CHEMISTRY
A European Journal

A Journal of
ChemPubSoc Europe

Accepted Article

Title: Unique stereoselective homolytic C-O bond activation in diketopiperazine-derived alkoxyamines via adjacent amide pyramidalization

Authors: Tynchtyk Amatov, Harish Jangra, Radek Pohl, Ivana Cisarova, Hendrik Zipse, and Ullrich Jahn

To be cited as: *Chem. Eur. J.* 10.1002/chem.201803284

Link to VoR: http://dx.doi.org/10.1002/chem.201803284

Supported by
ACES

WILEY-VCH

10.1002/chem.201803284

WILEY-VCH

FULL PAPER

Unique stereoselective homolytic C-O bond activation in diketopiperazine-derived alkoxyamines via adjacent amide pyramidalization

Tynchtyk Amatov, [a, b] Harish Jangra,[b] Radek Pohl,[a] Ivana Cisařová,[c] Hendrik Zipse,*[b] Ullrich Jahn*[a]

Abstract: Simple monocyclic diketopiperazine (DKP)-derived alkoxyamines exhibit an unprecedented activation of a remote C-O bond for homolysis by amide distortion. The combination of strain release-driven amide planarization and the persistent radical effect (PRE) enable a unique, irreversible and quantitative *trans*→*cis* isomerization under much milder conditions than typically observed for such homolysis-limited reactions. This isomerization is shown to be general and independent of the steric and electronic nature of both amino acid side chains and substituents at the DKP nitrogen atoms. Homolysis rate constants have been determined and they significantly differ for both, the labile *trans*-diastereomers and the stable *cis*-diastereomers. To reveal the factors influencing this unusual process, structural features of the kinetic *trans*- and thermodynamic *cis*-diastereomers were investigated in the solid state and in solution. X-ray crystallographic analysis and computational studies indicate a substantial distortion of the amide bond from planarity in the *trans*-alkoxyamines, which is the cause for the facile and quantitative isomerization. Thus, these amino acid-derived alkoxyamines are the first examples that exhibit a large thermodynamic preference for one diastereomer over the other upon thermal homolysis, which allows controlled switching of configurations and configurational cycling.

Introduction

The amide bond is one of the best-studied linkages because of its profound implications on the structure and functions of biomolecules as well as organo- and biocatalysts.[1] Strong $n_N \rightarrow \pi^*_{C=O}$ interaction, which is responsible for its planar nature, and hydrogen bonding abilities are central to making the amide unit a powerful conformation-controlling element.[2,3] Deviation from the planar geometry greatly alters both the physical and chemical properties of amide containing molecules.[4,5] Lukeš proposed the structure of bridgehead-nitrogen bearing lactams, 2-quinuclidone and its one-carbon shorter homologue,[6] as early as 1938 and pointed out the disruption of the amide resonance in such twisted amides for the first time because of violation of Bredt's rule.[7] Since then the chemistry of distorted amides, mostly incorporated into medium-sized bridged lactam architectures, has captured the imagination of chemists.[8] The unambiguous synthesis of 2-quinuclidonium tetrafluoroborate by Stoltz *et al.*[9,10] was a landmark achievement more than 68 years after Lukeš's publication.[11] Significant weakening of the N–C(O) bond is the most important consequence of amide nitrogen pyramidalization. The β-lactam antibiotic penicillin is a prime example of a distorted amide, making it the warhead against harmful bacteria, which saved countless human lives.[12] Very recently, a considerable interest in applications of non-planar amides **I**, which are not part of bridged lactam motives,[13] in transition-metal catalyzed N–C(O) bond activation by oxidative addition and coupling via acylmetal species **II** has emerged; its facility is a result of ground-state destabilization of the distorted amide bond (Figure 1).[14-16] This strategy can also be diverted to decarbonylation of acylmetal species and subsequent cross-coupling, thus formally activating the C–C(O) bond as a consequence of N–C(O) insertion.[17] Amide bond pyramidalization may also affect the strength of adjacent bonds. Scattered examples document C–N σ-bond cleavage reactions in twisted amides of type **V** and **VI** under reductive, oxidative and alkylative conditions as reported by the Aube[18,19] and Szostak[20,21] groups. The pK_A of the αC–H bond to the carbonyl group is dramatically lowered, and as a result of amide nitrogen pyramidalization in **VII** its use in aldol additions is enabled.[22,23] Similar effects were observed by Lloyd-Jones and Booker-Milburn in sterically hindered amides such as **VIII**,[24] which undergo rapid proton switch via a twisted conformer because of their enhanced αC–H acidity.

The strain associated with disruption of amide bond geometry should in principle also have significant implications for the C-Q bond strengths other than C-H bonds in **I** and enable their activation. This has been so far widely neglected; no studies exist. However, this principle may lay out new avenues for the design of catalytic and thermal reactions for selective functionalization of amide containing natural products and feedstock materials. We recently introduced alkoxyamines **IX** as DKP-radical surrogates and applied them in the synthesis of diverse bridged DKP motives, which are present in numerous biologically active alkaloids.[25-27] This transformation is controlled by the persistent radical effect (PRE),[28-31] a powerful principle that governs the selective radical coupling between transient and persistent radical species **X** and **XI**. The homolysis of alkoxyamines is a well-appreciated phenomenon, which is applied in nitroxide-mediated

[a] Dr. T. Amatov, Dr. R. Pohl, Dr. U. Jahn
Institute of Organic Chemistry and Biochemistry,
Academy of Sciences of the Czech Republic
Flemingovo náměstí 2, 16610 Prague (Czech Republic)
E-mail: ullrich.jahn@uochb.cas.cz
[b] Dr. T. Amatov, H. Jangra, Prof. Dr. H. Zipse
Ludwig Maximilian University
Department of Chemistry
Butenandstrasse 5-13, 81377 München (Germany) E-mail:
zipse@cup.uni-muenchen.de
[c] Dr. I. Cisařová
Department of Inorganic Chemistry, Faculty of Science,
Charles University in Prague
Hlavova 2030/8, 12843 Prague (Czech Republic)

Supporting information for this article is given via a link at the end of the document.

10.1002/chem.201803284

polymerization (NMP),[32-34] tin-free radical transformations[35] as well as in materials research, which is a testament to the power of PRE. However, the vast majority of these transformations require temperatures beyond 100 °C to proceed, which prohibits their application under milder conditions. Thus, an enormous interest exists in designing more labile alkoxyamines,[36] homolysis of which can be triggered by external stimuli under controlled conditions.[37,38] Such labile alkoxyamines have been suggested as novel theranostic agents, applying transient and highly reactive alkyl radicals to irreversibly damaging unhealthy cells and using the simultaneously formed persistent nitroxide radicals as diagnostic tools.[39,40] For such biological applications, the structure of alkoxyamines should play an important role; ideally it should be biocompatible and assist binding to desired biological targets, a feature that is not given in current compounds of this type. Given that DKPs constitute a large class of biologically active medicinally privileged scaffolds,[41-43] we hypothesized that a combination of amino acid-derived DKPs with nitroxides may prove attractive for potential biomedical applications as theranostic agents.

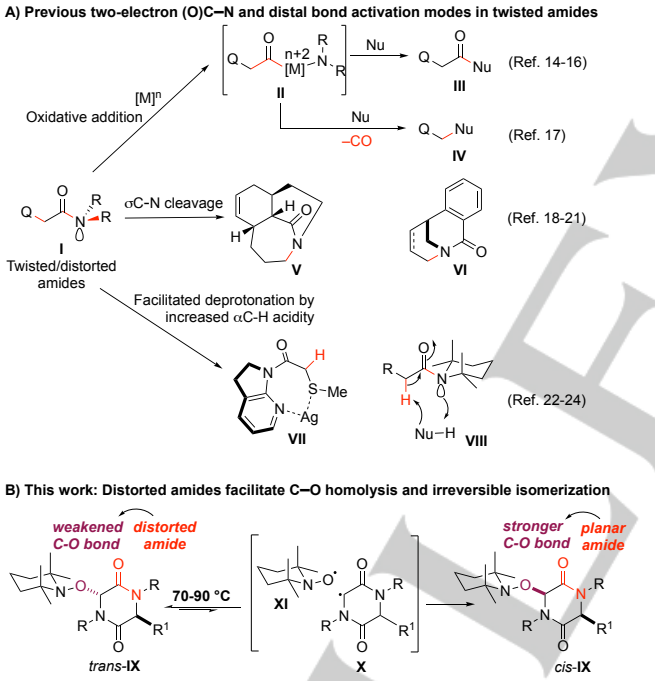


Figure 1. A) Known examples of amide twisting-mediated bond activation modes. B) Proposed selective homolytic cleavage of an adjacent C–O bond controlled by amide bond distortion.

Herein we report that *trans*-substituted diketopiperazine-derived alkoxyamines *trans*-**IX** are indeed a step on the way to this goal, since homolysis starts surprisingly at temperatures as low as 70 °C for tertiary alkoxyamines and even below room temperature for quaternary alkoxyamines. Preparative, structural and computational studies demonstrate that deviation of the amide bonds from planarity is the cause for the significant weakening of the adjacent C–O bond. This effect can be used as a steering element for configurational switching to *cis*-**IX** by a radical mechanism.

Results

Preparative *trans*→*cis* isomerization reactions.
During a temperature screening to find optimum conditions for PRE-mediated cyclization reactions, a *trans*-*cis* isomerization of DKP alkoxyamines was discovered. Heating a 5:1 *trans/cis* mixture of **1**[44] in *t*BuOH at 80 °C for 2 h provided pure *cis*-**1**, whose spectral data matched the minor component in the original mixture (Figure 2A). Both isomers of **1** were individually crystallized and their configurations were confirmed by X-ray crystallography (Figure 3). Similarly, an inseparable 11:1 *trans*-**2**/*cis*-**2** mixture with a benzyl group, converged to pure *cis*-**2**. Enantiomerically pure tryptophan-derived DKP *trans*-**3**, bearing *N*-Me groups, also isomerized cleanly to the *cis*-isomer upon heating without compromising the residing stereocenter. It is noteworthy that the isomerization proceeded quantitatively regardless of the steric features of the nitrogen substituents.

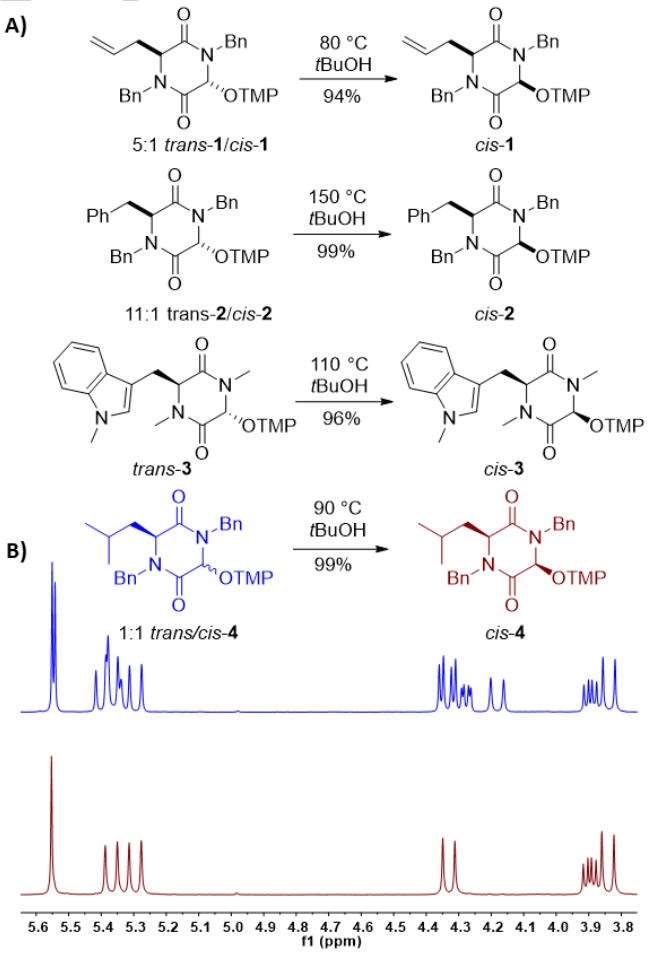


Figure 2. A) Thermal *trans*→*cis* isomerization of DKP-derived alkoxyamines. B) Comparison of the ^{1}H NMR spectra of a 1:1 *trans/cis*-**4** mixture before heating (blue) and after heating (maroon).

Hybridization and steric bulk of the C-substituent also did not influence the direction of the isomerization, since a 1:1 *trans/cis* mixture of aliphatic *L*-leucine-derived alkoxyamine **4** cleanly and quantitatively isomerized on heating at 90 °C as revealed by their ^{1}H NMR spectra (Figure 2B). These results show that the radical coupling during isomerization occurs with exclusive diastereoselectivity, thus the isomerization of diketopiperazine alkoxyamines is unidirectional toward the *cis*-isomers regardless of the steric and electronic features of nitrogen and carbon substituents.

Solid state and solution structures of *trans*- and *cis*-DKP alkoxyamines.

X-Ray crystallographic investigation of DKP alkoxyamines *cis*-**1** and *trans*-**1**, *cis*-**2**, *cis*-**3** and *trans*-**3**, *cis*-**4** and *trans*-**5** unambiguously confirmed the relative *trans*-configuration of the alkyl and alkoxyamine substituents in the starting DKP alkoxyamines and their *cis*-configuration in the products (Figure 3). None of the crystallographically determined structures reveals significant steric interactions of the substituents. An immediately recognizable feature in all molecular structures is that the alkoxyamine unit always occupies a pseudoaxial position in both *trans*- and *cis*-diastereomers. NOE experiments for *cis*-**1** and *trans*-**1** as well as *cis*-**2** and *trans*-**2** pairs also support a strong bias for axial orientation of the alkoxyamine unit in solution (See the Supporting information (SI), Figure S1). The large difference in thermodynamic stability and the dramatic difference in the C–ON bond strengths of *cis*- and *trans*-diastereomers of alkoxyamines **1**-**4** should have a significant stereoelectronic origin. It has been noted in the literature that simple alkoxyamines having a heteroatom in the α-position such as α-alkoxy, α-ethylaminyl and α-phenylsulfanyl substituents have small homolysis rate constants k_d, and consequently high carbon-oxygen bond dissociation energies BDE(C–ON), which however, poorly correlate with the BDE(C–H) of the corresponding non-alkoxyamine-substituted precursors.[45-48] The common rationalization for these observations invoked the anomeric effect as the origin of unusually strong C–ON bonds in those cases, which was also supported by computational studies, revealing the importance of hyperconjugative interactions between the lone pair of the oxygen atom of the alkoxyamine and the antibonding σ*-orbital of the neighboring αC–heteroatom bond.[49]

Several features of the solid-state structures are noteworthy (Table 1). The bond lengths of the C4–OTMP unit vary in a rather small range of 0.01 Å (Atom numbering of X-ray structures in Figure 3) and are somewhat shorter than in comparable simpler cyclic α-carbonyl substituted alkoxyamines (cyclic ketones[50] 1.454 Å, esters[51] 1.435 Å), but longer than α-amino-substituted alkoxyamines. Surprisingly, the C3-N2 distance varies and is, except for *trans*-**3**, longer than in the corresponding *cis*-isomers, whereas the C1–N1 bond lengths do not differ very much in both isomers.

The C3,N2,C21,C2 dihedral angles of the *trans*-DKP units as visualized in Figure 3 surprisingly show with 157-165°, a strong deviation from planarity, whereas the same dihedral angle amounts to 172-178° in the corresponding *cis*-isomers. At the same time, the dihedral angles involving the nitrogen atom N1 also deviate, but not that strongly. Notable twisting of the N2–C(O) amide bond with twist angles τ = 9.1° and 9.8°, respectively, is also observed in *trans*-**1** and *trans*-**5**. The twist angles go in opposite directions for both nitrogen atoms in that they are larger at N2 in the *trans*-isomers, but except for *cis*-**3** larger at N1 in the *cis*-isomers.

Pyramidalization of the N2 atom is significant as determined by calculation of the classical Winkler-Dunitz distortion parameter χ_{N2} and χ_{N1}.[52] In all characterized *trans*-alkoxyamines, a significant pyramidalization of N2 with χ_{N2} = 14.6-22.1° was found and N1 is also distorted, though with χ_{N1} = 5.5-11.3° less strongly. In contrast, deviation from planarity of both amide nitrogen atoms is small in the *cis*-isomers, except for *cis*-**2**. These data collectively demonstrate significant amide bond twisting and pyramidalization in all *trans*-alkoxyamine diastereomers, whereas the distortion is much less marked in all *cis*-isomers.

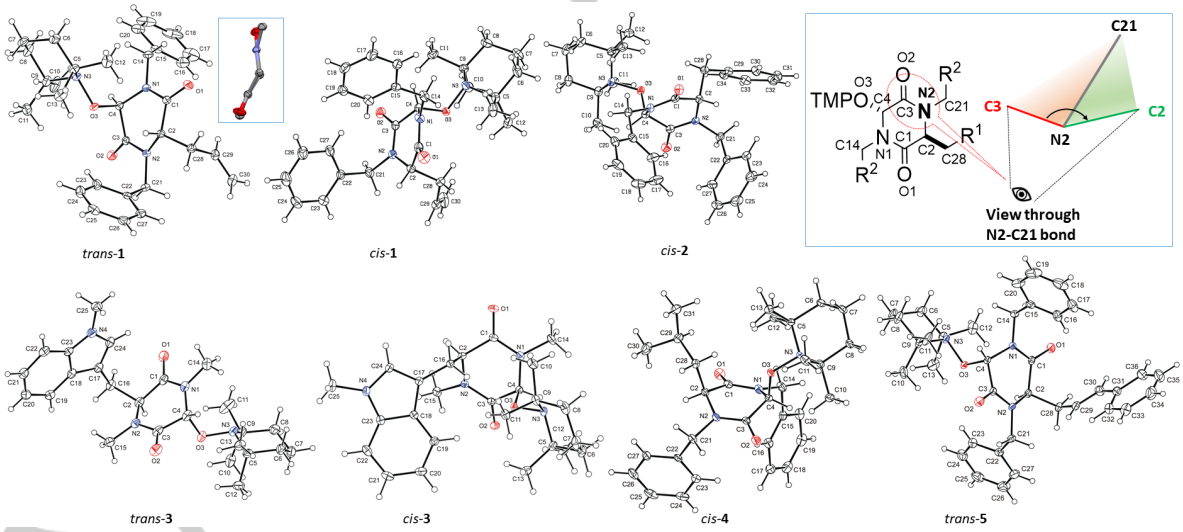


Figure 3. X-ray structures of alkoxyamines *cis/trans*-**1**, *cis*-**2**, *cis/trans*-**3**, *cis*-**4** and *trans*-**5**. The insets show the Newman projection of the DKP core along the N2–C(O) and N1–C(O) bonds for *trans*-**1**, the common numbering scheme of the DKP skeleton and the definition of the important C3,**N2**,C21,C2 dihedral angle. For *trans*-**5**, R^1 = *trans*-CH=CHPh, R^2 = Ph.

Table 1. Important structural/distortion parameters of alkoxyamines **1-5** characterized by X-ray crystallography.

Parameter	*trans*-**1**	*cis*-**1**	*cis*-**2**	*trans*-**3**	*cis*-**3**	*cis*-**4**	*trans*-**5**
d(C4—OTMP) (Å)	1.436	1.429	1.428	1.429	1.433	1.426	1.429
d(C3—N2) (Å)	1.355	1.341	1.344	1.344	1.340	1.345	1.351
d(C1—N1) (Å)	1.351	1.354	1.355	1.354	1.352	1.363	1.350
Dihedral angle C3,N2,C21,C2 (°)	157.9	178.3	171.9	165.0	177.0	178.1	165.0
Dihedral angle C1,N1,C14,C4 (°)	169.0	174.7	179.2	174.4	174.9	178.2	170.9
Sum of angles at N2 (at N1) (°)	356 (359)	360 (360)	360 (360)	358 (360)	360 (360)	360 360	358 (359)
Twist angle (τ) at N2 (at N1) **(°)**	**9.1** (0.5)	2.7 (8.2)	3.0 (10.1)	3.3 (7.4)	1.8 1.6	3.4 (8.6)	**9.8** (5.1)
χ_{N2} (°)	**22.1**	1.8	8.2	**14.6**	3.1	1.8	**15.0**
χ_{N1} (°)	**11.3**	5.3	0.7	**5.5**	5.1	1.8	**9.2**

Computational study of the structural effects in alkoxyamines 1.

The relative importance of anomeric effect and amide pyramidalization for the observed reactivity for DKP-derived alkoxyamines *cis*-**1** and *trans*-**1** was first evaluated by optimizing their structures at the B3LYP/6-31G(d) level of theory and comparing them with the X-ray crystallographic results, which are in good agreement (see SI, Figures S7). Subsequently, the magnitude of these interactions was quantified using the Natural Bond Orbital (NBO) analysis at the B3LYP/6-31G(d) level of theory (Figure 4 and SI, Figure S21 and Table S3). Indeed, the alkoxyamine oxygen lone pair interacts favorably with the neighboring C–N, C–C, and C–H bonds, speaking for an anomeric effect.

However, the cumulative energies for these interactions as well as their individual components are essentially identical for both isomers (–75 kJ/mol for *cis*-**1** vs. –74 kJ/mol for *trans*-**1**), which implies that the stability difference of *trans*- vs. *cis*-diastereomers must have other origins than the anomeric effect. The strongest donor/acceptor interactions in these systems concern the C3/N2 amide resonance interaction, which amounts to 308 kJ/mol in *cis*-**1**, but to only 284 kJ/mol in *trans*-**1**. This difference is accompanied by larger differences in amide bond planarity in these two stereoisomers, where the calculated (O)C3–N2–C21–C2 dihedral angles amount to 166° in *trans*-**1** and 175° in *cis*-**1**. These values differ somewhat from the experimentally obtained 157.9° and 178.3° but show the trend very well.

Kinetics of isomerization, reductive radical quenching and cyclization of alkoxyamines 1 and 2.

With solid structural information at hand, DKP alkoxyamines **1** and **2** were studied with respect to their potential for radical generation under mild conditions by determination of their homolysis, reduction and cyclization kinetics.

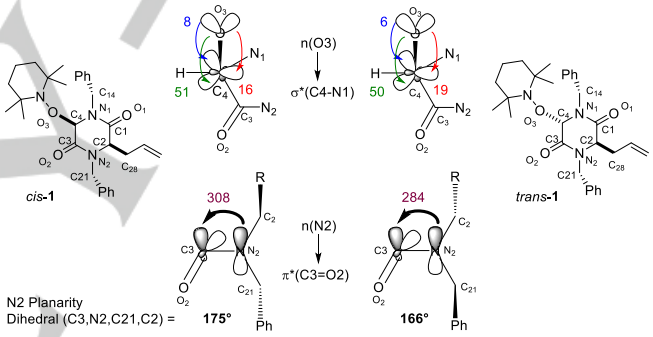


Figure 4. Important hyperconjugation interactions (in kJ/mol, NBO) in *cis*-**1** and *trans*-**1** calculated at the B3LYP/6-31G(d) level of theory.

The homolysis rate constants k_d showed dramatic differences for *trans*- and *cis*-diastereomers of alkoxyamines **1** and **2**. The isomerization of *trans*-**1** was monitored by ^{1}H NMR spectroscopy at four different temperatures and the experimental data fit to first-order kinetics (Figure 5A, 5B). Homolysis of *trans*-**1** was reasonably fast and is rate determining, since no observable cyclization took place compared to formation of *cis*-**1** when it was heated in the 75-85 °C temperature range, which allowed determination of its kinetics (Table 2, Figure 5, Figure S2). The activation enthalpy was determined to be $\Delta H^{\ddagger}$ = 128 kJ/mol and the corresponding activation entropy to $\Delta S^{\ddagger}$ = 54 J/(K×mol); the activation energy amounts to E_a = 131 kJ/mol using the Arrhenius equation.

10.1002/chem.201803284

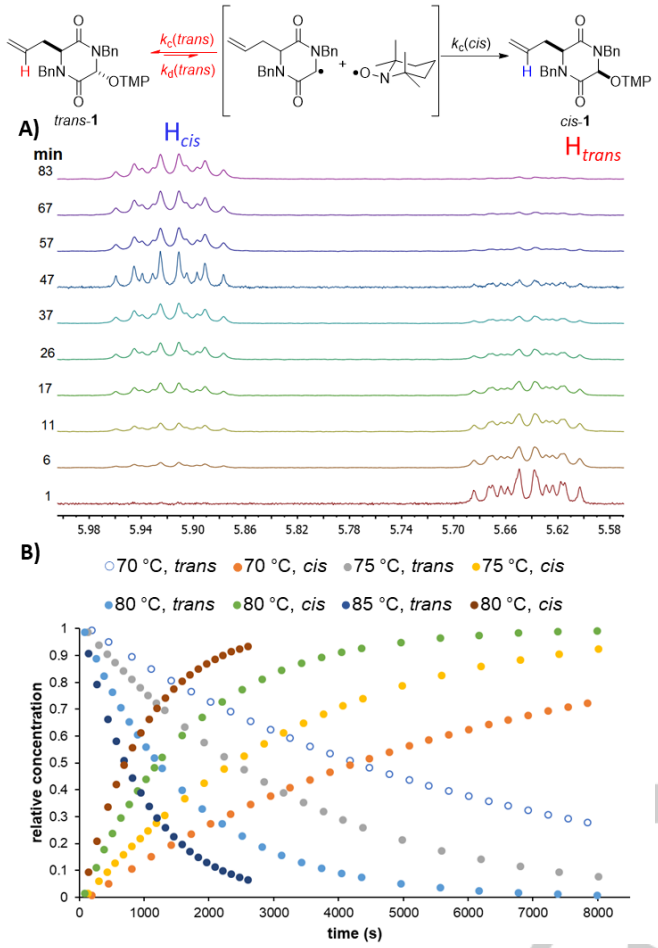


Figure 5. A) A typical ^{1}H NMR profile of the vinylic proton region at 80 °C. B) Kinetic traces for the isomerization of *trans*-**1** between 70 °C and 85 °C.

The isomerization of *trans*-**2**, bearing a benzyl side chain, to *cis*-**2** was similarly studied and shown to proceed ca. 1.6 times faster than isomerization of *trans*-**1** (Table 2 and Figure S3). The activation enthalpy of $\Delta H^{\ddagger}$ = 125 kJ/mol and activation entropy of $\Delta S^{\ddagger}$ = 52 J/(K×mol) for the overall transformation translate into an activation energy of E_a = 128 kJ/mol (Figure S4). In the 70-85 °C temperature range the homolysis of the *cis*-diastereomers must be at least 2-3 orders of magnitude slower or even negligible compared to homolysis of the *trans*-diastereomer, i.e. $k_{d(trans)} >> k_{d(cis)}$ (vide infra). This allows approximation of the observed rate constants for the isomerization process to the homolysis rate constants of the *trans*-diastereomers, i.e. $k_{obs} \sim k_{d(trans)}$.

These results are fully supported by a computational investigation performed at the (U)B2PLYP/G3MP2Large//(U)B3LYP/6-31G(d) level in combination with the SMD continuum model for DMSO solution (Figure 6A, and SI, Figures S11-S13 and Table S8): DKP alkoxyamine *cis*-**1** is in Gibbs free energy terms 12.1 kJ/mol more stable than *trans*-**1** at 298.15 K. The barrier for radical pair formation amounts to +120.5 kJ/mol for *trans*-**1**, whereas that for *cis*-**1** is with +126.1 kJ/mol as expected higher. The barrier for homolysis for *trans*-**1** is slightly higher than the +109 kJ/mol calculated from the experimentally determined activation parameters (Table 2).

Table 2. Kinetic data for the thermal isomerization of *trans*-**1** and *trans*-**2**.

trans-**1**			
T (K)	$k_d \times 10^{-4}$ (s^{-1})	$t_{1/2}$ (min)	$\Delta G^{\ddagger}$ (kJ/mol)
343.15	1.6	72	109.3
348.15	3.3	35	109.0
353.15	6.1	19	108.8
358.15	11	11	108.5
A (s^{-1})	E_a (kJ/mol)	$\Delta H^{\ddagger}$ (kJ/mol)	$\Delta S^{\ddagger}$ (J/(K×mol)
13.5×10^{15}	131	128	54
trans-**2**			
T (K)	$k_d \times 10^{-4}$ (s^{-1})	$t_{1/2}$ (min)	$\Delta G^{\ddagger}$ (kJ/mol)
343.15	2.9	40	107.7
353.15	10	11	107.2
358.15	19	6	106.9
A (s^{-1})	E_a (kJ/mol)	$\Delta H^{\ddagger}$ (kJ/mol)	$\Delta S^{\ddagger}$ (J/(K×mol)
9.83×10^{15}	128	125	52

Quaternary DKP alkoxyamines remained so far elusive, any attempt to isolate them failed so far. Their formation can be inferred experimentally from successful cyclization reactions that culminated in an approach to asperparaline C.[27] To define the reasons for their instability and to draw conclusions that may lead to the design of DKP alkoxyamines that only slowly homolyze at physiological temperatures, quaternary DKP alkoxyamines *trans*-**q1** and *cis*-**q1** with fully substituted carbon atoms were computationally investigated (Figure 6B) and compared to the isomers of **1** (Figure 6A). On one hand, both the stereoelectronic and thermodynamic trends are conserved compared to **1**. Significant pyramidalization of the N2-atom in *trans*-**q1** is observed with a dihedral angle (O)C3–N2–C21–C2 amounting to 166° compared to 171° in *cis*-**q1** (see SI, Figs. S22-S24, Tables S4 and S6). On the other hand, coupling of the transient tertiary DKP radical with persistent TEMPO becomes endergonic for *trans*-**q1** and at the same time the activation barrier for homolysis is significantly reduced in both isomers, thus making DKP-derived quaternary alkoxyamines **q1** extremely labile (see SI, Figs. S25-S27 and Table S9). These results, however, clearly point to opportunities to design DKP alkoxyamines with a defined homolysis range, if the homolysis rate constant of at least the *cis*-isomer can be decreased by increasing the C-O bond strength through optimizing the substitution pattern at C2.

10.1002/chem.201803284

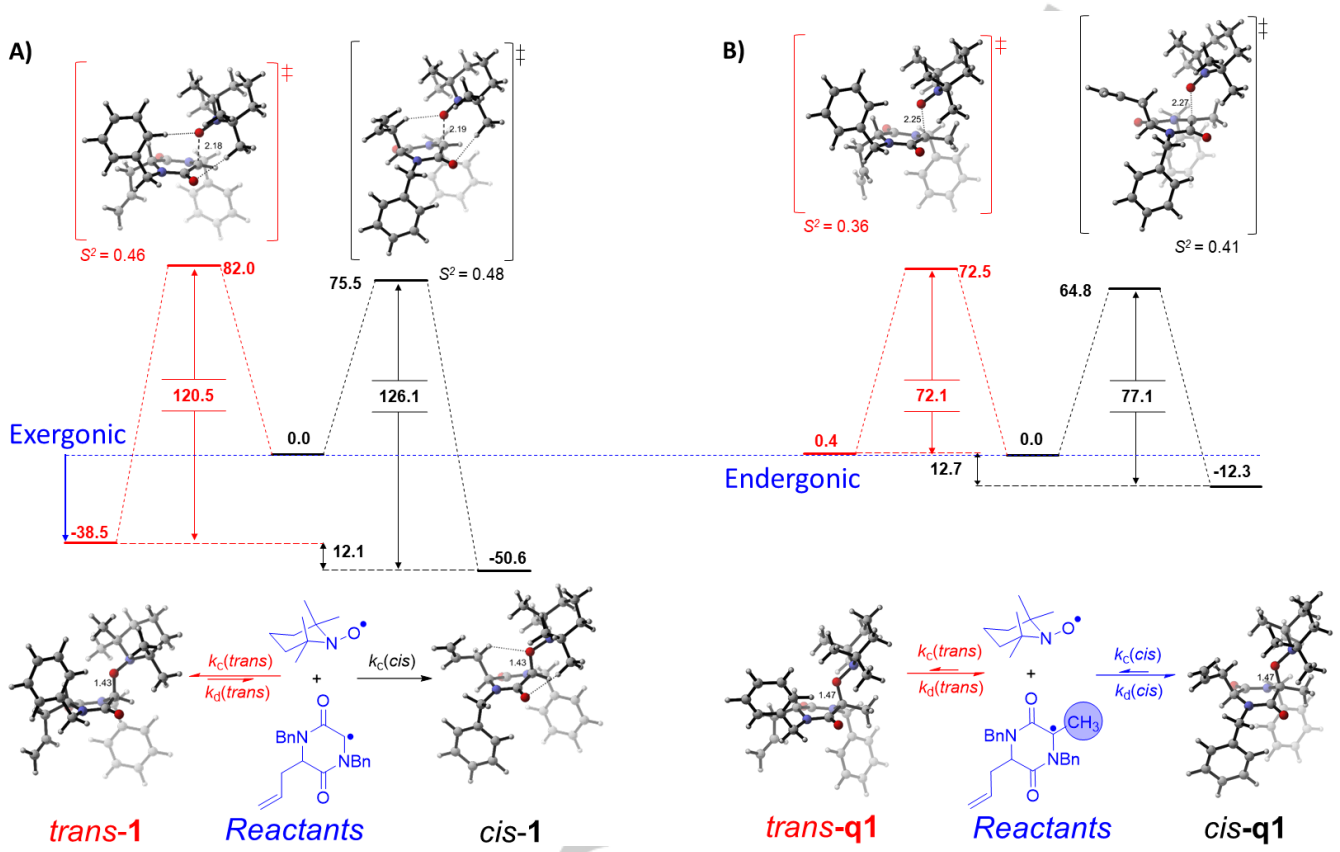


Figure 6. Solvation-corrected Gibbs energy (*ΔG*sol-sp, kJ/mol) profile for A) *trans*→*cis* isomerization of DKP-alkoxyamine **1** and B) its hypothetical quaternary analog **q1**, both calculated at the (U)B2PLYP/G3MP2Large//(U)B3LYP/6-31G(d) level of theory. Single point solvation energies were calculated for DMSO at the SMD/(U)B3LYP/6-31G(d) level of theory.

The assumption that homolysis of the *cis*-diastereomers of **1** and **2** is negligible at lower temperatures is additionally supported by a radical reduction experiment (Figure 7A). Heating the 11:1 *trans*/*cis*-**2** mixture in the presence of excess thiophenol (13 equivalents) at 70 °C and monitoring by ^{1}H NMR spectroscopy showed that isomerization to *cis*-**2** effectively competed with radical reduction by thiophenol. Moreover, when *trans*-**2** was fully consumed, the ratio of *cis*-**2** to reduced DKP red-**2** was ca. 50:50, and most importantly it remained essentially constant on further heating for three hours. In contrast, heating *cis*-**2** with thiophenol under identical conditions, but at 110 °C leads to clean formation of fully reduced DKP red-**2** (Figure 7B). Taken together, these experiments convincingly demonstrate that *cis*-**2** does not undergo homolysis of the C–O bond at 70 °C.

Knowing the homolysis rate constants k_{isom}~$k_{d(trans)}$ for *trans*-isomers **1** and **2** (cf. Table 2), and that isomerization is not competing upon homolysis of *cis*-isomers because of clean pseudo-first order reduction (Figure 7B), $k_{d(cis)}$ for *cis*-**1** and *cis*-**2** were obtained applying the method developed by Edeleva et al.,[53] which is based on thermolysis of alkoxyamines in the presence of excess PhSH. A clean first-order consumption of *cis*-**1** and *cis*-**2** took place and rate constants $k_{d(cis)}$ were obtained in the temperature range between 90 °C and 115 °C (Table 3, Figure S5). It is noteworthy that under these conditions potential cyclization reactions of both substrates were not observed, showing that the rate of reduction is orders of magnitude faster.[54-58] Comparison of these values with the homolysis rate constants for *trans*-**2** (cf. Table 2) shows that homolysis of *cis*-**2** at 90 °C is 1.5 times slower than the homolysis of *trans*-**2** at 70 °C, whereas the homolysis of *cis*-**1** at 90 °C is 1.8 times slower compared to *trans*-**1** at 70 °C. This confirms that the thermodynamic preference for the *cis*-configuration is undoubtedly a consequence of a significant difference in the bond dissociation energies (BDE) of the C–O bond between the *trans*- and *cis*-isomers as was also confirmed by the computational study.

To determine the relative facility of the isomerization reaction of the isomers of **1** and potential subsequent C-C bond formation reactions, the cyclization kinetics were determined by thermolysis of pure *cis*-**1** in the absence of PhSH at 100 °C, 110 °C and 115 °C and monitoring the progress by ^{1}H NMR spectroscopy (See the SI, Figure S6). A clean first-order decay of the signals corresponding to *cis*-**1** and the appearance of signals corresponding to 6-exo-trig cyclization products *syn*/*anti*-**6** and 7-endo-trig cyclization product **7** was observed (Figure 8A). The

10.1002/chem.201803284

cyclization was slow at 100 °C and required ca. three hours to reach completion. However, the rate of cyclization increased eightfold at 115 °C. The obtained rate constants for the first-order decay of *cis*-**1** were with 3.7×10^{-4} s^{-1}, 1.6×10^{-3} s^{-1}, and 2.8×10^{-3} s^{-1} at 100 °C, 110 °C and 115 °C, respectively, slightly smaller than those determined for reduction in the presence of thiophenol (*cf.* Table 3).

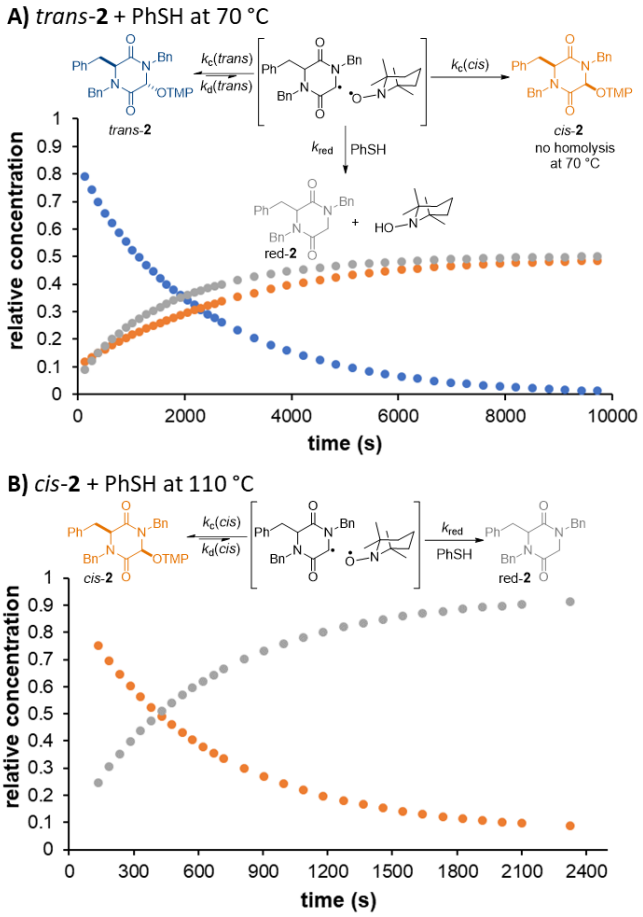


Figure 7. Kinetic traces of thermolysis of *trans*-**2** and *cis*-**2** in the presence of excess radical scavenger PhSH. A) Competitive fast isomerization *vs.* hydrogen abstraction upon thermolysis of *trans*-**2** with excess PhSH at 70 °C. B) Thermolysis of pure *cis*-**2** in the presence of PhSH at 110 °C.

This indicates that cyclization rates are in the same range as reduction, and therefore a mechanism for the overall cyclization can be derived, which proceeds via a slow homolysis of *cis*-**1** followed by a slightly faster radical cyclization, which is terminated by fast radical coupling of the bicyclic radical intermediates with TEMPO. This is supported by calculations at the (U)B2PLYP/G3MP2large//(U)B3LYP/6-31G(d) level in combination with the SMD continuum model for DMSO (Figure 8B and SI, Figs. S14-S20). The Gibbs free energy barrier for 6-exo cyclization starting from the corresponding DKP radical derived from *cis*-**1** amounts to only 70.5 kJ/mol, which is thus over 50 kJ/mol less than the barrier for formation of the respective radical pair. The barrier for 7-endo cyclization is somewhat higher at +82.8 kJ/mol, in full agreement with the formation of 6-exo products *syn/anti*-**6** as the major products under the experimental conditions.[21]

Table 3. Kinetic data for the thermal homolysis of *cis*-**1** and *cis*-**2** in the presence of excess PhSH.

cis-**1**			
T (K)	$k_d\times10^{-4}$ (s^{-1})	$t_{1/2}$ (min)	$\Delta G^{\ddagger}$ (kJ/mol)
363.15	2.8	41.1	114.2
373.15	9.7	12.0	113.7
388.15	47	2.4	113.1
A (s^{-1})	E_a (kJ/mol)	$\Delta H^{\ddagger}$ (kJ/mol)	$\Delta S^{\ddagger}$ (J/(K×mol)
2.92×10^{15}	132	129	41
cis-**2**			
T (K)	$k_d\times10^{-4}$ (s^{-1})	$t_{1/2}$ (min)	$\Delta G^{\ddagger}$ (kJ/mol)
363.15	1.9	62.1	115.9
373.15	4.0	28.6	115.5
383.15	16	7.3	115.2
388.15	30	3.9	115.0
A (s^{-1})	E_a (kJ/mol)	$\Delta H^{\ddagger}$ (kJ/mol)	$\Delta S^{\ddagger}$ (J/(K×mol)
1.69×10^{15}	132	129	36

Discussion

The 15-22° deviation of the amide nitrogen atom from planarity in *trans*-DKP alkoxyamines **1-5**, which are normal ring-sized lactams, is a significant distortion for an amide bond.[59] Nitrogen atom pyramidalization in DKPs was observed before, however only in proline- or pipecolic acid-fused DKPs, where it is enforced by the conformation of the pyrrolidine and piperidine rings.[60,61] In the monocyclic DKP alkoxyamines reported here, amide pyramidalization is the main contributor to the significantly more facile homolysis of *trans*-diastereomers compared to their *cis*-isomers. Strain release as a result of planarization of the distorted amide bond and concomitant conjugation with the incipient radical center leads to a significant lowering of the transition state energy required for homolytic bond cleavage. It is significant that ground-state destabilization of the amide bond in *trans*-alkoxyamines leads to a decrease of the strength of a bond, which is two skeletal bonds away. This C–O bond weakening is conceptually different from the amide bond twisting-induced C–N weakening of adjacent nitrogen substituents or the distorted N–C(O) bond itself.[62,63] To the best of our knowledge, such a mechanism for adjacent bond activation is very rare.[64] A computational investigation of

10.1002/chem.201803284

quaternary DKP alkoxyamine analogs shows that substituent effects offer opportunities to significantly modulate the temperature window at which controlled homolysis can occur, thus providing prospect for future theranostic applications.

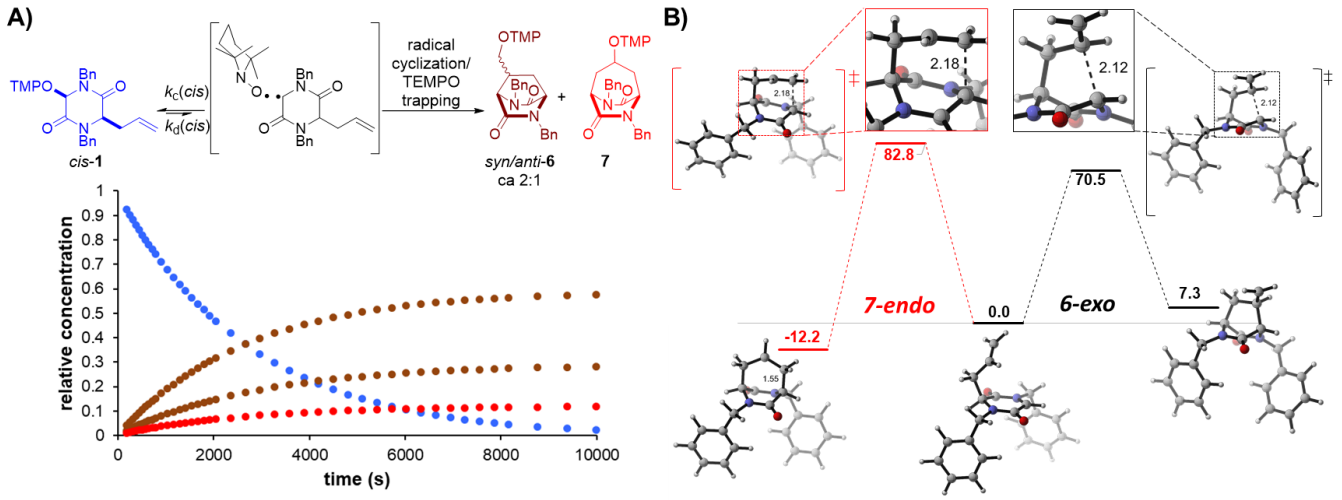


Figure 8. Thermal cycloisomerization of *cis*-**1** to bridged DKPs *syn/anti*-**6** and **7**. A) First order decay of *cis*-**1** and formation of cyclization products **6** and **7** at 100 °C. B) *ΔGsol-sp* profile in kJ/mol for the cyclization steps calculated at the (U)B2PLYP/G3MP2Large//(U)B3LYP/6-31G(d) level of theory. Single point solvation energies were calculated for DMSO at the SMD/(U)B3LYP/6-31G(d) level of theory.

A second potential prospect is the possibility of temporary information or energy storage by alkoxyamines (Figure 9), since the DKP skeleton *red*-**A** can be charged by deprotonation and oxygenation under kinetically controlled conditions providing *trans*-substituted alkoxyamines *trans*-**A** with often good diastereoselectivity (a). Thermal isomerization to the strain-free *cis*-diastereomers *cis*-**A** leads to release (b) and reductive removal of the alkoxyamine is restoring the original state *red*-**A** (c). In this way the system might be multiple times recycled. Significantly, this process occurs exclusively by directed configurational switching.

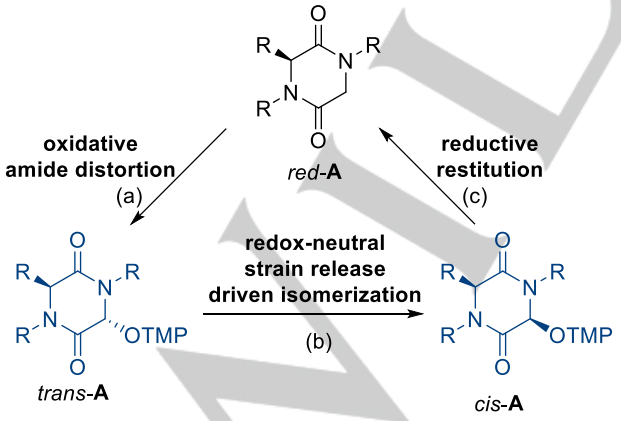


Figure 9. An overall reversible introduction of amide distortion into DKPs, its redox-neutral planarization and reductive restoration.

Diastereomeric excess has been previously noted for stereoisomeric alkoxyamines upon reversible homolysis and coupling,[65,66] where an achiral nitroxide radical couples to a chiral carbon-centered radical (Figure 10A). However, none of the so far investigated diastereomeric acyclic alkoxyamines **8-10**, described by Marque and Ananchenko,[67] Moad and Rizzardo,[68] or Georges[69] exhibited large diastereomeric preferences on thermal homolysis/radical coupling reactions. Only sterically very crowded SG1-derived alkoxyamines **9** equilibrated up to a 6:1 mixture when a 1:1 diastereomeric mixture or the individual diastereomers were heated at 100 °C. The most promising examples for directed isomerizations proved to be so far the cyclic sialic acid-derived anomeric alkoxyamines **11**, recently reported by Crich, providing a 7:1 ratio of α/β-anomers at 90 °C depending on the protecting groups.[70,71] Alkoxyamines **11** are also interesting in that the nitroxide unit is attached to a natural product core structure, providing the bias, but it shows that a simple cyclic constraint as in **11** is not sufficient to induce complete isomerization. However, combining the cyclic constraint with strain induced by amide distortion in DKP alkoxyamines (Figure 10B) provides the necessary driving force for a unidirectional three-point redox-fueled switching system based on central chirality (*cf.* Figure 9).

The here reported complete thermodynamic preference for the *cis*-isomer irrespective of steric and electronic factors is unique for 3,6-disubstituted DKPs. Except for fused proline-derived DKPs,[72] such high thermodynamic bias was observed only for a few *N*-alkyl-*N'*-acyl DKPs because of the specific distal effect of the *N*-acyl carbonyl group.[73]

Recently, it has been suggested that the additive Winkler-Dunitz parameter ($\sum\tau+\chi_N$) describes amide bond distortions more accurately based on the linear correlation between ($\sum\tau+\chi_N$) and

N–C(O) bond lengths or differences in N-/O-protonation aptitude.[74,75] The maximum possible value for a fully perpendicular amide bond amounts to $\sum\tau+\chi_N = 150°$. Compared to this value, the total distortion in our most non-planar DKP *trans*-**1** amounts to only 31.2° and our results thus show that even a small additive amide distortion of one fifth of the maximum value suffices in normal-sized lactams to trigger interesting and unusual reactivity. The here reported additive distortion values are similar to those found in sterically hindered amides **VIII** reported by Lloyd-Jones and Booker-Milburn and in *N*-acylazetidines studied by Ohwada[76] and Szostak.[77]

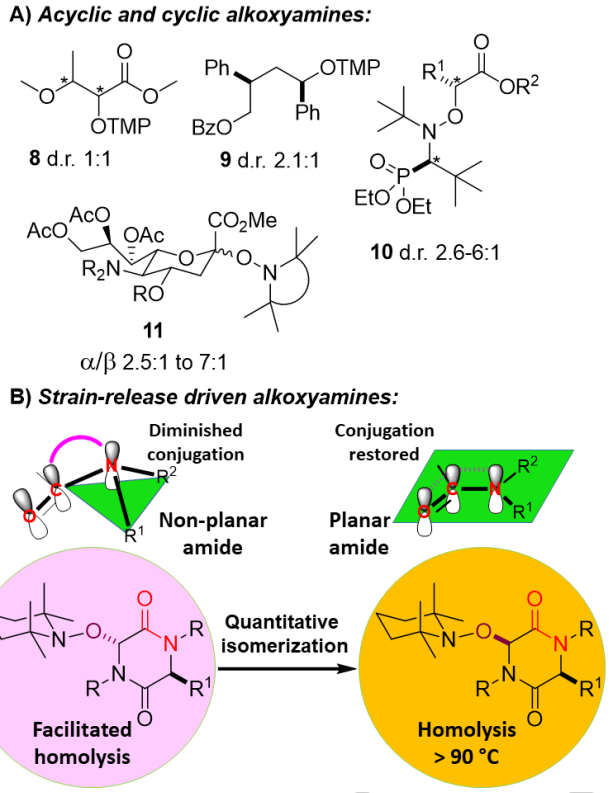


Figure 10. A) Previous thermal isomerization of diastereomeric alkoxyamine motives. B) Irreversible isomerization by strain release in a conformationally constrained cycle.

Conclusions

In summary, the first example of a quantitative and stereochemically unidirectional radical *trans*→*cis* isomerization of DKP alkoxyamines is presented. Although radical coupling reactions with nitroxides are generally known to be relatively unselective, the thermodynamic preference for the *cis*-configuration was shown to be general and complete for all studied DKP alkoxyamines irrespective of the electronic and steric nature of the amino acid side chains as well as the alkyl groups attached to the DKP nitrogen atoms. Structural studies with the help of X-ray crystallography unambiguously confirmed the stereochemistry of both, the kinetic and the thermodynamic products as well as a significant amide bond distortion from planarity in the *trans*-DKP alkoxyamines, but much less in their *cis*-isomers. Kinetic investigations of the isomerization by ^{1}H NMR spectroscopy revealed the rate constants of homolysis and allowed determination of the activation parameters for both, the *trans*-isomers and *cis*-isomers of two representative alkoxyamine pairs. These studies showed that isomerization of the initial *trans*-isomer to the more stable *cis*-isomer is faster than any follow-up transformation such as radical reduction or cyclization. Quantum chemical calculations proved to be very valuable in rationalizing the importance of structural and reactivity parameters governing the isomerization and further transformations. On this basis, they also allow the prediction of structure and reactivity of more labile, not isolable quaternary DKP alkoxyamines. The studies reported here have many implications. Generation of the kinetic *trans*-isomers having defined absolute configuration with good selectivity allows energy uptake through significant amide distortion, which can be released by quantitative thermal isomerization; significant are the complete stereoselectivity and stability under ambient conditions. The here gained knowledge may serve as a foundation for applications of this novel class of amino acid derived alkoxyamines for the design of smart and functional small molecules, in polymerization processes to access amino acid-derived or -terminated polymers, and as versatile amino acid surrogates. Studies toward envisioned applications of these alkoxyamines are ongoing in these laboratories and will be reported in due course.

Acknowledgements

Generous financial support by the Institute of Organic Chemistry and Biochemistry of the Czech Academy of Sciences (RVO: 61388963), the COST action CM1201 “Biomimetic Radical Chemistry”, the Gilead Sciences & IOCB Research Center and the European Regional Development Fund; OP RDE; Project: Chemical biology for drugging undruggable targets (ChemBioDrug) (No.CZ.02.1.01/0.0/0.0/16_019/0000729) is gratefully acknowledged. I.C. thanks the Ministry of Education, Youth and Sports of the Czech Republic (MSM0021620857) for financial support.

Keywords: alkoxyamines • distorted amide • isomerization • radicals • persistent radical effect

[1] *The Amide Linkage: Structural Significance in Chemistry, Biochemistry and Materials Science* (Eds.: A. Greenberg, C. M. Breneman, J. F. Liebman), Wiley, New York, **2000**.
[2] J. Clayden, N. Vassiliou, *Org. Biomol. Chem.* **2006**, *4*, 2667.
[3] B. A. F. Le Bailly, J. Clayden, *Chem. Commun.* **2016**, *52*, 4852.
[4] S. Z. Vatsadze, Y. D. Loginova, G. dos Passos Gomes, I. V. Alabugin, *Chem. - Eur. J.* **2017**, *23*, 3225.
[5] S. A. Glover, J. M. White, A. A. Rosser, K. M. Digianantonio, *J. Org. Chem.* **2011**, *76*, 9757.
[6] R. Lukeš, *Collect. Czech. Chem. Commun.* **1938**, *10*, 148.
[7] H. K. Hall, A. El-Sheikeil, *Chem. Rev.* **1983**, *83*, 549.
[8] M. Szostak, J. Aube, *Chem. Rev.* **2013**, *113*, 5701.
[9] K. Tani, B. M. Stoltz, *Nature* **2006**, *441*, 731.

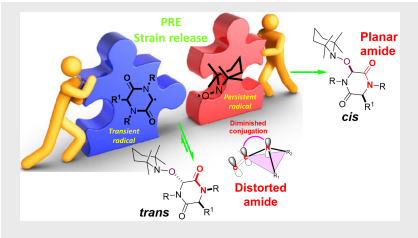
[10] M. Liniger, D. G. VanderVelde, M. K. Takase, M. Shahgholi, B. M. Stoltz, *J. Am. Chem. Soc.* **2016**, *138*, 969.
[11] J. Clayden, W. J. Moran, *Angew. Chem. Int. Ed.* **2006**, *45*, 7118.
[12] *The Chemistry of Penicillin* (Eds.: H. T. Clark, J. R. Johnson, R. Robinson), Princeton University Press, Princeton, **1949**.
[13] S. Adachi, N. Kumagai, M. Shibasaki, *Tetrahedron Lett.* **2018**, *59*, 1147.
[14] G. Meng, S. Shi, M. Szostak, *Synlett* **2016**, *27*, 2530.
[15] C. Liu, M. Szostak, *Chem. - Eur. J.* **2017**, *23*, 7157.
[16] J. E. Dander, N. K. Garg, *ACS Catal.* **2017**, *7*, 1413.
[17] S. Shi, G. Meng, M. Szostak, *Angew. Chem. Int. Ed.* **2016**, *55*, 6959.
[18] Y. Lei, A. D. Wrobleski, J. E. Golden, D. R. Powell, J. Aube, *J. Am. Chem. Soc*. **2005**, *127*, 4552.
[19] M. Szostak, L. Yao, V. D. Day, D. R. Powell, J. Aube, *J. Am. Chem. Soc*. **2010**, *132*, 8836.
[20] F. Hu, R. Lalancette, M. Szostak, *Angew. Chem. Int. Ed.* **2016**, *55*, 5062.
[21] F. Hu, P. Nareddy, R. Lalancette, F. Jordan, M. Szostak, *Org. Lett.* **2017**, *19*, 2386.
[22] K. Weidner, N. Kumagai, M. Shibasaki, *Angew. Chem. Int. Ed.* **2014**, *53*, 6150.
[23] S. Adachi, N. Kumagai, M. Shibasaki, *Chem. Sci.* **2017**, *8*, 85.
[24] M. Hutchby, C. E. Houlden, M. F. Haddow, S. N. G. Tyler, G. C. Lloyd-Jones, K. I. Booker-Milburn, *Angew. Chem. Int. Ed.* **2012**, *51*, 548.
[25] T. Amatov, R. Pohl, I. Cisařová, U. Jahn, *Angew. Chem. Int. Ed.* **2015**, *54*, 12153.
[26] T. Amatov, M. Gebauer, R. Pohl, I. Cisařová, U. Jahn, *Free Radical Res.* **2016**, *50*, S6.
[27] T. Amatov, R. Pohl, I. Cisařová, U. Jahn, *Org. Lett.* **2017**, *19*, 1152.
[28] H. Fischer, *Chem. Rev.* **2001**, *101*, 3581.
[29] A. Studer, *Chem. Eur. J.* **2001**, *7*, 1159.
[30] A. Studer, *Chem. Soc. Rev.* **2004**, *33*, 267.
[31] A. Studer, T. Schulte, *Chem. Rec.* **2005**, *5*, 27.
[32] C. J. Hawker, A. W. Bosman, E. Harth, *Chem. Rev.* **2001**, *101*, 3661.
[33] J. Nicolas, Y. Guillaneuf, C. Lefay, D. Bertin, D. Gigmes, B. Charleux, *Prog. Polym. Sci.* **2013**, *38*, 63.
[34] *Encyclopedia of Radicals in Chemistry, Biology, and Materials*, (Eds: C. Chatgilialoglu, A. Studer,), Eds.; Wiley: Chichester, **2012**.
[35] A. Studer, *Angew. Chem. Int. Ed*. **2000**, *39*, 1108.
[36] G. Audran, P. Bremond, S. R. A. Marque, *Chem. Commun*. **2014**, *50*, 7921.
[37] G. Gryn'ova, D. L. Marshall, S. J. Blanksby, M. L. Coote, *Nat. Chem.* **2013**, *5*, 474.
[38] G. Gryn'ova, M. L. Coote, *J. Am. Chem. Soc.* **2013**, *135*, 15392.
[39] D. Moncelet, P. Voisin, N. Koonjoo, V. Bouchaud, P. Massot, E. Parzy, G. Audran, J.-M. Franconi, E. Thiaudiere, S. R. A. Marque, P. Bremond, P. Mellet, *Mol. Pharmaceutics* **2014**, *11*, 2412.
[40] G. Audran, P. Bremond, J.-M. Franconi, S. R. A. Marque, P. Massot, P. Mellet, E. Parzy, E. Thiaudiere, *Org. Biomol. Chem.* **2014**, *12*, 719.
[41] A. D. Borthwick, *Chem. Rev.* **2012**, *112*, 3641.
[42] J. F. Gonzalez, I. Ortin, E. de La Cuesta, J. C. Menendez, *Chem. Soc. Rev.* **2012**, *41*, 6902.
[43] T. Amatov, U. Jahn, *Angew. Chem. Int. Ed*. **2014**, *53*, 3312.
[44] Previously characterized by X-ray crystallography, see Ref. 21.
[45] M. V. Ciriano, H.-G. Korth, W. B. van Scheppingen, P. Mulder, *J. Am. Chem. Soc.* **1999**, *121*, 6375.
[46] S. Marque, H. Fischer, E. Baier, A. Studer, *J. Org. Chem.* **2001**, *66*, 1146.
[47] J. L. Hodgson, C. Y. Lin, M. L. Coote, S. R. A. Marque, K. Matyjaszewski, *Macromolecules* **2010**, *43*, 3728.
[48] K. Molawi, T. Schulte, K. O. Siegenthaler, C. Wetter, A. Studer, *Chem. - Eur. J.* **2005**, *11*, 2335.
[49] A. Gaudel-Siri, D. Siri, P. Tordo, *ChemPhysChem* **2006**, *7*, 430.
[50] V. Kapras, V. Vyklicky, M. Budesinsky, I. Cisarova, L. Vyklicky, H. Chodounska, U. Jahn, *Org. Lett.* **2018**, *20*, 946.
[51] U. Jahn, unpublished.
[52] F. K. Winkler, J. D. Dunitz, *J. Mol. Biol.* **1971**, *59*, 169.
[53] M. Edeleva, S. R. A. Marque, D. Bertin, D. Gigmes, Y. Guillaneuf, E. Bagryanskaya, *Polymers* **2010**, *2*, 364.
[54] V. W. Bowry, K. U. Ingold, *J. Am. Chem. Soc*. **1992**, *114*, 4992.
[55] J. Chateauneuf, J. Lusztyk, K. U. Ingold, *J. Org. Chem.* **1988**, *53*, 1629.
[56] I. W. C. E. Arends, P. Mulder, K. B. Clark, D. D. M. Wayner, *J. Phys. Chem.* **1995**, *99*, 8182.
[57] A. L. J. Beckwith, V. W. Bowry, K. U. Ingold, *J. Am. Chem. Soc*. **1992**, *114*, 4983.
[58] E. G. Bagryanskaya, S. R. A. Marque, *Chem. Rev.* **2014**, *114*, 5011.
[59] J. D. Dunitz, F. K. Winkler, *Acta. Cryst.* **1975**, *B31*, 251.
[60] M. Budesinsky, I. Cisarova, J. Podlaha, F. Borremans, J. C. Martins, M. Waroquier, E. Powels, *Acta Cryst. B* **2010**, *B66*, 662.
[61] M. Budesinsky, I. Cisarova, F. Borremans, J. C. Martins, E. Powels, *Acta Cryst. B* **2017**, *B73*, 1179.
[62] J. Aube, *Angew. Chem. Int. Ed.* **2012**, *51*, 3063.
[63] G. Meng, S. Shi, R. Lalancette, R. Szostak, M. Szostak, *J. Am. Chem. Soc.* **2018**, *140*, 727 and references therein.
[64] A conceptually similar situation exists in reactions of strained aniline-derived cyclodecynes: T. Harris, G. P. Gomes, S. Ayad, R. J. Clark, V. V. Lobodin, M. A. Tuscan, K. Hanson, I. V. Alabugin, *Chem*, **2017**, *3*, 629.
[65] R. Braslau, N. Naik, H. Zipse, *J. Am. Chem. Soc.* **2000**, *122*, 8421.
[66] R. Braslau, L. C. Burrill II, L. K. Mahal, T. Wedeking, *Angew. Chem. Int. Ed.* **1997**, *36*, 237.
[67] G. Ananchenko, S. Marque, D. Gigmes, D. Bertin, P. Tordo, *Org. Biomol. Chem.* **2004**, *2*, 709.
[68] *Nitroxide Mediated Polymerization: From Fundamentals to Applications in Materials Science*; (Ed.: D. Gigmes), RSC, Cambridge, **2015**.
[69] L. Li, G. K. Hamer, M. K. Georges, *Macromolecules* **2006**, *39*, 9201.
[70] P. K. Kancharla, T. Kato, D. Crich, *J. Am. Chem. Soc.* **2014**, *136*, 5472.
[71] P. K. Kancharla, C. Navuluri, D. Crich, *Angew. Chem. Int. Ed.* **2012**, *51*, 11105.
[72] C. Eguchi, A. Kakuta, *J. Am. Chem. Soc.* **1974**, *96*, 3985.
[73] J. Ho, M. L. Coote, C. J. Easton, *J. Org. Chem.* **2011**, *76*, 5907.
[74] R. Szostak, J. Aube, M. Szostak, *Chem. Commun.* **2015**, *51*, 6395.
[75] R. Szostak, J. Aube, M. Szostak, *J. Org. Chem.* **2015**, *80*, 7905.
[76] Y. Otani, O. Nagae, Y. Naruse, S. Inagaki, M. Ohno, K. Yamaguchi, G. Yamamoto, M. Uchiyama, Y. Ohwada, *J. Am. Chem. Soc.* **2003**, *125*, 15191.
[77] C. Liu, M. Achtenhagen, M. Szostak, *Org. Lett.* **2016**, *18*, 2375.

Entry for the Table of Contents (Please choose one layout)

Layout 1:

FULL PAPER

Strain release drives isomerization: Amide pyramidalization in diketopiperazine-derived *trans*-alkoxyamines is the reason for facile homolytic bond cleavage at mild temperatures and quantitative isomerization to *cis*-isomers with nearly planar amide geometry.



Tynchtyk Amatov, Harish Jangra, Radek Pohl, Ivana Císařová, Hendrik Zipse and Ullrich Jahn**

Page No. – Page No.

Unique stereoselective homolytic C-O bond activation in diketopiperazine-derived alkoxyamines via adjacent amide pyramidalization