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Conrotatory Ring-Opening Reactions of Cyclopropyl Anions in Monocyclic and Tricyclic Systems

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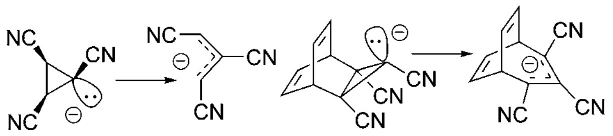
ABSTRACT

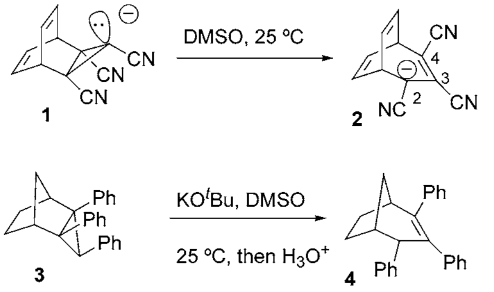


Only conrotatory transition structures were located by B3LYP6-311++G(3df, 2p) computations for the electrocyclic ring opening of cyclopropyl anions having different substituents (H, Me, CN). The transition structure for the similarly substituted cyclopropyl anion fused to a bicyclic system exhibits the same features, in apparent contradiction with the observed product. A reaction path where the direction of twist changes after the transition state provides an explanation alternative to those proposed in recent reports.

The possibility of a pericyclic reaction can be established, according to the Woodward–Hoffmann rules, through analysis of the pattern of interacting orbitals and consideration of the number of electrons involved.[1] For electrocyclic reactions in which a ring is opened (or formed), odd- and even-numbered electron systems are predicted to undergo disrotatory or conrotatory movements, respectively. The results of molecular orbital calculations and experimental work for cyclopropyl cations and anions[2] are consistent with dis- and conrotatory lowest energy ring-opening reaction pathways, respectively.

A recent paper[3] captured our attention at the time we were involved in the theoretical study of the solvolytic electrocyclic ring opening of substituted halocyclopropanes (see the accompanying paper[4]). It was reported that bicyclic allyl anion **2** was obtained by rearrangement of tricyclic anion **1** at room temperature, in what appears to be a Woodward–Hoffmann-forbidden process (Scheme 1). Precedents of similar "violations" of the orbital symmetry conservation rules, such as the related rearrangement of **3** to **4**, have been described as resulting from an electron transfer followed by anion-radical opening favored by the presence of the aryl groups.[5]

Scheme 1. Rearrangement of Cyclopropyl Anions Fused to Bicyclic Structures



To explain the outcome of the ring opening, **1** → **2**, formally the result of a disrotatory process, a mechanism

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[1] Woodward, R. B.; Hoffmann, R. *Angew. Chem., Int. Ed. Engl.* **1969**, *81*, 797.

[2] (a) Marvell, E. N. *Thermal Electrocyclic Reactions*; Academic Press: New York, 1980. (b) Chou, P. K.; Dahlke, G. D.; Kass, S. R. *J. Am. Chem. Soc.***1993**, *115*, 315 and references therein.

[3] Leivers, M.; Tam, I.; Groves, K.; Leung, D.; Xie, Y.; Breslow, R. *Org. Lett.* **2003**, *5*, 3407.

[4] Nieto Faza, O.; Silva López, C.; Álvarez, R.; de Lera, A. R. *Org. Lett.* **2004**, *6*, 905.

[5] (a) Mulvaney, J. E.; Londrigan, M. E.; Savage, D. J. *J. Org. Chem.* **1981**, *46*, 4592. (b) Newcomb, M.; Seidel, T.; McPherson, M. B. *J. Am. Chem. Soc.* **1979**, *101*, 777.

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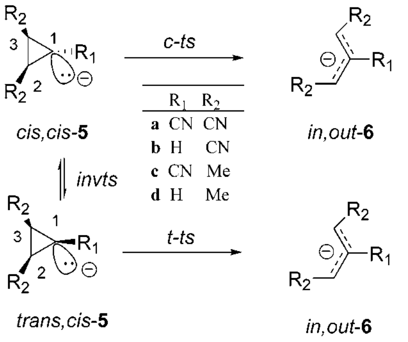
was proposed where the disrotatory motion of the cyano-substituted carbons opposite to the anion was considered to be favored over the conrotatory because it pushes the σ-electrons away from the carbanion, allowing them to "overlap with the empty hybrid orbital of the carbanion, thus resembling an allyl cation".[3] These electronic effects would be reminiscent of the backside preference for displacement reactions, in which the nucleophile electron pairs interact with σ^*, while avoiding the σ electrons of the leaving group. A disrotatory transition state for **1** was startling in light of previous knowledge about electrocyclic reactions.[2] We therefore set out to conduct a computational study of the rearrangement of cyclopropyl anions, including simple systems used as models, and the tricyclic **1** itself.

Previous ab initio computations at the MP2/6-31+G(d)//6-31+G(d) level have revealed the influence of the electronic effects of the substituents on the energetics and geometries for the rearrangement and ring inversion of C1-monosubstituted cyclopropyl anions.[2b] However, no such calculations have been carried out for di- or trisubstituted systems. Considering that the cyano groups might have a role in the energetics and stereoselectivity of the rearrangement (in fact, a stabilization of the antiaromatic cyclopropenyl anion by the three CN groups was also contemplated as an intervening factor on the "disrotation" of **1**), we started with simple cyclopropyl anions symmetrically substituted with H, Me, and CN groups (**5a**−**d**), having *cis* and *trans* configurations relative to the lone pair Csp^3 orbital. One stereochemical descriptor (*cis*/*trans*) suffices for depicting the relative configuration of R$_2$ and the anion on C1 on reactants, since the relative configuration of the R$_2$-substituted carbons was fixed as *cis*, as in **1**. Being equally substituted at the termini carbons, the two allowed conrotations are equivalent. The anion inversion accounting for the configurational instability of C1 in the cyclopropyl ring, was also considered, and transition structures labeled *invts* and activation energies for inversion were also computed (Scheme 2).

Scheme 2. Conrotatory Movement and Anion Inversion of Trisubstituted Cyclopropyl Anions **5a**−**d**



All the calculations were carried out with the Gaussian98 suite of programs.[6]

For the characterization of the stationary points (minima and transition structures), a dual-level technique was selected, where energy refinement and properties calculated with the 6-311++G(3df, 2p) basis set followed the geometry optimization, harmonic analysis, and wave function stability check calculated with the 6-31++G(d,p) basis set. In all cases, the density functional theory was selected, with the Becke three-parameter exchange functional[7] and the nonlocal correlation functional of Lee, Yang, and Parr.[8] To derive information about charges and bond orders, a NBO analysis was carried out on the high-level wave function, using the NBO 3.1 code,[9] as implemented in Gaussian98. Table 1 lists the relative free energies of reactants and transition structures of the reactions depicted in Scheme 2. *Transition structures for the alternative disrotatory movements could not be located.*

Table 1. Relative Free Energies for Reactants and Transition Structures for **5a**−**d** Ring Opening and Inversion, Computed at the B3LYP/6-311++G(3df,2p)//B3LYP/6-31++G(d,p) Level

	R$_1$	R$_2$	*c*-ts	*c*,*c*-**5**	invts	*t*,*c*-**5**	*t*-ts
a	CN	CN	16.27	0.00	7.32	2.93	
b	H	CN	17.35	1.95	14.41	0.00	17.75
c	CN	Me	26.32	0.00	4.77	1.81	
d	H	Me	25.63	0.00	10.57	3.97	

The activation energies computed for the electrocyclic ring opening range from 16.27 for **5a** to 26.32 kcal/mol for the dimethyl analogue **5c**. These values are in good agreement with the results reported by Kass et al.,[2b] who computed barriers of 31.4 kcal/mol (consistent with the lower limit for the experimental value of 36 kcal/mol in gas phase) and 28.7 kcal/mol, respectively, for the ring opening of 1-cyano and parent cyclopropyl anions at the MP2/6-31+G(d)//HF/6-31+G(d) level of theory.

The effect of the cyano substituents both on the ring-opening barrier and the anion inversion can be established by looking at the reaction profiles. Consistent with the results reported by Kass,[2b] a CN group at C1 lowers the anion inversion barrier by ca. 6−7 kcal/mol (cf. **5a** vs **5b** and **5c** vs **5d**), albeit the activation energies for the ring-opening process are not greatly affected (ca. 1 kcal/mol). When placed at C1, a CN forces a more planar structure for the anion (a

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(6) Gaussian 98; Gaussian 94 (Revision A.1). Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Gill, P. M. W.; Johnson, B. G.; Robb, M. A.; Cheeseman, J. R.; Keith, T. A.; Petersson, G. A.; Montgomery, J. A.; Raghavachari, K.; Al-Laham, M. A.; Zakrzewski, V. G.; Ortiz, J. V.; Foresman, J. B.; Cioslowski, J.; Stefanov, B. B.; Nanayakkara, A.; Challacombe, M.; Peng, C. Y.; Ayala, P. Y.; Chen, W.; Wong, M. W.; Andres, J. L.; Replogle, E. S.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Binkley, J. S.; Defrees, D. J.; Baker, J.; Stewart, J. P.; Head-Gordon, M.; Gonzalez, C.; Pople, J. A. Gaussian, Inc.: Pittsburgh, PA, 1995.

(7) (a) Becke, A. D. *Phys. Rev. A* **1988**, *38*, 3098. (b) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648.

(8) (a) Parr, R. G.; Yang, W. *Density Functional Theory of Atoms and Molecules*; Oxford: New York, 1989. (b) Ziegler, T. *Chem. Rev.* **1991**, *91*, 651. (c) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785. (d) For a description of density functionals as implemented in the Gaussian series of programs, see: Johnson, B. G.; Gill, P. M. W.; Pople, J. A. *J. Chem. Phys.* **1993**, *98*, 5612.

(9) Glendening, G. D.; Reed, A. E.; Carpenter, J. E.; Weinhold, F. NBO version 3.1.

difference between 5 and 12° was measured for the out-of-plane R_1 dihedral), which becomes structurally closer to the transition structure, and shows a greater tolerance for the C2C1C3 angle increase required for anion inversion. The rehybridization accompanying the rearrangement, with the transformation of a sp^3 lone pair in a p orbital, is also reflected in the shortening of the C1−C2 and C1−C3 distances and the resultant elongation of the C2−C3 bond. On the other hand, CN groups at C2 or C3 strongly stabilize the transition structure for the ring-opening process and have a more moderate effect on the inversion barrier (cf. **5b** vs **5d** and **5a** vs **5c**). This most likely results from the ability of the cyano group to stabilize anions in α by resonance (Supporting Information, Table G).

The effect of the CN groups located at C2 and C3 on the reaction barriers to inversion is the opposite to that observed for the ring opening. The transition structure for the conrotatory electrocyclic ring opening reaction involves a displacemente of the charge toward the termini of the incipient allyl anion. If resonance-stabilizing CN groups are present at the bond-breaking positions, a lowering of the energy of activation is expected. Activation free energy differences computed for this effect range from 8 to 10 kcal/mol. Kass et al.[2b] have attempted to correlate the flexibility (i.e., ease of ring inversion) of the series of C1-substituted cyclopropyl anions with their tendency to rearrange to the corresponding allyl anions. Good correlation was observed for most substituents, although an irregular behavior was reported for formyl and cyano derivatives, which displayed greater complexity. The overlap of the lone electron pair with the breaking σ bond is greater for a planar anion than for a pyramidal one when advancing toward the conrotatory transition state (Figure 1). Competition between orbital overlap in the transition structure on one hand and anion stabilization in the reactants **5a** and **5c** on the other could explain the anomalous energy ordering for the ring opening of the **5a**/**5b** and **5c**/**5d** pairs. The differential anion stabilization at C1 vs C2 and C3 overrides the effect of the anion planarity on the reaction profile. In **5a**, where the three cyano substituents ensure slight changes in anion stabilization from reactant to transition state, the increased orbital overlap (vide supra) is the determining factor. For the dimethyl analogue **5c**, the substituents fail to balance the anion stabilization along the reaction pathway and the charge stabilization in the reactant makes its activation energy higher than that of **5d**.

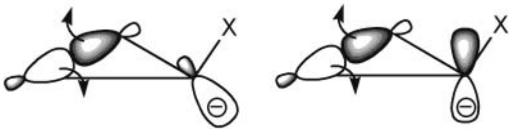

Figure 1. Overlap of the breaking σ orbital with the lone pair in the transition structure is greater for a planar anion than for a pyramidal one upon conrotatory ring opening of cyclopropyl systems.

The above discussion is restricted to the *cis*-*cis*-**5** series. Although the minima and the inversion barrier for the *trans*-cis-**5** series could be optimized uneventfully (Table 1), only the transition structure for the rearrangement of *trans*-*cis*-**5b** was located. Their lower barriers for inversion made the calculations for the remaining analogues readily converge to the corresponding *cis*-*cis*-**5a**,**c**,**d** isomers. Taking the computed value (17.7 kcal/mol for *trans*-*cis*-**5b** vs 17.35 kcal/mol for *cis*-*cis*-**5b**) as a reference, we would not expect significant differences between the activation energies of the electrocyclic processes for *cis*-*cis*-**5a**,**c**,**d**. As the two pathways converge to the same product, the fast anion inversion would not have relevant kinetic effects.

With the finding of a preferred conrotation path for the 1,2,3-tricyanocyclopropyl anion **5a**, having a relative low activation energy, our computational study was extended to the electrocyclic ring opening of **1** in order to assess the feasability of an allowed disrotatory motion for its transformation into **2** (Scheme 1). The relative free energies of the stationary points along this reaction path are shown in Table 2. Anion inversion of *cis*,*cis*-**1** leads to the thermodynamically more stable *trans*,*cis*-**1** isomer (energy difference of 0.61 kcal/mol). The low barrier of this process (2.79 kcal/mol) results in the same phenomenon observed for **5**, where all the ring-opening transition states converged to those corresponding to the *cis*,*cis* anions.

Table 2. Relative Free Energies for Reactants and Transition Structures in the **1**−**2** Rearrangement, Computed at the B3LYP/6-311++G(3df,2p)//B3LYP/6-31++G(d,p) Level

structure	free energy
cis,*cis*-**1**	0.61
1-ts	17.88
1-*invts*	3.40
trans,*cis*-**1**	0.00

Despite their different structure, a strikingly good similarity in the energy barrier to ring opening (17.27 for **1** vs 16.27 kcal/mol for **5a**) was found. Likewise, the geometries of both the reactants and the transition structures are quite similar for **1** and monocyclic **5a**. The constraints of the cyclopropyl ring as part of the tricyclic structure in **1** are reflected in the greater planarity of the carbanion. The transition state for the rearrangement is more advanced and asymmetric in **1**. While the breaking bond distance is 2.03 Å (the corresponding distance in **5a** is 1.93 Å) and the dihedral of the C2−CN group relative to C2C3C4 (see Scheme 1) is increased by 6.6° (123.9° in **1** vs 117.3° in **5a**), the dihedral of the C4−CN bond relative to C4C3C2 shows a smaller variation (89.6° in **1** vs 84.3° in **5a**). These changes, in a highly constrained skeleton, are likely adopted by the cyclic system in order to prevent the formation of a highly strained *E*-allylic anion.

An initial conrotatory motion is therefore proposed to operate in the ring opening of the cyclopropyl anion in **1**

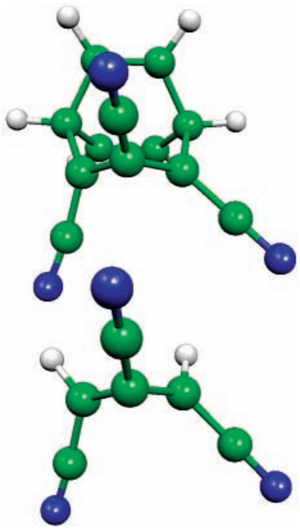

Figure 2. Transition structures for the ring opening of cyclopropyl anion in **1** and **5a**.

through a transition state that shows only minor geometrical deviations from the structure of the unconstrained system **5a** (Figure 2). Further along the reaction coordinate (as shown by IRC calculations), the rotation of the C2−CN substituent changes direction to avoid the highly hindered *in* position, yielding the observed product **2**.[10] When the change in the sense of this rotation takes place, the system has already crossed the transition state, and the breaking bond distance is 2.5 Å. The disrotatory mechanism proposed[3] is then unsupported by the present computations, and therefore, the rearrangement of **1** should instead be considered as another example of a Woodward−Hoffmann-allowed process.

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Supporting Information Available: Tables with thermodynamic data and geometric parameters and a file with the coordinates for the IRC of **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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[10] Dynamical effects (see, for example: Ammal, S. C.; Yamataka, H.; Aida, M.; Dupuis, M. *Science* **2003**, *299*, 1555) cannot be discarded, as a reviewer suggested. However, the calculations are beyond our present capabilities.