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Ring-Enlargement Reactions of Donor−Acceptor-Substituted Cyclopropanes: Which Combinations are Most Efficient?

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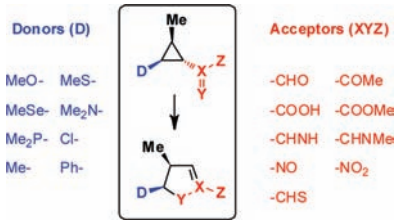
ABSTRACT



A detailed theoretical study of ring-enlargement reactions of 72 differently substituted donor−acceptor-substituted cyclopropanes is presented. Transition states, activation barriers, and, for representative examples, the behavior in solution were additionally determined using the B3LYP/6-311G(d) level of theory.

Three-membered rings are highly strained systems; nevertheless they are found in a variety of natural products.[1] The naturally occurring cyclopropane motifs are commonly substituted with either electron-neutral moieties (e.g., in **1**)[2] or with geminal donor and acceptor substituents (e.g., in **2**).[3] Rare examples, for instance the very unusual amino acid **3**, reveal also a nitro group as an acceptor unit attached to the three-membered ring system (Figure 1) which appears in the natural peptide Hormaomycin.[4] The stability of a cyclopropane unit is dramatically decreased by introducing an electron donor as well as an electron acceptor in vicinal positions—or in other words the tendency toward ring-opening or ring-enlargement reactions is highly increased. For this reason, vicinal donor−acceptor-substituted (D−A) cyclopropanes **4** are ordinarily not found in Nature but have

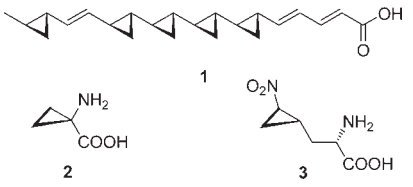


Figure 1. Three examples of natural products **1**−**3** containing cyclopropane moieties.

emerged as versatile building blocks in a plethora of synthetically useful organic reactions.[5] Due to the *push*−*pull* effect of the donor and the acceptor a high selectivity for the cleavage of the bond in between the two respective substituents is observed. This property leading formally to a 1,3-zwitterionic intermediate **5** has been intensively investigated and has already been used in a variety of natural product syntheses (Scheme 1).[6]

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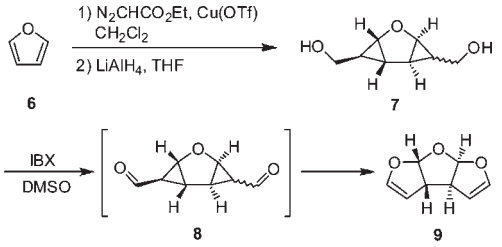
Scheme 1. 1,3-Zwitterionic Relationship in D−A Cyclopropanes

Due to the 1,3-relationship of the formal charges most of the reactions involving D−A cyclopropanes may be regarded as processes with an umpolung of reactivity.[7] Ring-opening reactions with electrophilic and nucleophilic double or triple bond systems have permitted the formation of heterocyclic compounds.[8] Spontaneous or acid-induced reactions have led to five-membered ring systems *via* a rearrangement.[9] We become involved in this issue by developing a strategy for the *anti*-annelation of tetrahydrofurane moieties using a sequence of cyclopropanation, reduction, and oxidation (Scheme 2).[10] The key step is the ring enlargement of a cyclopropane bearing an oxygen donor and an aldehyde acceptor **8** to the tricyclic bisacetal **9**. Carbonyl groups, especially esters and aldehydes, are well-known as acceptors whereas ether moieties are often employed as donors.

Scheme 2. Bisacetal Formation by D−A Cyclopropanes



During our continuing efforts in applying this reaction for the formation of other interesting heterocyclic compounds we became interested in the influence of various substituents on the tendency for ring-enlargement. To our surprise, despite the extensive use of D−A cyclopropanes in organic synthesis a detailed theoretical investigation elucidating the influence of different *push*−*pull* combinations is still lacking.[11]

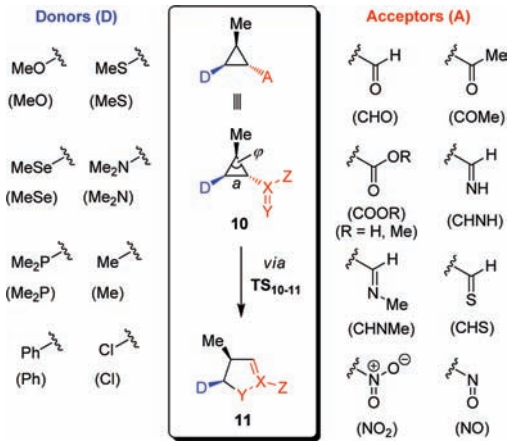


Figure 2. Donor (D) and acceptor (A) combinations investigated in this study.

The particular influences of different D−A combinations attached to a methyl-substituted cyclopropane were investigated by the model systems shown in Figure 2. Depicted are eight donor and nine acceptor functionalities.[12] For all 72 D−A combinations with the cyclopropane **10** as starting material, the respective product **11** (according to Figure 2) and the corresponding transition state $\mathbf{TS_{10-11}}$ were elucidated. As nomenclature for a distinct combination we utilize (**D/A**), e.g. **10(Me$_2$N/CHO)** for cyclopropane derivative **10** with a dimethylamino group as donor and an aldehyde as an acceptor.

The geometrical parameters were optimized (without any symmetry restrictions) using the density functional theory (DFT)[13] by applying the three-parameter hybrid functional by Becke (B3)[14] and the correlation functional by Lee, Yang, and Parr (LYP).[15] As a basis set we used 6-311G(d) as suggested by Pople et al.,[16] implemented in Gaussian 03.[17,18] Frequency calculations were undertaken to confirm the nature of the stationary points, yielding one imaginary frequency (NImag = 1) for transition states (TS) and none (NImag = 0) for minima. All energies were corrected for zero point.

The activation barriers of all *push*−*pull* combinations ordered from the most efficient (**Me$_2$N/NO**) to the least efficient **(Cl/COOMe)** are depicted in Figure 3. A general

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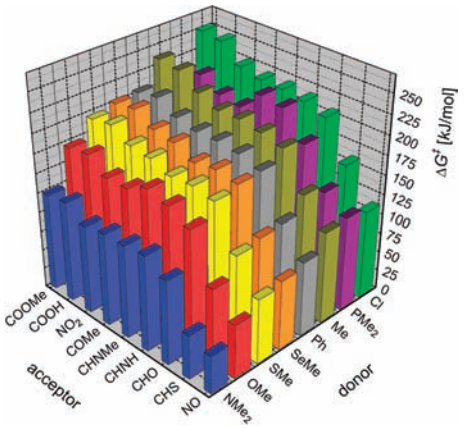

Figure 3. Transition state energies for the ring-enlargement from **10** to **11** derived by B3LYP/6-311G(d) calculations for different combinations of donor and acceptor substituents.

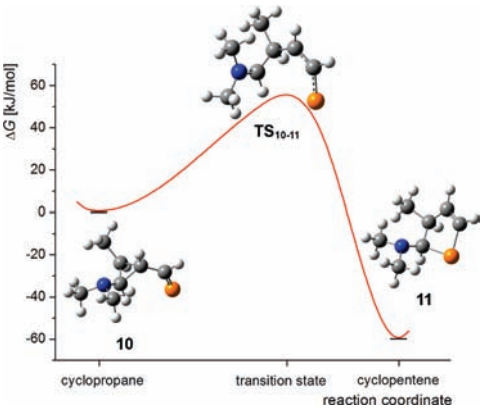

Figure 4. Optimized structures of **10(Me$_2$N/CHS)**, transition state **TS$_{10-11}$**, and dihydrothiophene **11(Me$_2$N/CHS)** as calculated at the B3LYP/6-311G(d) level.

tendency is observed: The more electron-donating (Me_2N, MeO) one of the two substituents and the more electron-withdrawing the other (NO, CHS, CHO), the smaller the transition state energy. The graphic reveals that also aromatic and aliphatic groups (Ph, Me) might be chosen as a donor. Whereas methoxy and thiomethyl groups show similar energetics, the difference between amine and phosphine substituents is very significant. With the exception of nitroso and thioaldehyde acceptors which highly decrease the transition state energies, the difference between the other acceptor moieties is relatively small. Even the commonly strongly electron-withdrawing NO_2 substituent does not show a special case. The complete list of activation barriers and the energetics of these reactions are provided in the Supporting Information.

NBO analyses[19a] have shown that the Wiberg bond indices (WBI)[19b] of the formal single bond between the donor and the acceptor substituent range from 0.86 (**10(MeS/CHS)**) to 0.94 (**10(Cl/NO$_2$)**) indicating a weakened bond. Late transition states revealing a small WBI of bond *a* and a large angle φ are observed in combinations such as (**Me$_2$N/CHS**) and (**MeO/NO**). In contrast early transition states are found for systems that have only a little tendency to stabilize zwitterionic intermediates. An example for a late transition state is depicted in Figure 4 presenting the facile ring-enlargement of **10(Me$_2$N/CHS)** to **11(Me$_2$N/CHS)**.

Of course, reactions are commonly carried out in a solvent. Thus, computational studies should also include realistic solvent effects.[20] Table 1 provides a comparison of activation barriers and reaction enthalpies *in vacuo* and in three different solvents (dichloromethane, toluene, and DMSO) for three selected examples. In general, solvents decrease the activation barrier of our systems; the most dramatic influence is observed when the highly polar solvent DMSO is used. This behavior can be easily understood by the most effective stabilization of zwitterionic transition states in DMSO.

Table 1. Comparison of Transition State Energies ($\Delta G^{\ddagger}$), Reaction Enthalpies (ΔG_R) *in Vacuo*, and Different Solvents Based on the PCM Model (Calculated at the B3LYP/6-311G(d) Level of Theory)

10 (D/A)	solvent	$\Delta G^{\ddagger a}$	$\Delta\Delta G^{\ddagger a,b}$	$\Delta G_R{}^a$	$\Delta\Delta G_R{}^{a,b}$
(MeO/CHO)	*in vacuo*	154.4		−25.7	
	PhMe	146.4	−8.0	−22.1	3.6
	$CHCl_2$	137.8	−16.6	−19.3	6.4
	DMSO	134.2	−20.2	−18.5	7.2
(MeO/COOMe)	*in vacuo*	171.6		8.0	
	PhMe	164.2	−7.4	14.2	5.9
	$CHCl_2$	154.5	−17.1	18.7	9.8
	DMSO	148.8	−22.8	18.9	10.9
(Me_2N/CHO)	*in vacuo*	108.2		−4.2	
	PhMe	92.0	−16.2	8.0	12.2
	$CHCl_2$	74.4	−33.8	10.6	14.7
	DMSO	67.2	−41.1	11.4	15.5

[a] Values are given in kJ/mol. [b] Differences of $\Delta G^{\ddagger}$ and ΔG_R, respectively, to the corresponding values *in vacuo*.

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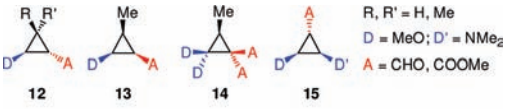


Figure 5. Further substitution patterns of D−A cyclopropanes.

So far, all substrates presented in this communication contain a *trans* arrangement of the vicinal donor and acceptor substituents and a methyl group as further residue of the cyclopropane. Thus, we were interested in whether the number of methyl groups in **12** (either none, one or two) has a significant influence on the reaction (Figure 5). In addition, we raised the question of whether a *cis* substitution (**13** in Figure 5) affords a similar outcome with respect to the ring enlargement. As a result, the number of methyl groups has no significant influence on the energetics. *Cis*-substituted D−A cyclopropanes which are higher in energy and commonly more difficult to obtain experimentally tend to have a smaller activation barrier than the corresponding *trans* isomers (Table 2).

Table 2. Influence of the Methyl Group and the Stereochemistry of the Donor−Acceptor Substitution (Calculated at the B3LYP/6-311G(d) Level of Theory)

12 (D/A)	R/R′	$\Delta G^{\ddagger a}$	$\Delta\Delta G^{\ddagger a,b}$	$\Delta G_R{}^a$	$\Delta\Delta G_R{}^{a,b}$
(MeO/CHO)	Me/H	154.4		−25.7	
	H/H	149.1	−5.3	−34.8	−9.1
	Me/Me	147.0	−7.4	−26.1	−0.4
(MeO/COOMe)	Me/H	171.6		1.8	
	H/H	168.6	−3.0	7.4	−6.2
	Me/Me	163.3	−8.4	8.0	−0.6
13 (D/A)	R/R′	$\Delta G^{\ddagger a}$	$\Delta\Delta G^{\ddagger a,b}$	$\Delta G_R{}^a$	$\Delta\Delta G_R{}^{a,b}$
(MeO/CHO)	Me/H	132.8	−21.6	−40.7	15.0
(MeO/COOMe)	Me/H	164.8	−6.8	30.6	22.6

[a] Values are given in kJ/mol. [b] Differences of $\Delta G^{\ddagger}$ and ΔG_R, respectively, to the corresponding values for system with one methyl substituent.

Moreover, we examined the influence of an additional acceptor as well as of a further donor attached to the three-membered ring (**14** in Figure 5). Table 3 summarizes the results for three selected examples. As anticipated, transition state energies are decreased whereas no clear-cut influence is observed for the reaction enthalpies. For a system with an amino and a methoxy donor (e.g., **15**, A = CHO) in a vicinal position the bond between the NMe_2 group and the acceptor is broken ($\Delta G^{\ddagger}$ = 84 vs 159 kJ/mol).

An interesting approach to seven-membered ring systems such as **17** might be the ring enlargement of D−A cyclopropane **16** (Scheme 3). Instead of a common formyl group a vinylogous aldehyde was employed. Due to the much less strained transition state in

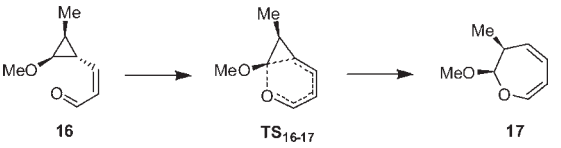
Table 3. Effects of Substitution with an Additional Acceptor and a Further Donor, Respectively (Calculated at the B3LYP/6-311G(d) Level of Theory)

14 (DD/AA)	$\Delta G^{\ddagger a}$	$\Delta\Delta G^{\ddagger a,b}$	$\Delta G_R{}^a$	$\Delta\Delta G_R{}^{a,b}$
(MeO/CHO)	154.4		−25.7	
(MeO/$(CHO)_2$)	94.9	−59.5	−60.0	−34.3
($(MeO)_2$/CHO)	85.0	−69.4	−41.9	−16.2
(MeO/COOMe)	171.6		1.8	
(MeO/$(COOMe)_2$)	147.1	−24.5	9.4	1.4

[a] Values are given in kJ/mol. [b] Differences of $\Delta G^{\ddagger}$ and ΔG_R, respectively, to the corresponding values in system **10**.

comparison with the system (**MeO/CHO**) we computed an activation energy of 110 kJ/mol and an energy gain of 57 kJ/mol whereas the five-membered ring analogue is only accessible *via* an activation barrier of 154 kJ/mol and 26 kJ/mol more stable than the starting material. Of course, other vinylogous systems might react in a similar way.

Scheme 3. Ring-Enlargement of Cyclopropane **16** Substituted with a Methoxy Donor and a Vinylogous Aldehyde Acceptor To Form the Seven-Membered Ring System **17**



In conclusion, we present a systematic investigation by means of B3LYP for the ring-enlargement of donor−acceptor-substituted cyclopropanes to afford five-membered ring systems. In total, 72 donor−acceptor combinations with respect to their activation barriers were elucidated. For representative examples, steric effects and the behavior in solution were also examined. These calculations may guide synthetic organic chemists to develop novel heterocycle syntheses. Experimental work based on this study is currently performed in our laboratory and will be reported in due course.

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Supporting Information Available. Gaussian Archive Entries, list of activation barriers, and optimized structures for all calculated species. Full ref 17. This material is available free of charge via the Internet at http://pubs.acs.org.