Theoretical Prediction of a Base-Catalyzed Bicyclic Boulton−Katritzky Rearrangement

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On the basis of quantum chemical calculations, the bicyclic Boulton−Katritzky rearrangement (BKR) has been classified as a pseudopericyclic reaction. Theoretical investigations extend the applicability of the BKR to classes of molecules other than those known from experiments.

Introduction

The Boulton−Katritzky rearrangement (BKR) is a fundamental reaction in heterocyclic chemistry and has been known for about 40 years.[1,2] While closely related in some mechanistic details, usually one distinguishes between monocyclic[3] and bicyclic BKRs.[4,5] Both reactions have been generalized[6] for whole classes of molecules as shown in Figure 1. The monocyclic BKR has been investigated theoretically[7−9] and experimentally.[10,11] Computational studies showed that the pivotal nitrogen atom is not a mandatory prerequisite for the reaction, although a number of experimental attempts in that direction failed.[12] As a consequence, experimental studies almost exclusively focused on species with pivotal nitrogen atoms. Base catalysis plays an important role since a proton shift is required for the mechanism shown above.

One major difference between the monocyclic and the bicyclic BKRs is the π-shift in the case of the bicyclic BKR.[7] This π-shift initiated speculations about the underlying mechanism of the reaction in terms of frontier orbital theory. On the basis of experimental studies of 7-acetyl-3-methylanthranil, Parry and Rees classified the bicyclic BKR as a [1,9]-sigmatropic rearrangement.[13,14] In contrast to the monocyclic BKR, all studied bicyclic BKRs have the pivotal nitrogen atom in common. Hence, a prototype of this reaction is the molecular rearrangement of nitrobenzofuroxan (see Figure 2). This particular reaction has been investigated in detail.[15,16] In agreement

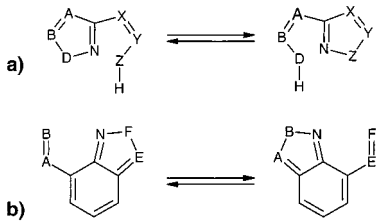

Figure 1. Generalized schemes of the (a) monocyclic and the (b) bicyclic Boulton−Katritzky rearrangements.

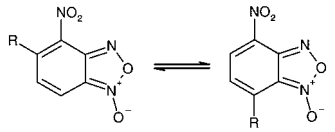

Figure 2. Tautomerism of 5-*R*-nitrobenzofuroxans.

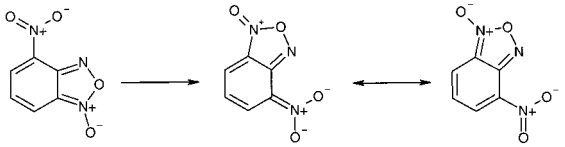

Figure 3. A formal characterization of the bicyclic Boulton−Katritzky rearrangement.

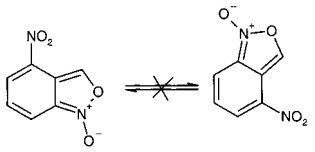

Figure 4. Due to competitive ring opening processes the Boulton−Katritzky rearrangement of 4-nitro-benzo[*c*]isoxazole-*N*-oxide is unlikely.

with experimental results it was found that the substituent in the 5-position has a major impact on the rate constant. For example, a methyl group accelerates the BKR toward the 7-methyl-nitrobenzofuroxan while an anilino or hydroxy group reverts the equilibrium leading to the retro-BKR.[17,18] Consequently, the reaction can be

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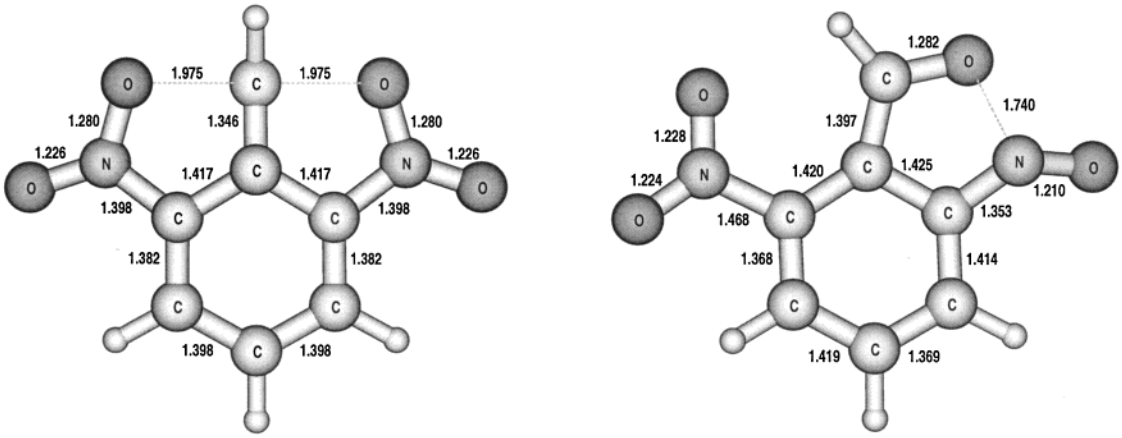

Figure 5. Structures of the transition states of the competitive reactions of 4-nitro-benzo[*c*]isoxazole-*N*-oxide. All values are given in Å.

Table 1. Reaction Barriers and Energies of the Boulton−Katritzky Rearrangement of 5-*R*-4-Nitroso-benzo[*c*]isoxazole[a]

		B3-LYP		CCSD(T)	
substituent	charge	ΔE_{act}	ΔE_0	ΔE_{act}	ΔE_0
H	0	44.2	0.0	46.2	0.0
H	−1	31.7	0.0	35.0	0.0
NMe_2	−1	25.6	−10.1	(28.9)	
Cl	−1	29.7	−4.5	(33.0)	

[a] Relative energies are corrected for the zero-point vibrational energy.

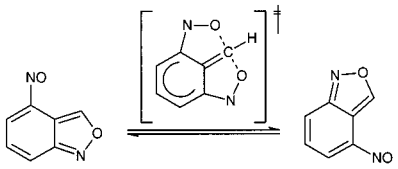

Figure 6. The Boulton−Katritzky rearrangement of 4-nitroso-benzo[*c*]isoxazole.

controlled by appropriate substituents. Moreover, quantum chemical calculations showed that the reaction is a one-step mechanism via a tricyclic transition state, which appears to be always planar.[15,19,20] Even if the nitro group in the 4-position was distorted out of the ring plane in the educt, the transition state was found to be planar. Moreover, the active orbitals of the breaking and the new σ-bond in the transition state all lie in the ring plane.[19,20] These results indicate that the bicyclic BKR should not be classified as a [1,9]-sigmatropic rearrangement but rather as a pseudopericyclic reaction,[21] which are known to have low activation barriers.[22,23] The latter can be distinguished from conventional pericyclic reactions by the fact that they do not involve the rotation of $p(\pi)$-AOs or, more generally, that $p(\pi)$-AOs are not involved in any bond-building or bond-breaking processes of σ-bonds. Consequently, these reactions are not characterized by a closed loop of *interacting* orbitals although their depiction in terms of Lewis structures would suggest such a viewpoint. Thus, the BKR of nitrobenzofuroxans can formally be written as an intramolecular nucleophilic substitution with a simultaneous π-shift as shown in Figure 3.

On the basis of this knowledge, it is the purpose of this study to investigate the mechanism of the BKR with respect to the variations of the active orbitals. Furthermore, an extension of the applicability of the BKR is proposed by changing the pivotal atom. The proposed new class of BKRs would be controlled by the same factors (i.e. the substituents in the 5- or 7-positions) as the original ones. All studies were carried out by quantum chemical calculations using density functional theory and ab initio electron correlation methods up to the coupled-cluster level.

Computational Details

Geometries of all systems were obtained from B3-LYP/6-311+G(2d,p) calculations.[24−27] Stationary points were confirmed by frequency calculations and by following the intrinsic reaction coordinate (IRC). All activation energies, ΔE_{act}, and reaction energies, ΔE_0, include corrections for the zero-point vibrational energy. Since the B3-LYP functional has a tendency to underestimate reaction barriers,[28,29] additional CCSD(T)/6-311+G(2d,p) calculations were performed for some smaller model systems. Total energies and geometrical parameters are provided in the Supporting Information section of this journal. Canonical Kohn−Sham orbitals along the IRC were used for studying mechanistic aspects. Although multireference calculations would have been more convincing for the orbital considerations, the large number of active orbitals resulting from the π-shift and the nonnegligible lone pairs made these calculations basically unfeasible. All calculations were performed with the Gaussian98[30] and Molpro2000.7[31] suites of ab initio programs.

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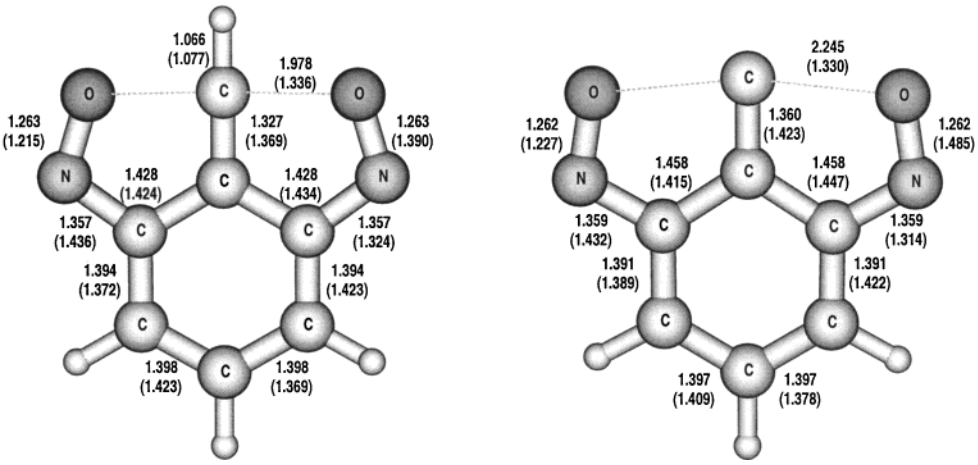

Figure 7. Structures of the transition states of the competitive reactions of 4-nitro-benzo[*c*]isoxazole and its anion. Bond lengths in parentheses refer to the educt. All values are given in Å.

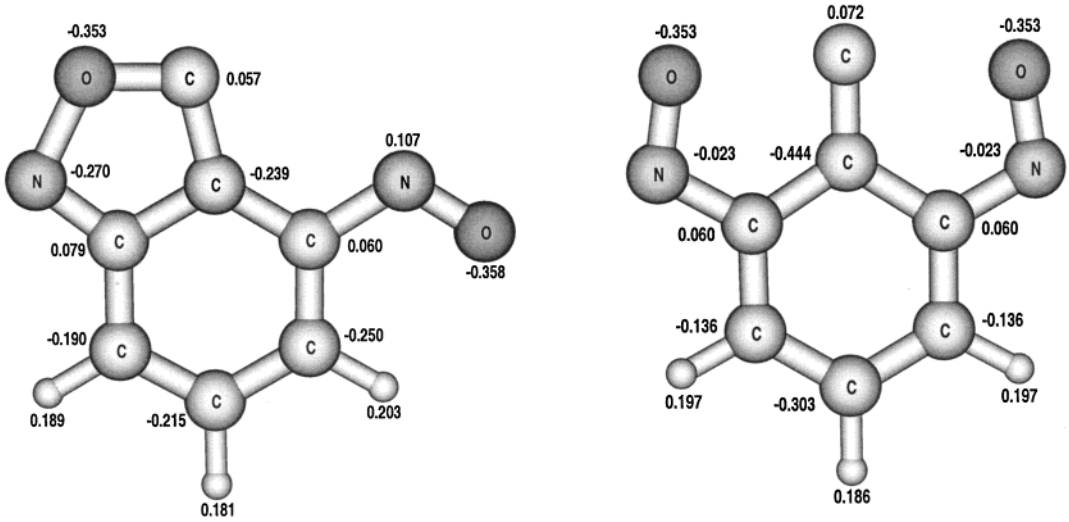

Figure 8. NBO charges of the educt and the transition state of the BKR of the 4-nitroso-benzo[*c*]isoxazole anion.

Results and Discussion

Searching for a bicyclic BKR with a pivot atom other than nitrogen, an obvious starting point is the modification of the pivotal nitrogen in nitrobenzofuroxan. Introducing a =CH— moiety instead, results in 4-nitro-benzo[*c*]isoxazole-*N*-oxide. However, although a tricyclic BKR transition state could be found for this species on the DFT potential energy surface (PES), it is evident that this reaction cannot have any experimental relevance (Figure 4). The activation energy of this process is far too high (DFT: $\Delta E_{act} = 40.3$ kcal/mol) with respect to the opening of the heterocyclic furoxan ring (DFT: $\Delta E_{act} = 4.2$ kcal/mol) toward 2-nitro-6-nitroso-benzaldehyde which is the preferred reaction (DFT: $\Delta E_0 = -12.9$ kcal/mol). The structures of the transition states of both reactions are depicted in Figure 5. However, since the competitive ring opening reaction is without relevance for the BKR it shall not be considered here in detail. To rule out the undesired ring-opening pathways the model system had to be truncated to 4-nitroso-benzo[*c*]isoxazole. For the BKR pathway of this compound an activation barrier even higher (DFT: $\Delta E_{act} = 44.2$ kcal/mol, cf. Table 1) was found. This high barrier was expected, since the proton connected to the pivot atom hinders the pseudopericyclic in-plane reaction and must therefore be moved out of the way. However, with this species the BKR does not have

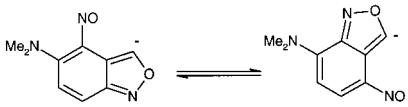

Figure 9. The Boulton−Katritzky rearrangement of the 5-(dimethylamino)-4-nitroso-benzo[*c*]isoxazole anion.

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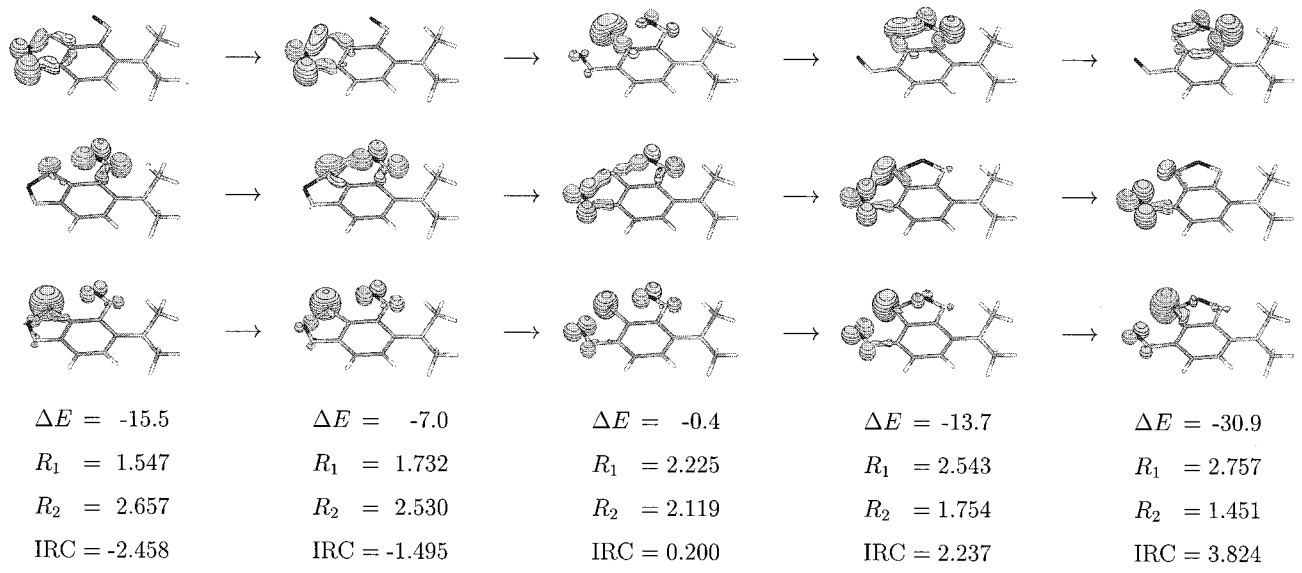

Figure 10. Canonical orbitals along the intrinsic reaction coordinate (IRC) of the Boulton−Katritzky rearrangment of the 5-(dimethylamino)-4-nitroso-benzo[*c*]isoxazole anion. (Δ*E* denotes the difference of the total energy relative to the transition state in kcal/mol. R_1 and R_2 represent the two C−O distances of the pivot atom in Å. The IRC parameter specifies the position of the shown orbitals along the intrinsic reation coordinate in mass weighted coordinates.)

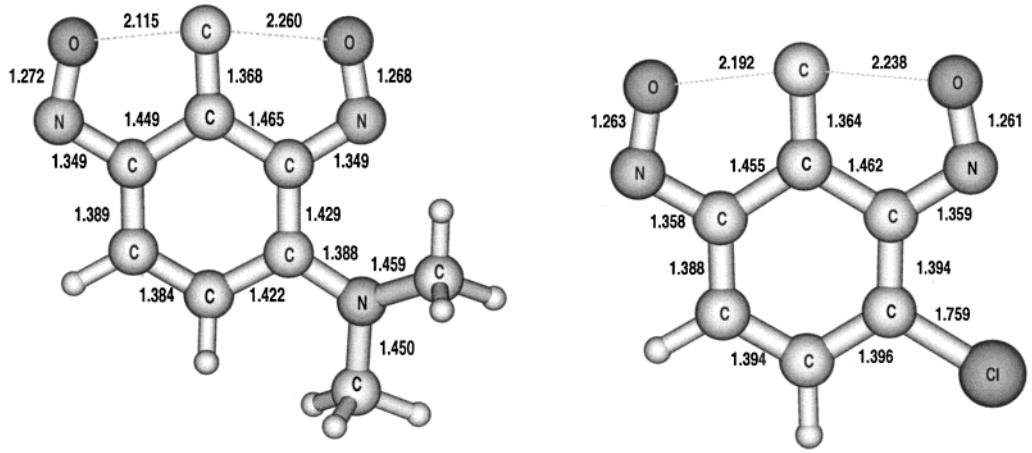

Figure 11. Structure of the transition states of the BKR of the 5-(dimethylamino)-4-nitroso-benzo[*c*]isoxazole anion and the 5-chloro-4-nitroso-benzo[*c*]isoxazole anion. All values are given in Å.

to compete with the ring-opening and hence the rearrangement shown in Figure 6 remains the only feasible reaction. Most remarkably the transition state of this reaction is still planar as shown in Figure 7. Obviously, the *p*-orbital of the pivot atom that contributes to the π-bond of the central C=C double bond is not directly involved in the mechanism. The structure of the transition state exhibits C_{2v} symmetry while the transition state of a corresponding pericyclic reaction should have lower symmetry due to symmetry breaking caused by the rotation of the $p(\pi)$-AOs.

The activation barrier of this reaction must be expected to decrease by the introduction of more electronic flexibility. This can in principle be achieved by deprotonating the system resulting in a species that is electronically closely related to the nitrobenzofuroxans. Indeed, deprotonation lowers the activation energy by about 10 kcal/mol thus leading to a barrier of about $\Delta E_{act} = 31.7$ kcal/mol (DFT, cf. Table 1). The reason for lowering of the barrier is not completely clear but two explanations appear to be feasible: (1) The lone pair at the pivot atom may be involved in the reaction mechanism and may thus assist the reaction by lowering the transition state energy. (2) Due to delocalization of the electron in the anionic species (a) the absolute energy of the educt may be shifted to higher values or (b) the absolute energy of the transition state is shifted to lower values. However, an investigation of atomic charges based on an NBO analysis[32] shows that in both cases, i.e., the educt and the transition state, the negative charge is delocalized over the entire system (see Figure 8). Most remarkably, the pivotal carbon atom has a positive charge. A perturbative analysis of the Fock matrix in the NBO basis indicates considerable interactions between a virtual lone pair orbital at the pivotal carbon atom with the occupied lone pairs of both oxygens. Therefore, the energy of the anionic transition state may be lowered due to these favorable interactions. As a consequence, the first explanation provides arguments for the lowering of the transition state (2b) rather than a shift of the educt to higher values (2a). In addition, an investigation of the canonical

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Kohn−Sham orbitals along the intrinsic reaction coordinate suggests the lone pair of the pivot atom to be actively involved in the reaction mechanism (vide infra). However, it must be kept in mind that the orbital of the lone pair has the same symmetry as the other in-plane orbitals. Since the energy of a system is invariant with respect to any unitary transformation of the occupied orbitals the canonical orbitals are just one feasible choice for representing the MOs involved in the reaction mechanism. Other representations may be possible that exclude the lone pair from the reaction. Therefore, it cannot be definitely concluded that the lone pair is actively involved in the mechanism. However, the participation of π-orbitals can be excluded since they belong to a different symmetry and cannot mix with the in-plane orbitals. Therefore, a conventional pericyclic mechanism can definitely be ruled out.

Since the activation barrier is still very high and cannot be measured by ^{1}H NMR experiments, further lowering is desirable. By analogy to the well-known examples of the Boulton−Katritzky rearrangement this can be achieved by introducing an appropriate substituent in the 5-position, a modification that will also lead to a favorable exothermicity. A dimethylamino substituent has been chosen for two reasons. First, it will lead to a stabilization of the 7-tautomer due to interaction with the nitroso groups in the *ortho* and *para*-positions. Second, and most importantly, the educt (the 5-(dimethylamino)-4-nitroso-benzo[*c*]isoxazole anion) should be experimentally accessible.[33] The activation barrier for the BKR shown in Figure 9 was found to be $\Delta E_{act} = 25.6$ kcal/mol at the B3-LYP/6-311+G(2d,p) level. The reaction is exothermic by $\Delta E_0 = -10.1$ kcal/mol (cf. Table 1). Three sets of canonical orbitals along the intrinsic reaction coordinate of this reaction are depicted in Figure 10. Although all structures along the IRC show C_1 symmetry and thus allow for a mixing of the π-orbitals with the in-plane orbitals, this could not be observed. This again shows that the bond-building/breaking process does not directly involve any *p*-orbitals perpendicular to the ring plane. Formally, this systems fulfills all requirements to be observed under moderate conditions. However, against chemical intuition, quantum chemical calculations at the DFT and MP2 levels consistently suggest that the protons of the dimethylamino group are more acidic than the proton at the pivot atom, i.e., the respective absolute acidities (ΔE_0 values only) are 273.1 kcal/mol vs 286.6 kcal/mol at the B3-LYP/6-311+G(2d,p) level. Therefore, alternative synthetic routes than the use of a base may be more appropriate for the generation of the anion of 5-(dimethylamino)-4-nitroso-benzo[*c*]isoxazole. Another possibility would be to use a different substituent than the proposed dimethylamino group. DFT calculations on the reaction of the 5-chloro-4-nitroso-benzo[*c*]isoxazole anion result in a reaction barrier of $\Delta E_{act} = 29.7$ kcal/mol and a reaction energy of $\Delta E_0 = -4.3$ kcal/mol (cf. Table 1). This substituent would avoid any problems concerning the acidity of the proton bound to the pivotal carbon atom. However, this reaction has a slightly higher barrier and is considerably less exothermic than the corresponding reaction with a dimethylamino substituent. The structures of the transition states of both reactions are provided in Figure 11.

Due to the orientation of the nitroso group all systems considered in this study allow for at least two rotamers. However, for the most relevant anionic systems the energetical differences between the different conformers are very small and do not affect the discussed energetical aspects at all. For the anions of 4-nitroso-benzo[*c*]isoxazole and 5-(dimethylamino)-4-nitroso-benzo[*c*]isoxazole the energetic differences between the two rotamers account for less than 0.3 kcal/mol. For the anion of 5-chloro-4-nitroso-benzo[*c*]isoxazole the difference is slightly larger (DFT: 1.8 kcal/mol). The impact of higher electron correlation effects appears to be more important. CCSD(T)/6-311+G(2d,p) calculations have been performed for the reaction of 4-nitroso-benzo[*c*]isoxazole and its anion. For the anionic reaction the coupled-cluster approach predicts a barrier being 3.3 kcal/mol higher than at the DFT level, i.e., $\Delta E_{act} = 35.0$ kcal/mol (cf. Table 1). The slightly higher coupled-cluster barrier is consistent with the findings of other authors, who observed an underestimation of activation energies by the B3-LYP functional.[28,29] For the substituted systems the CCSD(T) calculations could not be performed due to technical reasons. However, transferring the increase of the unsubstituted systems to the substituted one leads to an estimate of $\Delta E_{act} = 28.9$ kcal/mol for the reaction of the 5-(dimethylamino)-4-nitroso-benzo[*c*]isoxazole anion and of $\Delta E_{act} = 33.0$ kcal/mol for the 5-chloro-4-nitroso-benzo[*c*]isoxazole anion, which must be considered more reliable than the B3-LYP data.

Summary

DFT and CCSD(T) calculations show that the bicyclic Boulton−Katritzky rearrangement (BKR) must be considered as a pseudopericyclic reaction rather than proceeding via a conventional pericyclic mechanism. Moreover, on the basis of quantum chemical calculations, a novel BKR with a pivotal carbon atom is suggested. This reaction may be accelerated by deprotonation. Experiments confirming the predicted reaction are currently in progress.[33]

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Supporting Information Available: Optimized geometries and absolute energies of all stationary points are available in Cartesian coordinates. This material is free of charge via Internet at http://pubs.acs.org.

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