Intramolecular conjugate displacements are stepwise: Computational evaluations of the mechanism

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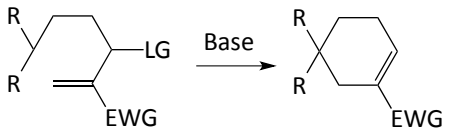
Abstract

Intramolecular conjugate displacement (ICD) reactions, developed by the Clive group, form carbocycles and cyclic amines by intramolecular nucleophilic attack on a Michael acceptor with an allylic leaving group. Quantum mechanical investigations with density functional theory show that ICDs involve a stepwise addition, forming an intermediate stabilized carbanion, followed by elimination. The electron-withdrawing nature of the allylic leaving group facilitates the addition by negative hyperconjugation; the twist-boat conformation of the addition and intermediate is stabilized by this interaction. In the absence of an activating electron-withdrawing group as part of the Michael acceptor a high-energy concerted $S_N2`$ reaction occurs. The reactions of carbon nucleophiles have lower activation energies than those of amines.

Background

The Clive group has developed the intramolecular conjugate displacement (IDC) reaction for ring closure with a variety of substrates (**Eq 1**).[1] The reaction is base-promoted and requires a nucleophile, Michael acceptor, and leaving group. These reactions occur with nitrogen nucleophiles as well.[2] The leaving group facilitates the reaction.[3] Reactions involving acetate as a leaving group are faster than those involving the poor leaving group, triethylsiloxy.[1] Probes of the mechanism of the reaction by the

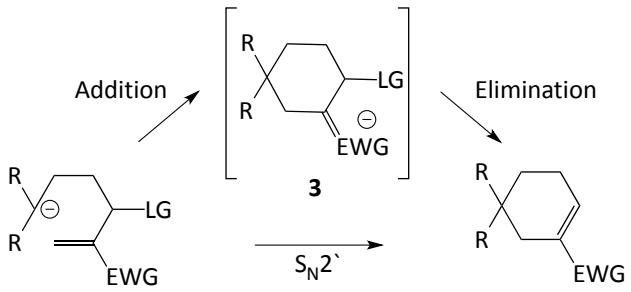
Clive group examined whether the ICD reaction is stepwise, or concerted with an intramolecular $S_N2`$ mechanism (**Eq 2**). They questioned whether intermediate **3** is formed. Trapping experiments in methanol show that the mechanism is stepwise for substrates with the poor siloxy leaving group (**Eq 3**). Here products formed from ICD, **5**, and from Michael addition, **6**, were obtained. No trapped product was obtained with the acetate leaving group, indicating either a concerted mechanism or short-lived intermediate that cannot be trapped.[1b]



(1)

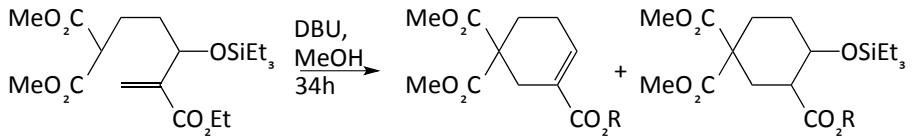
1 **2**

Base: DBU, Cs_2CO_3 or Et_3N (200 mol %)
EWG: CO_2Et, CN, or SO_2Ph
R: CO_2Me, SO_2Ph
LG: OAc, or $OSiEt_3$
Solvent: MeCN, or THF



(2)

1 **2**



(3)

4 **5** **6** R = Me or Et

ICD product Michael addition product

Methods

All calculations we preformed with Gaussian09.[4] Optimizations were performed with B3LYP/6-31G(d) and an implicit solvent model, IEF-PCM[5], for acetonitrile. Single

point energy calculations were run with the same solvent model with the higher accuracy density functional M06-2X/6-311+G(2d,p).[6] Relative Gibbs free energies are reported in kcal/mol. Several ring conformers and rotamers are found, for reactant, intermediates and transition states, but only the lowest energy structures are reported here.

Experimentally, geminal diester or phenylsulphonate carbanions are the nucleophiles, but we modeled these with malononitrile carbanions. These are conformationally simpler, and have similar electron-withdrawing ability.[7] The acrylate Michael acceptor was also modeled by acrylonitrile. This has also been used experimentally.[1] We modeled DBU with the smaller amidine (*Z*)-*N*,*N*,*N*'-trimethylacetimidamide, **7**, shown in **Figure 1**.

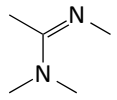


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Figure 1. Computational model for DBU.

Results and Discussion

We first explored the mechanism of the model reaction lacking a leaving group, shown in **Figure 2**. Both the twist-boat, and chair conformations were formed and these are labeled "t", and "c" respectively. The lowest energy transition state for addition is in a chair conformation and is 17.0 kcal/mol, which is 1.6 kcal/mol lower in energy than the twist-boat conformation. The product also prefers a chair conformation, but its energy is 8.9 kcal/mol above the reactant energy. The product prefers the chair conformation by 5.2 kcal/mol, similar to the difference in energy in the chair and twist-boat conformations of cyclohexane, which is 5.5 kcal/mol.[8]

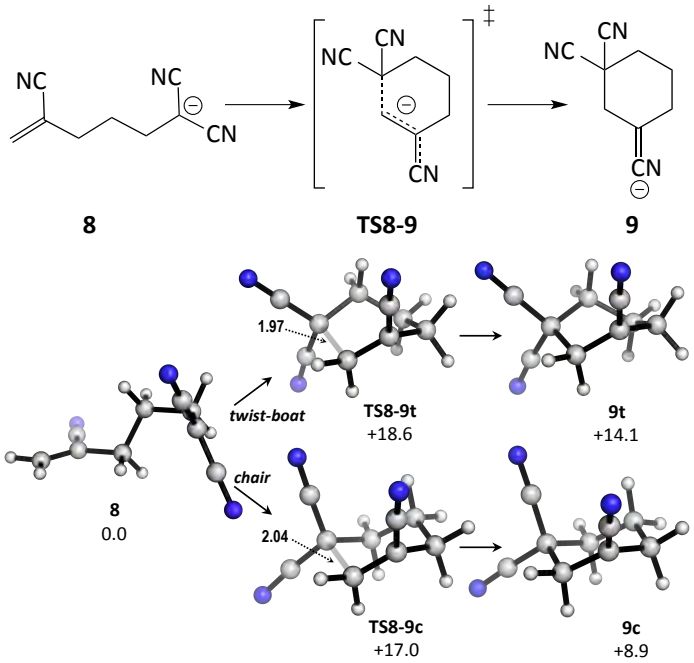

Figure 2. Reactant, transition states, and product for the ICD reaction of malononitrile anion with an acrylonitrile moiety.

Figure 3 shows the reactant, transition states, and product for an ICD reaction. The acetate leaving group prefers the axial position in all cases. The addition is stabilized in both the twist-boat and chair conformations by the acetate leaving group. Now the transition state (**TS10-11**) favors the twist-boat conformation, which is stabilized more so than the chair conformation, and is 12.8 kcal/mol, 5.8 kcal/mol below the case lacking the acetate. The intermediate, **11**, formed from the addition is 0.4 and 3.9 kcal/mol for the chair, and twist-boat conformations, respectively. These intermediates are significantly stabilized relative to the model system lacking the acetate. Although the chair conformation is favored, the twist-boat conformation is more stabilization by the acetate. The chair and twist-boat conformations are stabilized by 8.5 and 10.2 kcal/mol, respectively. The intermediate is in a very shallow well, and the elimination step has a barrier of only 2.1 kcal/mol in the chair conformation. This is in good agreement with the

experimental observation that this intermediate could not be detected by trapping experiments. The reaction forms **12**, and is exothermic by 16.4 kcal/mol.

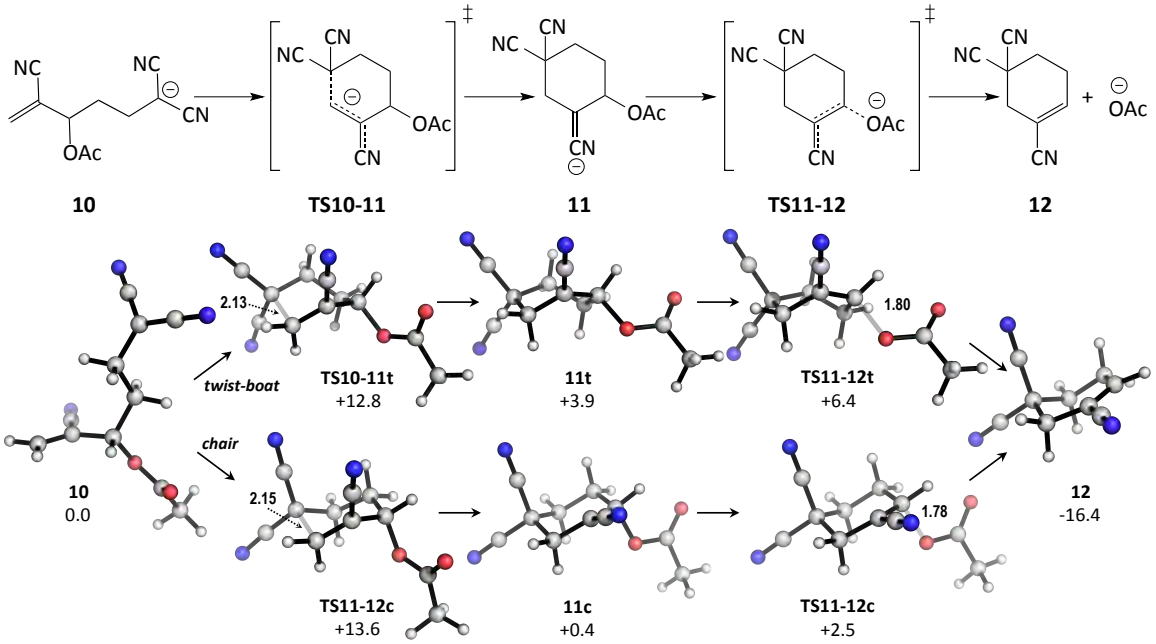

Figure 3. ICD reaction stationary points.

Figure 4 shows the stepwise ICD reaction with a mild promoter trimethylsiloxy (TMSO) leaving group. The addition and elimination transition states, **TS13-14**, **TS14-15**, respectively, and the intermediate between them, **14**, are higher in energy compared to the system with the acetate leaving group. The barrier for the addition is 15.0 kcal/mol. Here the chair is minimally favored over the twist-boat conformation (0.3 kcal/mol). The addition intermediate, **14**, is 3.9 kcal/mol above reactants in the favored, chair conformation. The TMSO leaving group stabilizes the addition transition state and intermediate, particularly in the twist-boat conformation, but much less so than the allylic acetate.

The barrier for the elimination to form the product is 15.3 kcal/mol in the favored chair conformation, which is nearly the same energy as the addition step. With the poor TMSO leaving group, the elimination (**TS14-12**) is greatly disfavored compared to that

of the acetate leaving group, and intermediate **14**, is in a deeper energy well. This is in good agreement with the experimental trapping of this intermediate. This overall ICD reaction is calculated to be endergonic by 2.3 kcal/mol from the anion.

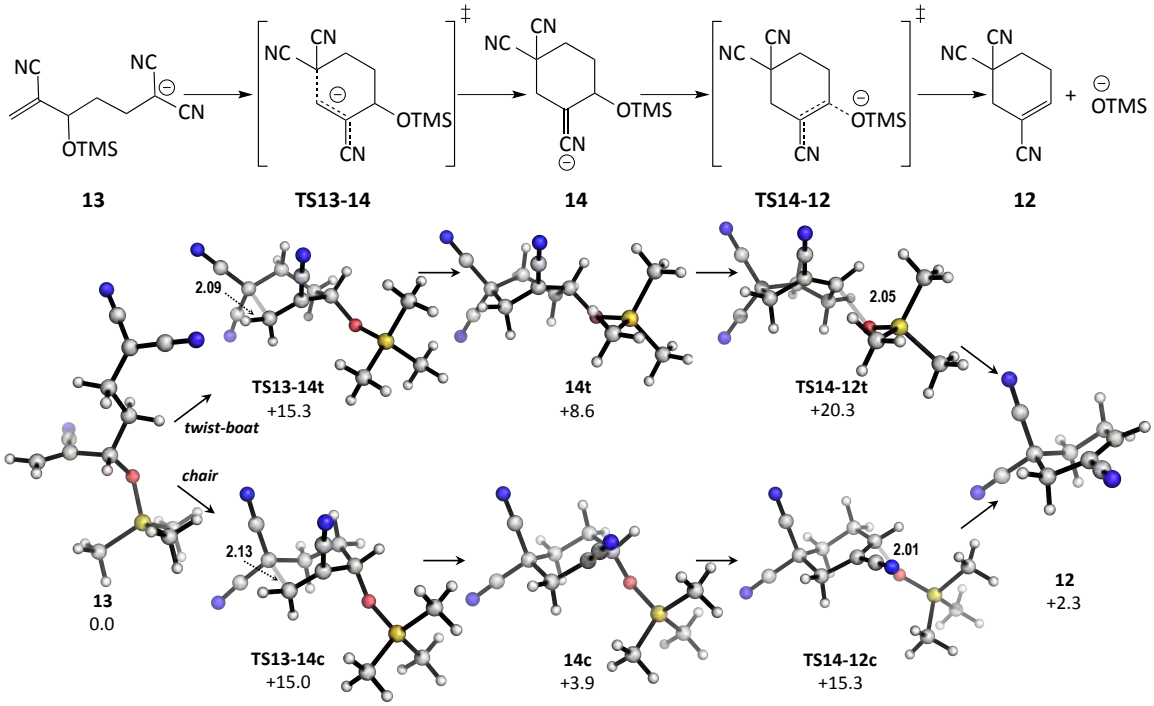

Figure 4. Stationary points calculated for the ICD reaction of OTMS derivate , **13**.

The calculations indicate a stepwise mechanism regardless of the leaving group. The electron-withdrawing allylic leaving group stabilizes the addition transition state and intermediate, and stabilizes the twist-boat more so than the chair conformation. **Figure 5** shows the CCCO dihedral angles from the cyano group to the leaving group, which is given for **TS10-11**, **TS13-14**, and intermediates **11**, **14** in **Table 1** and **Figure 6**. **Table 1** gives this dihedral angle and the stabilization energy due to the leaving group, which are correlated. The stabilization is due to negative hyperconjugation by the leaving group. In the twist-boat conformation of the addition transition state, and intermediate the leaving group is perpendicular to the cyano group of the Michael acceptor, that is in part to

overlay and stabilize the carbanion. There is more stabilization in the conformation that places the dihedral nearer to 90°. This enables the negative charge from the nucleophile to donate into the π orbital of the cyano group and into the σ* orbital of the leaving group.

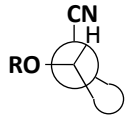

Figure 5. Newman projection of the CCCO dihedral from the cyano group to the leaving group. **Table 1** gives this dihedral for conformations of **TS10-11**, **TS13-14**, **11** and **14**.

Table 1. The CCCO dihedral and stabilization energy for the twist-boat and chair conformations of **TS10-11**, **TS13-14**, **11** and **14**.

	CCCO Dihedral (degrees)	Stabilization Energy[a] (kcal/mol)
TS10-11t	111.3	-5.8
TS10-11c	136.8	-3.5
TS13-14t	111.7	-3.4
TS13-14c	138.2	-2.0
11t	91.2	-10.3
11c	93.1	-8.6
14t	94.3	-5.6
14c	107.6	-5.0

a. Stabilization energy is ΔG- ΔG(no leaving group)

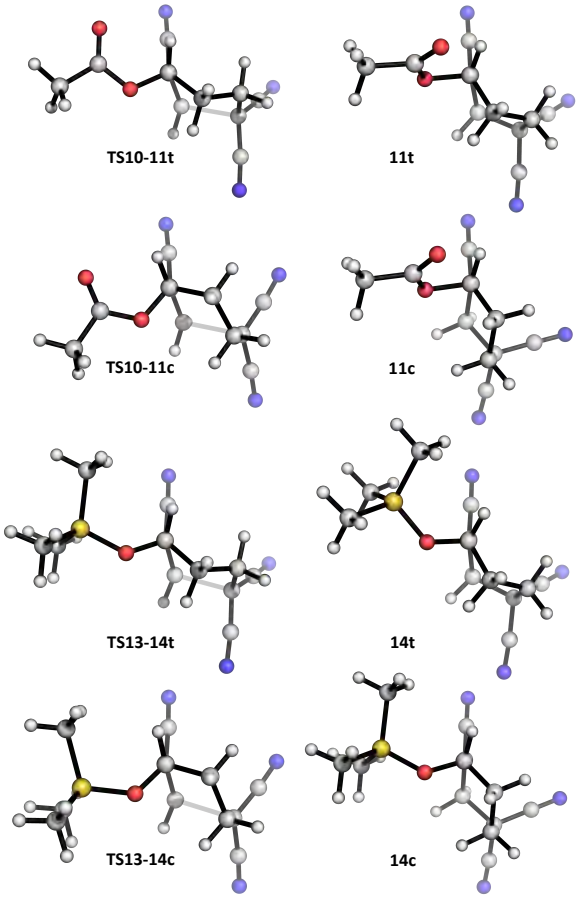

Figure 6. Addition transition states **TS10-11**, and **TS13-14**, and intermediates **11**, and **14** in the twist-boat and chair conformations, showing the dihedral between the cyano group and leaving group.

We next determined the influence of the absence of the Michael acceptor as shown in **Figure 7**. Without a Michael acceptor, the reaction is a concerted $S_N2`$ reaction, but the activation energy is high (**TS15-16c**, 31.5 kcal/mol). Here the chair conformation is preferred, and the acetate leaves from the axial position. When the acetate is equatorial the reaction is stepwise, but the activation energy is even higher (37.9 kcal/mol) and would form a very high energy intermediate (33.2 kcal/mol).

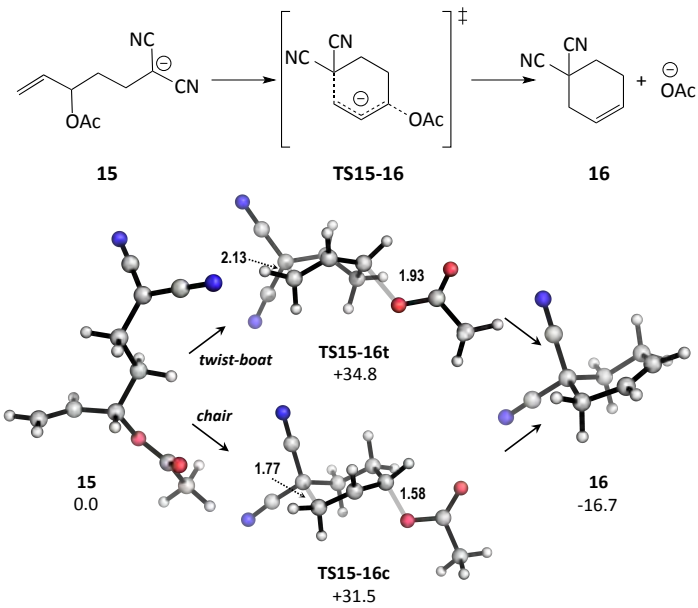

Figure 7. Stationary points calculated for the ICD reaction lacking a Michael acceptor.

The reaction with an amine nucleophile follows an analogous, stepwise mechanism to that of the carbon nucleophile, and is shown in **Figure 8**. The reaction with the amine has higher barriers, and is endergonic. The barrier for addition with the amino group is 19.5 and 20.3 kcal/mol for the twist-boat (**TS17-18t**), and chair (**TS17-18c**) conformations, respectively. This is 6.7 kcal/mol higher than the addition of the carbanionic nucleophile, because the amine is less nucleophilic. The zwitterionic intermediate, **18**, favors the chair conformation, and undergoes elimination via **TS18-19c** with a barrier of 19.3 kcal/mol. The addition and elimination have roughly the same energy. The aminuim product, **19**, is 6 kcal/mol.

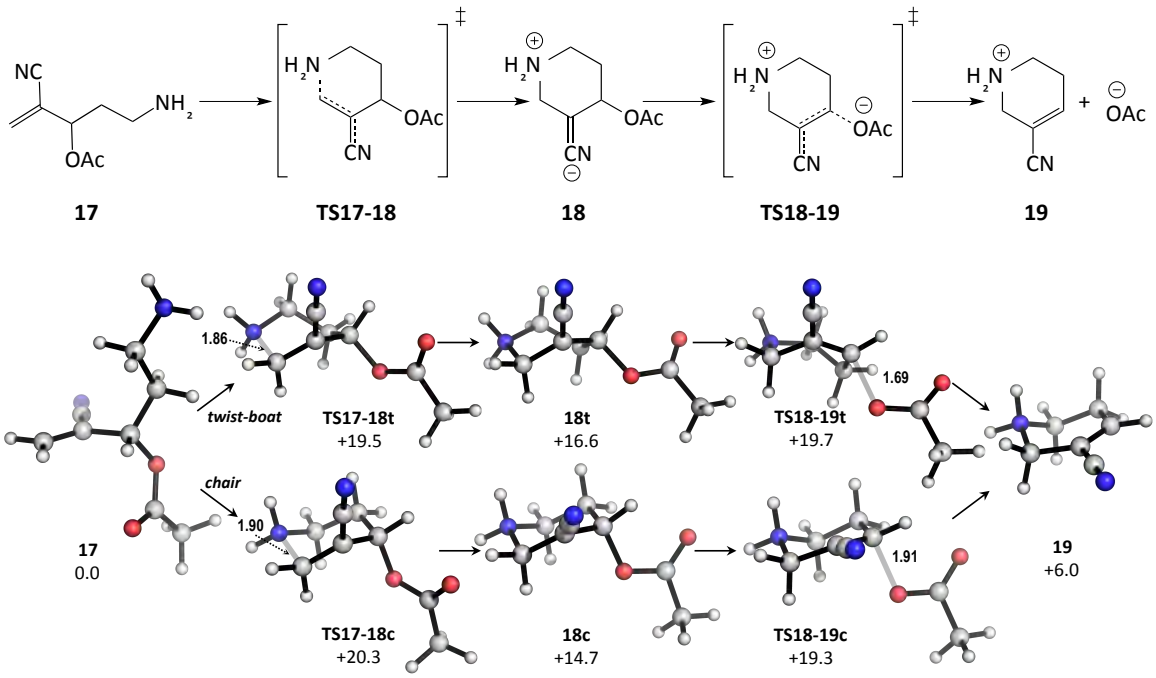

Figure 8. ICD reaction mechanism with an amine nucleophile

Conclusion

The mechanism by which the ICD reaction occurs is elucidated. The reaction proceeds by a stepwise mechanism as long as a Michael acceptor is present. The electronegative leaving group stabilizes the addition transition state and intermediate by negative hyperconjugation. In the transition state, the closer the leaving group is to antiperiplanar to the incoming nucleophile, and perpendicular to the cyano group, the greater the stabilizing effect. The stabilizing negative hyperconjugation results in faster reaction rates with more electron-withdrawing leaving groups.

With the acetate leaving group the addition is the rate determining step. With the siloxy leaving group both the addition and elimination are slowed, especially the elimination, and the addition and elimination transition states have roughly the same energy. The reaction with a nitrogen nucleophile follows an analogous, stepwise

mechanism to that of the carbon nucleophile. The reaction with the nitrogen nucleophile has higher barriers and is endergonic because the amine is less nucleophilic than the carbanion. The addition and elimination have similar activation energies.

These studies enable better design of this important class of reactions, which can form complex, functionalized carbocycles and heterocyclic amines. Development of the reaction to use more electron-withdrawing leaving groups and stronger nucleophiles will enable faster reaction rates. Further development of these reactions is an active area of study.

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