S. Steenken, *J. Am. Chem. Soc.* **1983**, *105*, 1504.

[17] B. Zwanenburg, W. E. Weening, J. Strating, *Recl. Trav. Chim. Pay-Bas* **1965**, *84*, 408.

Stable and Selective Hybridization of Oligonucleotides with Unnatural Hydrophobic Bases**

Markus Berger, Anthony K. Ogawa, Dustin L. McMinn, Yiqin Wu, Peter G. Schultz,* and Floyd E. Romesberg*

DNA duplex stability and sequence specificity are based on the complementary Watson–Crick hydrogen-bonding (H-bonding) patterns of adenine with thymine (dA:dT base pair) and cytosine with guanine (dC:dG base pair). Additional, stable and selective base pairs would facilitate hybridization or encoding experiments in cases where natural sequences cross hybridize, or where increased information storage is desirable.[1–4] Moreover, the characterization of DNA containing such base pairs may provide increased insight into DNA structure and function.[5–15] We recently reported the synthesis and characterization of several unnatural nucleosides that possess hydrophobic groups instead of a purine or pyrimidine base.[2, 3] Among these, hydrophobic nucleosides containing the isocarbostyril core were particularly interesting due to their ability to form stable self-pairs in duplex DNA (Isocarbostyril = 1-hydroxyisoquinoline).[3] We now describe a series of isocarbostyril derivatives that culminate in a self-pair which is both more stable and more selective than either a dA:dT or a dC:dG pair in the same sequence context.

The isocarbostyril core was derivatized with a propynyl group at C7, a substitution known to impart increased stability to both natural[9, 16] and unnatural DNA,[2, 3] as well as with a C3 methyl group, which is expected to pack in the hydrophobic base interface. The 7-propynyl-3-methylisocarbostyril nucleoside (**PIM**) was synthesized and converted to phosphoramidites **5** as shown in Scheme 1.[17] The free base **2** was generated according to the procedure of Hirato et al.,[18] and

[*] Prof. P. G. Schultz, Prof. F. E. Romesberg, Dr. M. Berger, Dr. A. K. Ogawa, Dr. D. L. McMinn, Dr. Y. Wu
Department of Chemistry
The Scripps Research Institute
10550 North Torrey Pines Road
La Jolla, CA 92037 (USA)
Fax: (+1) 858-784-7472
E-mail: floyd@scripps.edu

[**] This work was supported by the National Institutes of Health (GM 60005 to F.E.R.) and the Skaggs Institute for Chemical Biology (F.E.R. and P.G.S.). A.K.O. thanks the National Institutes of Health for a postdoctoral fellowship (F32 GM19833-01).