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The Woodward–Hoffmann–De Puy Rule Revisited†

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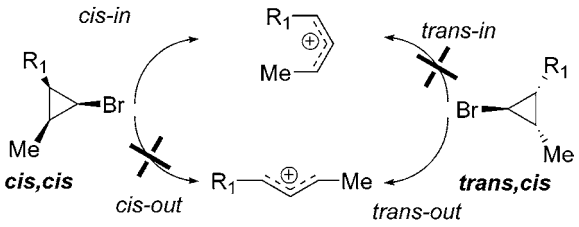
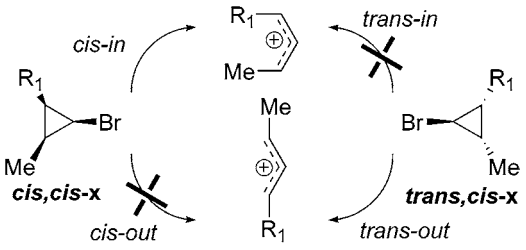
ABSTRACT



An estimate of the kinetic advantage, in the gas phase and in MeOH, of one of the two allowed disrotatory movements in the electrocyclic ring opening of cyclopropyl derivatives has been theoretically obtained at the B3LYP/6-311++G level. Confirming the Woodward–Hoffmann–DePuy rule, the torquoselectivity of this process is attributed to charge donation from the dissociating C–C bond to the antibonding orbital of the breaking C–Br bond. Substituents do not modify the inherent torquoselectivity.**

The solvolysis of cyclopropyl halides and pseudohalides to allyl cations is a prototype of the $2\pi-e^-$ electrocyclic reactions (Figure 1).[1] The opening of the cyclopropyl ring takes place in concert with the departure of the leaving group[2] and shows an "unusual restriction to a single disrotatory direction".[1] Only products resulting from one of the two symmetry-allowed disrotatory motions were observed in substituted cyclopropyl tosylates or halides, and the sense of rotation was found to depend on the relative configuration of the leaving group:[3] substituents cis to the leaving group rotate *inwardly*, whereas those trans rotate *outwardly*, a generalization known thereafter as the Woodward−Hoffmann−DePuy rule.[4] The favored disrotatory motion is the one that enforces electronic assistance to C−X bond cleavage by the breaking the C_2-C_3 bond.[5] The Woodward−Hoffmann−De Puy rule proved fully consistent[6] with the experimental relative rates of solvolysis of 2,3-disubstituted cyclopropylbromides and tosylates.



x	R_1	x	R_1	x	R_1
1	Me	**4**	$CHCH_2$	**7**	OMe
2	H	**5**	F	**8**	CHO
3	*t*-Bu	**6**	NH_2	**9**	NO_2

Figure 1. Disrotatory electrocyclic solvolytic ring-opening reactions of *cis,cis*- and *trans,cis*-1-bromo-2,3-disubstituted cyclopropanes **1**−**9**.

† Dedicated to Professor Charles H. DePuy on occasion of his 75th birthday.

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(5) Within this analysis the reaction could alternatively be considered as an S_N2-type displacement of X by the electrons of the breaking cyclopropyl σ bond.

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Table 1. Activation Free Energies (kcal/mol) for the Transition Structures Corresponding to the Electrocyclic Ring Opening of *cis,cis*- and *trans,cis*-1-Bromo-2,3-disubstituted Cyclopropanes **1**−**9**

R_1	**1** Me	**2** H	**3** *t*-Bu	**4** $CHCH_2$	**5** F	**6** NH_2	**7** OMe	**8** CHO	**9** NO_2
$\Delta G^{\ddagger}$-*cis*-in	36.08	38.82	36.67	30.29	35.33	16.60	28.50	37.04	37.93
$\Delta G^{\ddagger}$-*cis*-out	46.29	51.31	43.56	42.89	49.37	31.66	45.30	53.68	54.82
$\Delta G^{\ddagger}$-*trans*-in	60.62	57.57	64.33	55.10	63.53	49.50	55.40		61.58
$\Delta G^{\ddagger}$-*trans*-out	30.26	36.83	26.85	22.98	33.02	17.26	22.91	31.09	35.20
c-$\lvert\Delta G^{\ddagger}$-in- $\Delta G^{\ddagger}$-out$\rvert$	10.21	12.49	6.89	12.60	14.04	15.06	16.80	16.65	16.89
t-$\lvert\Delta G^{\ddagger}$-in- $\Delta G^{\ddagger}$-out$\rvert$	30.36	20.74	37.48	32.12	30.51	32.24	32.49		26.38

To our knowledge, the Woodward−Hoffmann−DePuy rule represents the first documented explanation of *torquoselectivity* or stereoselectivity due to the preference for one of the two symmetry-allowed conrotatory or disrotatory modes in electrocyclic reactions. Houk et al. demonstrated that torquoselectivity in the $4\pi-e^-$ conrotatory ring-opening of substituted cyclobutenes was primarily dependent upon the electronic, rather than the steric, effect of the substituents: in substituted cyclobutenes electron donors at C3 rotate away (*outward*) from the breaking bond, whereas strong electron acceptors rotate *inward*.[7]

In contrast to the ring opening of cyclobutenes, no theoretical treatment of the electrocylic ring-opening of cyclopropyl derivatives using the tools of modern computational chemistry exists. We therefore decided to study computationally the rearrangement of *cis,cis*- and *trans,cis*-1-bromo-2,3-disubstituted cyclopropanes **1**−**9**, both in the gas phase and in solution, and addressed the structural factors that restrict the disrotatory ring-opening to a single direction as formulated in the Woodward−Hoffmann−DePuy rule.

Becke's three-parameter functional[8] (B3LYP) DFT method as implemented in GAUSSIAN 98,[9] with the 6-311++G** basis set, was selected for the computations due to its proven accuracy in the prediction of experimental activation barriers[10] for a variety of pericyclic reactions (both open- and closed-shell systems). The SKBJ[11] pseudopotential was selected to describe the bromine atom, with two d and one f functions added to the published base for the valence electrons. All stationary points were characterized by harmonic analysis, and the unscaled[12] computed frequencies were used to obtain zero-point energies and thermodynamic parameters.

Solvent effects were computed using geometry optimizations with the Onsager method (with cavity radii taken from previous gas-phase optimizations).[13] In several significant cases, intrinsic reaction coordinate (IRC) calculations were performed to unambiguously connect transition structures with reactants and products. Bond orders and atomic charges were calculated with the natural bond orbital (NBO)[14] method.

Table 1 lists the activation energies for the two alternative disrotatory ring opening reactions of *cis,cis*-**1** and *trans,cis*-**1**[15] (Figure 1) depicted as *in* and *out*. Geometric parameters for reactants and transition structures are listed in the Supporting Information.

To establish the origin of the experimental torquoselectivity, we chose system **1**, where the two substituents on the ring are methyl groups, as a model.

The results for the rearrangement of each stereoisomeric reactant of the model system confirm the Woodward−Hoffmann−DePuy rule: the *inward* disrotatory motions of the groups located cis to bromine (methyl for *cis,cis*-**1** and hydrogen for *trans,cis*-**1**) are of lower energy than the alternative *outward* disrotational direction of bond breaking. The disfavored *cis-out* and *trans-in* transition structures lie 10.18 and 30.07 kcal/mol above the favored pathway of each series. The *cis-out* movement, although electronically disfavored, does not incur in severe steric interactions in the transition state leading to the *out,out* allyl cation. In contrast, the highly energetic transition structure for the *trans-in* disrotation is severely congested and does not benefit from electronic stabilization. The relative values computed for the energies of the two pairs of disrotatory processes can be

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(15) The cis and trans descriptors denote the relative configuration of the chiral centers at C1, C2, and C3.

Table 2. Activation Free Energies (kcal/mol) for the Favored Transition Structures Corresponding to the Electrocyclic Ring Opening of *cis*-*cis*- and *trans*,*cis*-1-Bromo-2,3-dimethylcyclopropanes **1**−**9** in MeOH Computed Using an Onsager-Type SCRF

R_1	**1** Me	**2** H	**3** *t*-Bu	**4** $CHCH_2$	**5** F	**6** NH_2	**7** OMe	**8** CHO	**9** NO_2
$\Delta G^{\ddagger}$-*cis*-in	29.47	32.85	32.26	26.63	31.09	13.65	25.59	35.92	36.04
$\Delta G^{\ddagger}$-*trans*-out	21.77	31.44	21.47	17.04	26.15	11.70	16.19	27.59	32.25

considered an estimate of the Woodward−Hoffmann−DePuy rule.[16] Moreover, the activation energies for the preferred disrotation in each stereoisomer differ by ca. 5 kcal/mol and favor the *trans-out* motion over the *cis-in*. The results are consistent with the relative rate differences between both reactants, $k_t/k_c = 6{,}030$ determined experimentally.[6] This difference might then be confidently attributed to the greater steric congestion in TS-*cis-in* relative to TS-*trans-out*.

NBO analysis of the transition structures revealed that *cis-in*-**1** and *trans-out*-**1**, show a highly dissociated C−C bond, accompanying the rotational movement of the methyl substituents. and emphasizes the main role of the breaking C−C bond in facilitating the departure of the leaving group through stabilization of the $\sigma^*_{(C-Br)}$ orbital, in line with the assumption made by Woodward, Hoffmann and DePuy.[17]

Activation energies using the Onsager model for the two allowed disrotations in a polar solver (MeOH, $\epsilon = 32.63$) are listed in Table 2. Solvation stabilizes all structures, in particular those of the transition states, in which charges are dissociated. For reactants, stabilization (0.4 kcal/mol) is small, whereas for transition structures is much higher, leading to a considerable reduction in activation energies. The magnitude of the stabilization correlates with the computed dipole moments and is, therefore, more significant for *trans-in* and *trans-out* than for the stereoisomeric *cis-in* and *cis-out* disrotations. Nevertheless, both the energy ordering of transition structures and the torquoselectivity of the ring-opening are not altered by solvation. Transition structures in MeOH are found earlier in the reaction coordinate relative to gas phase, and exhibit shorter C−C bond distances and smaller dihedral angles for methyl group rotation. They are more asynchronous, with longer C−Br distances relative to the values computed in vacuo.

The inclusion of solvent effects allows for a comparison of computed and experimental values. Although the reaction conditions are quite different (AcOH vs MeOH), the energy values fall within the same range. For example, activation enthalpies ($\Delta H^{\ddagger}$) of 33.3 and 27.1 kcal/mol were determined experimentally for acetolysis of *cis*,*cis*- and *trans*,*cis*-1-bromo-2,3-dimethylcyclopropane **1**, respectively, at 100 °C.[6b]

Besides the driving force provided by the electronic effects underlying the Woodward−Hoffmann−DePuy rule, it was considered that the stereoselectivity of the ring opening of cyclopropyl halides could also benefit from the interaction of the breaking bond C−C with the substituents, in keeping with Houk's finding on cyclobutenes.[7] At the outset, however, moderate effects should be expected, since disrotatory motions are less sensitive to the direction of twist of the substituents upon bond-breaking and three-membered rings show greater R−C2C3 angles (ca. 120°).

Using the reaction profiles for the disrotatory motions of the model reactions as reference, reaction energies and geometries for reactants and transition structures for the processes depicted in Figure 1 were computed at the same level of theory. Table 1 lists the energies of the species involved in the reaction.[18] Similar to the parent system, **1**,solvent (MeOH) has no differential effect on the ring-opening of cyclopropanes **2**−**9**, and the transition state stabilization relative to reactant is general.

No change in the simple torquoselectivity established for the model system is observed, the reactions proceeding through *cis-in* and *trans-out* being favored for the *cis*,*cis* and *trans*,*cis* diastereomers of the cyclopropyl derivatives, respectively. This disrotational preference is attributed, based on NBO estimates, to charge donation to the antibonding orbital of the breaking C−Br bond either from the dissociating C−C bond or from the nonbonding pairs or π systems formed thereof; the assistance to bond dissociation is greater in the favored TS-*cis-in* and TS-*trans-out* in all cases examined. Thus, from the early stages of the reaction, the breaking C−C bond is committed to interact with the antibonding orbital of the C−Br bond, and the two-electron stabilization becomes the dominant interaction responsible for the disrotational movement. As a consequence, the breaking C2−C3 bond becomes less available for additional interactions with the neighboring substituents. Consistent with this view, the C−C bond can be considered fully dissociated in the favored processes (except when the substituent is an amino group, which shows a very early transition state). The role of the substituents seems to be secondary, and it is only reflected in the stabilization of the

(16) A lower limit of 6.6 kcal/mol was estimated for the difference in activation energy between the two rotational directions available for the acetolysis of *exo*-7-tosyloxybicyclo[4.1.0]heptane at 150 °C (ref 6c,d).

(17) Transition structures for reactions *cis-out* and specially *trans-in* are more asynchronous. In both cases, the C−Br bond is almost entirely dissociated and the C−C bond distances are shorter than for the favored transition structures. Nevertheless, the activation energy for *cis-out* is lower than for *trans-in*, partly due to a residual interaction between the breaking C−C bond and the σ^*(C−Br) orbital which is maintained in the less compact transition structure for the methyl rotating outward, and partly to the smaller steric hindrance to bond rotation. NBO analysis for *trans-in* reveals that the C−Br bond is fully dissociated and might better be described as an interaction of one empty orbital centered on carbon and another filled orbital on bromide. Although IRC analysis shows clearly that the computed transition structure connects reactants and products, TS-*trans-in* is similar to a cyclopropyl cation. All these features raise concerns on the consideration of the solvolytic ring-opening of *trans*,*cis*-**1** by inward rotation of the methyl substituents as a concerted process.

(18) Only inclusion of solvent allowed to locate the highly disfavored *trans-in*-**7**. This result indicates the destabilized nature of the forming carbenium ion in the *trans-in*-**7** disrotation, particularly in the gas phase, due to the electron-withdrawing effect of the formyl group combined with the steric hindrance incured upon inward rotation.

incipient carbenium ion and its distribution along the carbon skeleton, in other words, on the activation energies. In cyclopropanes substituted with electron acceptors (CHO, NO_2) and π-systems ($CH{=}CH_2$) the positive charge is more localized on the proximal carbon (C_2), whereas the electron donors (NH_2, OMe) contribute to place more positive charge at the distal atom (C_3). Activation energies are consistently lowered for strong electron donors, and increased for strong electron acceptors, in line with the main role of the substituents on positive charge stabilization. However, the small size of the system does not allow a clear separation of steric and electronic effects, and that is reflected on the trends in activation energies for cyclopropyl derivatives with R_1 = H, Me, ^{t}Bu.

Only the gas-phase ring-opening of bromoaminomethylcyclopropane computations predict a reversal of the reactivity, with *cis,cis*-**4** reacting faster than the *trans,cis*-**4** diastereomer. This is not due to a change in the dominant electronic interaction, since NBO analysis shows that the breaking $C_2{-}C_3$ bond is compromised with the stabilization of the $\sigma^*_{(C1-Br)}$ orbital. The proximity of the N−H bond to the leaving bromide in the *cis-in* disrotation stabilizes this transition structure relative to the *trans-out*, the preferred pathway for the remaining groups. However, despite the reversal in the general trend, the difference in activation energy for the *inward* disrotation relative to the *outward* is only modest in gas phase. Inclusion of solvent (MeOH) in the computations stabilizes all transition structures relative to reactants and also restores the regular kinetic preference for the *trans*-out disrotation of *trans,cis*-**1**−**9** over the cis,in disrotation of the *cis,cis*-**1**−**9** diastereomer.

Electrocyclic ring opening of cyclopropyl derivatives *cis,cis*-**1**−**9** and *trans,cis*-**1**−**9** follows one of the two allowed disrotational movements, *cis-in* and *trans-out*, respectively. In keeping with the intuitive viewing of the Woodward−Hoffmann−DePuy rule, the preference is attributed to charge donation from the dissociating C−C bond to the antibonding orbital of the breaking C−Br bond. As a consequence, it can be predicted that the C2−C3 breaking bond becomes less available for additional interactions with the neighboring substituents. In contrast to the finding of Houk in the ring opening of 3-substituted cyclobutenes, the role of the substituents seems to be secondary. Work along the prediction of torquoselectivity in cyclopropyl derivatives substituted with groups of different electronic nature at C2 and C3, and its potential use in synthesis, is in progress and will be reported in due time.

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Supporting Information Available: Tables with thermodynamic and geometric parameters for the reactions described in the text. This material is available free of charge via the Internet at http://pubs.acs.org.

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