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Solvolytic Ring-Opening Reactions of Cyclopropyl Bromides. An Assessment of the Woodward−Hoffmann−DePuy Rule

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A theoretical study on the torquoselectivity of the electrocyclic ring opening of 2,3-disubstituted-mono and dibromo cyclopropanes was carried out at the B3LYP/6-311++G* level. As a result of charge donation from the dissociating C−C bond to the antibonding orbital of the breaking C−Br bond, only one of the two allowed disrotatory paths for the disrotatory ring opening, which takes place in concert with the C−Br bond cleavage, is energetically accessible, both in the gas phase and in solution. The general trends in torquoselectivity for these systems are not significantly affected by stereoelectronic effects of the substituents or the introduction of a second bromine in C1. For the Woodward−Hoffmann−DePuy-allowed processes, the remarkable lowering in energy when the OH or NH_2 groups rotate inward can be attributed to the formation of an intramolecular X−H−Br hydrogen bond in the transition state. Aromaticity in reactants and transition states for the model systems is evaluated using a ring current model to shed light on the reaction mechanism.

1. Introduction

The solvolysis of cyclopropyl halides and pseudohalides[1] is both the prototype of the 2π-e^- electrocyclic reactions and their most complex model from the mechanistic and conceptual point of view, since the opening of the cyclopropyl ring has been shown to take place in concert with the departure of the leaving group.[2,7]

Although two disrotatory motions are symmetry-allowed in the electrocyclic ring opening of cyclopropyl halides and tosylates, only the products of the inward rotation of the substituents *cis* to the leaving group were found.[8,9] The generalization of these observations resulted in what is known as the Woodward−Hoffmann−DePuy rule,[10−13] which relates the geometry of the resulting allyl cation to the relative configuration of the ring substituents and the leaving group (Figure 1).

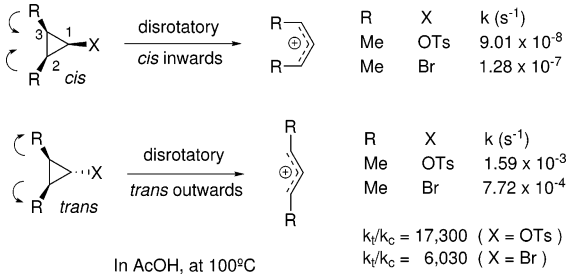

FIGURE 1. Torquoselectivity in the solvolytic disrotatory ring opening of cyclopropyl derivatives.[14,15]

Extended Hückel computations by Woodward and Hoffmann[11] suggested an intuitive explanation of the Woodward−Hoffmann−DePuy rule: the favored disrotatory motion is the one that provides electronic assistance to the C−X bond cleavage through the breaking C2−C3 bond.[12] The inward movement of the R groups upon the disrotatory ring opening of *cis*-2,3-disubstituted cyclopropyl derivatives shifts the electron density of the C2−C3 bond from the plane of the ring toward the rear of the breaking C−X bond (Figure 2), assisting the departure of the leaving group and stabilizing the developing cation on C1. The opposite disrotation (R groups rotating outward) should be favored for the *trans* diastereomer. In this framework, the reaction could be treated as a S_N2-type displacement of X by the electrons of the breaking cyclopropyl σ bond.

This explanation proved to be fully consistent (see values in Figure 1 for the dimethyl derivatives)[14] with the experimental relative rates of solvolysis of 2,3-disubstituted cyclopropylbromides and tosylates. The

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(1) Marvell, E. N. *Thermal Electrocyclic Reactions*; Academic Press: New York, 1980.

(2) The rate of solvolysis of arylcyclopropyltosylates showed good correlation with the bond angles at the reaction sites.[3−6]

(3) Foote, C. S. *J. Am. Chem. Soc.* **1964**, *86*, 1853−1854.

(4) Schleyer, P. v. R. *J. Am. Chem. Soc.* **1964**, *86*, 1854−1856.

(5) DePuy, C. H.; Schnack, L. G.; Hausser, J. W. *J. Am. Chem. Soc.* **1966**, *88*, 3343−3346.

(6) Roberts, J. D.; Chambers, V. C. *J. Am. Chem. Soc.* **1951**, *73*, 5034−5040.

(7) Radom, L.; Hariharan, P. C.; Pople, J. A.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1973**, *95*, 6531−6544.

(8) Witham, G. H.; Wright, M. *J. Chem. Soc. C* **1971**, *5*, 883−885.

(9) Cristol, S. J.; Sequeira, R. M.; DePuy, C. H. *J. Am. Chem. Soc.* **1965**, *87*, 4007−4008.

(10) Hoffmann, R.; Woodward, R. B. *Acc. Chem. Res.* **1968**, *1*, 17−22.

(11) Woodward, R. B.; Hoffmann, R. *J. Am. Chem. Soc.* **1965**, *87*, 395−397.

(12) Woodward, R. B.; Hoffmann, R. *Angew. Chem., Int. Ed.* **1969**, *8*, 781−853.

(13) DePuy, C. H. *Acc. Chem. Res.* **1968**, *1*, 33−41.

(14) Parham, W. E.; Yong, K. S. *J. Org. Chem.* **1970**, *35*, 683−685.

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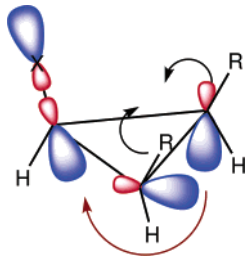


FIGURE 2. S_N2-like displacement of the leaving group in cyclopropyl halide ring-opening reactions. In the inward disrotation of the R groups, the shift of the breaking C−C bond electron density weakens the C−X bond.

extraordinary rate enhancement of the solvolysis of *trans* disubstituted substrates relative to that of the corresponding *cis* systems was explained as a consequence of the electronic assistance indicated above (it forces a transition structure with a high steric penalty for the *cis* isomers), and the lower barrier for the substituted compared to the unsubstituted systems is justified by the hyperconjugative stabilization of the incipient allyl cation in the former.

This reaction of cyclopropyl derivatives was soon synthetically exploited[17] for the stereoselective formation of a variety of medium-sized rings having either *cis* or *trans* double bonds,[18] becoming part of synthetic sequences that include ring-expansion processes induced by solvolysis after formation of the corresponding adducts between cycloalkenes and (di)halocarbenes. (The synthesis of longifolene by McMurry must be highlighted,[19] along with more recent applications).[20−23]

To our knowledge, the Woodward−Hoffmann−DePuy rule represents the first documented example of stereoselectivity due to the preference for one of the two orbital symmetry-allowed conrotatory or disrotatory (depending on the number of electrons involved) processes in electrocyclic reactions. The term torquoselectivity in electrocyclic ring-opening reactions (also termed *rotoselectivity*)[24] was later coined by Houk to describe this selectivity in the 4π-e^- conrotatory ring opening of substituted cyclobutenes. Through extensive computational and experimental studies, Rondan and Houk showed that the torqueselectivity in these systems depends on the electronic rather than steric effect of the substituents: electron donors at C3 of substituted cyclobutenes rotate away (outward) from the breaking bond in order to avoid destabilizing four-electron two-orbital interactions, and conversely, strong electron acceptors rotate inward, thus stabilizing two-electron two-orbital interactions.[25−35]

In contrast with the wealth of information on the ring opening of cyclobutenes, no example of solvolysis of cyclopropyl halides substituted with functional groups has been reported, and therefore the nature of the interactions of the breaking bonds with different substituents and their effect on the torquoselectivity of these systems are unknown. Early ab initio studies[7,36] clarified the mechanistic issue of the concerted versus the two-step pathway for the rearrangement of the parent system, and studies of other three-atom two-electron systems, such as the opening of allene oxides to oxyallyls, have been published more recently,[37] but they lack the complexity associated with the concerted two-bond breaking of the solvolytic ring opening of cyclopropyl derivatives. Despite the spate of theoretical and experimental studies more than 30 years ago, no theoretical treatment of the electrocyclic ring opening of cyclopropyl derivatives using the tools of modern computational chemistry existed before we started this study.

We have recently reported[38] a computational study for the rearrangement of *cis*,*cis*- and *trans*,*cis*-1-bromo-2,3-dimethylcyclopropane and their derivatives, both in the gas phase and in solution. We first addressed the structural factors that restrict the disrotatory ring opening to a single direction, confirming the Woodward−Hoffmann−DePuy rule. NBO analysis helped clarify the role of the electronic stabilization as the reaction progresses and its effect on the stereoselectivity. After analyzing the torquoselectivity due to the relative configuration of the starting cyclopropyl bromide, we studied the effect that the change of one methyl substituent for another group (R) has on the rotational preferences, with the expectation that additional torquoselective effects could be uncovered. After examining the steric and electronic interactions of a variety of R groups with the breaking and forming bonds, we found no inversion of the stereoselectivity trends upon changes on the steric and electronic nature of the R substituents, contrary to

(15) Buss, V.; Gleiter, R.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1971**, *73*, 3927−3933.
(16) de Meijere, A., Guest Ed. Cyclopropanes and Related Rings. *Chem. Rev.* **2003**, *103*, (4).
(17) For a monograph issue reviewing small-sized rings, see ref 16.
(18) Whitham, G. H.; Wright, M. *J. Chem. Soc. C* **1971**, *5*, 883−885.
(19) McMurry, J. E.; Isser, S. J. *J. Am. Chem. Soc.* **1972**, *94*, 7132−7137.
(20) Banwell, M.; Edwards, A.; Harvey, J.; Hockless, D.; Willis, A. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2175−2178.
(21) Banwell, M. G.; Harvey, J. E.; Hockless, D. C. R. *J. Org. Chem.* **2000**, *65*, 4241−4250.
(22) Banwell, M. G.; Ebenbeck, W.; Edwards, A. J. *J. Chem. Soc., Perkin Trans. 1* **2001**, *1*, 114−117.
(23) Banwell, M. G.; Harvey, J. E.; Jolliffe, K. A. *J. Chem. Soc., Perkin Trans. 1* **2001**, *1*, 2002−2005.
(24) Houk, K. N. Stereoselective electrocyclizations and sigmatropic shifts of strained rings: Torquoelectronics. In *Strain and Its Implications in Organic Chemistry*; Kluwer Academic Publishers: Dordrecht, 1989.
(25) Houk, K. N.; Li, Y.; Evanseck, J. D. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 682−708.
(26) Dolbier, W. R.; Koroniak, H.; Houk, K. N.; Sheu, C. *Acc. Chem. Res.* **1996**, *29*, 471−477.
(27) Kirmse, W.; Rondan, N. G.; Houk, K. N. *J. Am. Chem. Soc.* **1984**, *106*, 7989−7991.
(28) Rondan, N. G.; Houk, K. N. *J. Am. Chem. Soc.* **1985**, *107*, 2099−2111.
(29) Houk, K. N.; Spellmeyer, D. C.; Jefford, C. W.; Rimbault, C. G.; Wang, Y.; Miller, R. D. *J. Org. Chem.* **1988**, *53*, 2125−2127.
(30) Niwayama, S.; Kallel, A. E.; Sheu, C.; Houk, K. N. *J. Org. Chem.* **1996**, *61*, 2517−2522.
(31) Kallel, E. A.; Houk, K. N. *J. Org. Chem.* **1989**, *54*, 6006−6008.
(32) Smith, D. A.; Ulmer, C. W., II. *J. Org. Chem.* **1993**, *58*, 4118−4121.
(33) Wiest, O.; Houk, K. N.; Black, K. A.; Thomas, B. T., IV. *J. Am. Chem. Soc.* **1995**, *117*, 8594−8599.
(34) Walker, Matthew, J.; Hietbrink, B. N.; Thomas, B. E., IV; Nakamura, K.; Kallel, E. A.; Houk, K. N. *J. Org. Chem.* **2001**, *66*, 6669−6672.
(35) Lee, P. S.; Zhang, X.; Houk, K. N. *J. Am. Chem. Soc.* **2003**, *125*, 5072−5079.
(36) Merlet, P.; Peyerimhoff, S. D.; Buenker, R. J.; Shih, S. *J. Am. Chem. Soc.* **1974**, *96*, 959−969.
(37) Hess, B. A., Jr.; Eckart, U.; Fabian, J. *J. Am. Chem. Soc.* **1998**, *120*, 12310−12315.
(38) Faza, O. N.; López, C. S.; Álvarez, R.; de Lera, A. R. *Org. Lett.* **2004**, *6*, 905−908.

what has been documented for the 4-πe^- electrocyclic ring opening of substituted cyclobutenes to stereodefined butadienes.[26] We provide herein a full account of our work, including in-depth NBO analysis and characterization of transition-state aromaticity. In addition, we extend our studies to the 1,1-dibrominated analogues.

2. Computational Methods

The selection of Becke's three parameter functional[39−43] (B3LYP) was based on its proved suitability to describe reaction profiles in a variety of pericyclic reactions (both open- and closed-shell systems), especially the accurate prediction of experimental activation barriers.[44] Pople's standard 6-311++G** basis set was used for all atoms except bromine, which was described with an effective core potential. The 28 core electrons of this heavy atom are thus replaced, using the SKBJ pseudopotential,[45] by an expresion that reproduces their effect on the valence electrons and the remaining system. Polarization and diffuse functions were added to the basis set of bromine, to better balance the description of all atoms in the system. The optimization of two d and one f functions[46] was iteratively carried out with GAMESS[47] using the bromide ion as a reference, so as to accurately describe a process with negative charge build up.

In the description that follows, unless otherwise stated, all calculations were carried out using the Gaussian 98 package[48] with an SKBJ ECP for bromine, two d and one f functions being added to the SKBJ basis set for the valence electrons of bromine, and the 6-311++G** basis set for the remaining atoms.

All stationary points on the potential energy surface were characterized by harmonic analysis, and the computed frequencies were used to obtain zero-point energies and thermodynamic parameters, applying the free particle, harmonic oscillator, and rigid rotor approximations at the high-temperature limit in a canonical ensemble. Frequency values are uncorrected, based on Scott and Radom estimation of a correction coefficient very close to unity (1.0015) for calculations using B3LYP/6-31G(d).[49] For each located transition structure, only one negative eigenvalue was found in the diagonalized Hessian matrix, and its corresponding normal mode was associated with the nuclear motion along the reaction coordinate under study. 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) method.[50,51]

Despite the rather polar reaction conditions for the solvolysis of cyclopropyl bromides, which at the outset makes it possible to discard radical intermediates, the possible diradical character of the transition states was studied using a CAS-MCSCF-[2-2] method (the window used is formed by the HOMO and LUMO orbitals), since the preliminary estimation of the reaction profile will be carried out in the gas phase. Electron populations were thus estimated to be 1.79 for the configuration with the two electrons in the lower energy orbital and 0.21 for the configuration where the two electrons are in the more energetic orbital. As MCSCF slightly overestimates the stabilities of the biradical relative to the corresponding concerted pathways and the inclusion of heteroatoms tends to exalt the ionic character of these processes, these results discard the need of multiconfigurational methods for the present study.[52]

Solvent effects were evaluated using the Onsager method[53,54] for a spherical cavity, the size of which was estimated using a geometry optimization in the gas phase and then calculating a "cavity volume" as the radii of a contour surface that corresponds to an electronic density of 0.001 e bohr^{-3}, with an appropriate scale factor (0.5 Å is added to the obtained radii). Despite not considering the dispersion and cavity formation energies, this method provides at a low computational cost a quite accurate description of compact (a spherical cavity is more realistic the more spherical the molecule is) polar molecules (the dominant term in the solvation energy is then the electrostatic) when relative energies are used.

For the characterization of aromaticity of the reactants and transition structures, Schleyer's nucleus independent chemical shift (NICS)[55] values were computed using gauge-independent atomic orbitals (GIAO method).[56]

3. Results and Discussion

3.1. Torquoselectivity: DePuy Rule. For each of the diastereomeric reactants, *cis*-1-bromo-2-methyl-3-R-cyclopropane[57] and *trans*-1-bromo-2-methyl-3-R-cyclopropane, the two disrotatory ring-opening transition states were obtained (Figure 4). They are labeled *out* or *in* to highlight the disrotatory movement of the substituents as either outward or inward.

Table 1 lists the activation free energies of these symmetry-allowed processes, as well as the difference in $\Delta G^{\ddagger}$ for each pair of competing pathways. No particular attention was paid to the energy of the reaction products (nonisolable entities), and both edducts (bromide anion

(39) Becke, A. D. *Phys. Rev. A* **1988**, *38*, 3098−3100.
(40) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648−5652.
(41) Parr, R. G.; Yang, W. *Density Functional Theory of Atoms and Molecules*; Oxford: New York, 1989.
(42) Ziegler, T. *Chem. Rev.* **1991**, *91*, 651−667.
(43) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785−789.
(44) Houk, K. N.; Beno, B. R.; Nendel, M.; Black, K.; Yoo, H. Y.; Wilsey, S.; Lee, J. K. *J. Mol. Struct. (THEOCHEM)* **1999**, *398*, 169−179.
(45) Stevens, W. J.; Krauss, M.; Basch, H.; Jasien, P. G. *Can. J. Chem.* **1992**, *70*, 612−630.
(46) Only the exponents are optimized, because the program does not allow the use of contracted basis functions: d → 0.558675, d → 0.182450, f → 0.934198.
(47) Schmidt, M. W.; Baldridge, K. K.; Boatz, J. A.; Elbert, S. T.; Gordon, M. S.; Jensen, J. J.; Koseki, S.; Matsunaga, N.; Nguyen, K. A.; Su, S.; Windus, T. L.; Dupuis, M.; Montgomery, J. A. *J. Comput. Chem.* **1993**, *14*, 1347.
(48) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B. G.; Chen, W.; Wong, M. W.; Andres, J. L.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98*, revision A.9; Gaussian, Inc.: Pittsburgh, PA, 1998.
(49) Scott, A. P.; Radom, L. *J. Phys. Chem.* **1996**, *100*, 16502−16513.
(50) Reed, A. E.; Curtiss, L. A.; Weinhold, F. *Chem. Rev.* **1988**, *88*, 899−926.
(51) Glendening, E. D.; Reed, A. E.; Carpenter, J. E.; Weinhold, F. *NBO*, version 3.1.
(52) Li, Y.; Houk, K. N. *J. Am. Chem. Soc.* **1993**, *115*, 7478−7485.
(53) Onsager, L. *J. Am. Chem. Soc.* **1936**, *58*, 1486−1493.
(54) Wong, M. W.; Wiberg, K. B.; Frisch, M. *J. Chem. Phys.* **1991**, *95*, 8991−8008.
(55) Schleyer, P. v. R.; Maerker, C.; Dransfeld, A.; Jiao, H.; Hommes, N. J. R. v. *J. Am. Chem. Soc.* **1996**, *118*, 6317−6318.
(56) Wolinski, K.; Hinton, J. F.; Peter, P. *J. Am. Chem. Soc.* **1990**, *112*, 8251−8260.
(57) The IUPAC names, including stereochemical descriptors for the reactants having a pseudoasymmetric center would be (*s*,*R**,*S**)-1-bromo-2-methyl-3-R-cyclopropane for *cis* and (*r*,*R**,*S**)-1-bromo-2-methyl-3-R-cyclopropane for *trans*, but the *cis* and *trans* descriptors of relative configuration at the chiral centers at C2 and C3 were preferred, and to allow comparison, we paid no attention to the CIP priority ordering of the substituents.

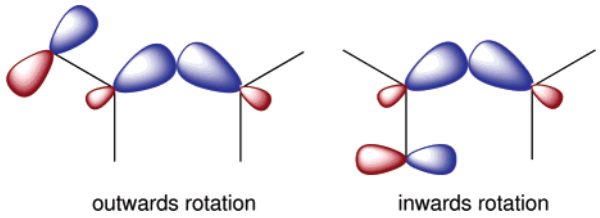
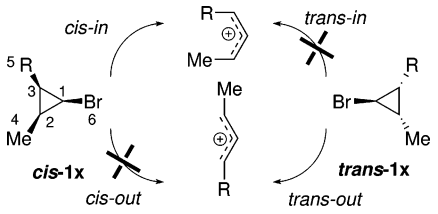


FIGURE 3. Interaction of a p (or π) orbital of the substituent with the breaking bond in the two allowed disrotatory motions.



x	R	x	R	x	R
a	Me	**e**	F	**i**	CN
b	H	**f**	NH_2	**j**	NO_2
c	*t*-Bu	**g**	OH	**k**	CHO
d	$CHCH_2$	**h**	OMe		

FIGURE 4. Disrotatory electrocyclic solvolytic ring opening reactions of *cis*- and *trans*-1-bromo-2-methyl-3-R-cyclopropanes.

and allyl cation) of these highly exothermic reactions were computed separately without consideration of other association phenomena such as the formation of ion pairs. As these features do not affect the outcome of the processes, they will not be addressed in this study.

The energy values confirm the Woodward−Hoffmann−DePuy rule: for the rearrangement of each reactant, the inward disrotatory motion of the groups located *cis* to bromine (*cis-in* and *trans-out*) are of lower energy than the alternative outward disrotational direction of bond breaking. The disfavored *cis-out* and *trans-in* transition states lie between 6.9 and 19.1 kcal/mol and 20.8 and 37.5 kcal/mol above the favored pathway of each series. This variation of the difference $\Delta G^{\ddagger}_{\text{favored}} - \Delta G^{\ddagger}_{\text{disfavored}}$ between the two diastereomers can be readily explained resorting to steric considerations. Despite the two paths being electronically disfavored, the *cis-out* movement does not incur in severe steric interactions in the TS leading to the *out*,*out* allyl cation, while the highly energetic TS for *trans-in* disrotation is severely congested.

The relative values computed for the barriers of the two pairs of disrotatory processes can be considered an estimate of the Woodward−Hoffmann−DePuy preference. When R = Me, the activation energies for the most favored disrotation in each stereoisomer differ by ca. 6 kcal/mol in favor of the *trans-out* motion over the *cis-in*. This result is in agreement with the experimental lower limit of 6.6 kcal/mol, estimated for the difference in activation energy between the two rotational directions available for the acetolysis−ring opening of *exo*-7-tosyloxybicyclo[4.1.0]heptane at 150 °C[58,59] and is also consistent with the experimental relative rates between both reactants, $k_t/k_c = 6030$ (Figure 1).

(58) Schleyer, P. v. R.; Van Dine, G. W.; Schöllkopf, U.; Paust, J. *J. Am. Chem. Soc.* **1966**, *88*, 2868−2869.
(59) Schöllkopf, U.; Fellenberger, K.; Patsch, M.; Schleyer, P. v. R.; Su, T.; van Dine, G. W. *Tetrahedron Lett.* **1967**, *8*, 3639−3644.

As can be seen in Table 1, which shows the difference in the activation energies for the opening of the *cis* and *trans* diastereomers, the opening of the *trans* isomer is easier than that of the *cis* isomer, and the difference is higher as the bulk of the R group increases for the majority of the substituents. This may, as explained, be attributed to the greater steric congestion in TS-*cis-in* relative to TS-*trans-out*. For the amino and hydroxyl groups the trend is reversed, and the barrier is lower for the opening of the *cis* isomer. This apparent contradiction that could be attributed to electronic effects is explained in absence of any remarkable interaction in the NBO analysis of the wave function, by the formation of a hydrogen bond between a hydrogen on the heteroatom and the bromide leaving group in the transition state (2.45 Å for R = OH and 2.83 Å for R = NH_2).

NBO analysis supports the explanation provided by Woodward−Hoffmann−DePuy for the observed torquoselectivity: the application of second-order perturbation theory to the proposed Lewis structure for the *cis* diastereomer reveals an important interaction in the inward rotation that is absent in their outward-rotating counterparts (Table 2). Transition structures for the favored disrotation of each diastereomer, *cis-in* and *trans-out*, show a highly dissociated C−C bond accompanying the rotational movement of the substituents. In fact, NBO values show in most cases virtually no bond between C2 and C3, and the breaking σ bond is treated instead as a nonbonding pair at one carbon and a nonbonding empty orbital at the other. Enforced by the favored disrotatory movement on each stereoisomer, the secondary interaction of these two orbitals with $\sigma^*_{\text{C−Br}}$ is the most important contribution to the stabilization of the transition structure, emphasizing the main role of the breaking C−C bond in facilitating the departure of the leaving group through stabilization of the $\sigma^*_{\text{C−Br}}$ orbital, in line with the intuitive assumption made by Woodward−Hoffmann−DePuy. Thus, the high selectivity of these processes can be explained through a S_N2-like orbital interaction where the breaking C−C bond or the resulting p orbitals are donating charge to the antibonding $\sigma^*_{\text{C−Br}}$ orbital, thus lowering the activation barrier for the C−Br bond cleavage. A schematic representation of this orbital interaction can be seen in Figure 2.

The transition structures for the favored paths correspond to a concerted process where the cleavage of the C−Br bond takes place concomitantly with the C−C bond breaking. Transition structures for reactions *cis-out* and *trans-in* are more asynchronous, in particular that of the latter (Table 3). In the *cis-out* structures, the C−C bond is shorter (i.e., less advanced cleavage), and the C−Br bond is significantly more dissociated for R substituents unable to interact by resonance and less or equally dissociated for donor or acceptor groups. In the *trans-in* structures, the C−Br bond is more dissociated for the disfavored structures (the differences are higher for the neutral or donor groups than for the acceptors), while the C−C bond is shorter (a more pronounced difference is again found for the neutral or donor groups). The positive charge concentration on C1 for the less favored transition structures also reveals their inability to efficiently delocalize charge along a conjugated system that is not yet formed (the breaking of the C−Br bond is more

TABLE 1. Activation Energies (kcal/mol) for Each of the Two Available Paths for *cis* and *trans* Cyclopropyl Bromides Shown in Figure 4[a]

	cis-**1x**			*trans*-**1x**			
R	$\Delta G^{\ddagger}_{in}$	$\Delta G^{\ddagger}_{out}$	$\Delta\Delta G^{\ddagger}_{out\text{-}in}$	$\Delta G^{\ddagger}_{out}$	$\Delta G^{\ddagger}_{in}$	$\Delta\Delta G^{\ddagger}_{in\text{-}out}$	$\Delta\Delta G^{\ddagger}_{cis\text{-}in-trans\text{-}out}$
Me	36.08	46.29	10.21	30.26	60.62	30.36	5.82
H	38.83	51.31	12.48	36.83	57.58	20.75	2.00
^{t}Bu	36.67	43.56	6.89	26.85	64.32	37.47	9.82
$CHCH_2$	30.29	42.89	12.60	22.98	55.10	32.12	7.31
F	35.33	49.36	14.03	33.02	63.53	30.51	2.31
NH_2	16.60	31.66	15.06	17.26	49.50	32.24	−0.66
OH	22.44	34.53	12.09	24.95	56.87	31.92	−2.51
OMe	26.18	45.30	19.12	22.91	55.40	32.49	3.27
CN	35.67	52.58	16.91	33.84	61.90	28.06	1.83
NO_2	37.92	54.81	16.89	35.19	61.57	26.38	2.73
CHO	37.04	53.68	16.64	31.09	*b*		5.95

[a] The difference in activation barriers for each reactant ($\Delta\Delta G^{\ddagger}$), as well as the difference in the barriers for the favored ring-openings for each pair of diastereomers are also listed. [b] Only inclusion of solvent made it possible to locate the highly disfavored *trans-in*-**1k** (R = CHO). This result indicates the destabilized nature of the forming carbenium ion in the *trans-in*-**1k** disrotation, particularly in the gas phase, due to the electron-withdrawing effect of the formyl group combined with the steric hindrance incurred upon inward rotation. Thus, this reaction path will not be used in most comparisons.

TABLE 2. Energy Associated with the $\sigma_{C-C}-\sigma^{*}_{C-Br}$ Charge Donation[a]

R	*cis-in*	*cis-out*	*trans-out*	*trans-in*
Me	122/122	49	136/136	
H				
^{t}Bu	149/120	42	137/142	
$CHCH_2$	104/103	37	107/99	
F		50	133	
NH_2	71	18	94	24
OH	119/85	25		44
OMe	109/98	23	113	40
CN	105/41	52	103	59/18
NO_2	80/17	36	86/41	*b*
CHO	115/56	40	102/47	*c*

[a] When more than one number per entry is listed, the NBO analysis no longer finds a C2−C3 bond and the perturbation energies for the two resulting lone pairs (the first occupied, the second empty) are reported. In some cases, specially when R is a good electron-withdrawing group, one of these lone pairs can interact with the leaving bromide. In the *trans* models or when R is small, the lone pair can also form a π bond with the p orbital on C1 after the bromide departure. Only the values higher than 12 kcal/mol have been included. [b] No interaction. [c] No structure available.

TABLE 3. Average Values for Variation (in Å and deg) of Selected Geometric Parameters from Reactants to Transition Structures of the Systems Depicted in Figure 4

	reaction				
	r_{23}	r_{16}	α_{213}	d_{4213}	d_{5312}
cis-in	0.76	0.43	47.05	53.52	49.37
cis-out	0.50	0.49	29.26	23.62	26.60
trans-out	0.67	0.45	41.36	22.82	23.69
trans-in	0.57	0.64	33.47	53.16	39.43

advanced than that of the C−C bond), leading to a high energy transition state.

However, TS-*cis-out* shows an activation energy lower than that of TS-*trans-in*, due partly to a residual interaction between the breaking C−C bond and the σ^{*}_{C-Br} orbital that is maintained in the less congested transition structure for the groups rotating outward and partly to the smaller steric hindrance to bond rotation. NBO analysis for TS-*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 TS connects reactants and products, TS-*trans-in* is similar to a cyclopropyl cation.[7] All of these features raise some concerns on the consideration of the solvolysis and ring opening of *trans*-1-bromo-2-methyl-3-R-cyclopropanes by inward rotation of the substituents as concerted processes.

3.2. Substituent Effects. For the electrocyclic ring opening of 3-substituted and 3,4-disubstituted cyclobutenes to the corresponding butadienes, Houk et al. have computed the effect of a diverse range of substituents on the stereoselectivity of the process. Torquoselective ring opening for the π-donors (outward conrotation) and π-acceptor (inward conrotation) substituents at C3 and C4 were predicted and experimentally corroborated in many cases, even against severe steric odds.[26]

It was considered that the stereoselectivity of the ring opening of cyclopropyl halides could also benefit from the interaction of the breaking bond with the substituents, in keeping with Houk's finding on cyclobutenes, since electronic effects should be more exacerbated in the smaller, more compact rings.[60] At the outset, however, the disrotatory nature of the ring opening in these two-electron systems[62] was expected to make interaction of the substituents with the breaking bond less dependent upon the sense of bond rotation (Figure 3) than in the case of the four-electron system, where conrotation moves the substituents either away or toward the breaking bond.

Analysis of the influence of the substituents on the activation energies for the processes shown in Figure 4 indicates the relevance of both steric and electronic effects, in contrast to the dominance of the latter for the

(60) When studying torquoselectivity, electronic effects seem to become less important as the ring size of the reacting polyene or cycloalkene is increased. The electrocyclic ring-closure reactions involving 6 and 8 electrons[61] revealed only moderate torquoselectivity, primarily because in these more flexible transition structures the interaction between the forming C−C bond and the substituents at the polyene termini is basically independent of their sense of rotation (and the small preferences computations predict for these systems have been adscribed to steric effects instead).[34]

(61) Thomas, B. E., IV; Evanseck, J. D.; Houk, K. N. *J. Am. Chem. Soc.* **1993**, *115*, 4165−4169.

(62) Dolbier, W. R., Jr.; Phanstiel, O., IV. *Tetrahedron Lett.* **1988**, *29*, 53−56.

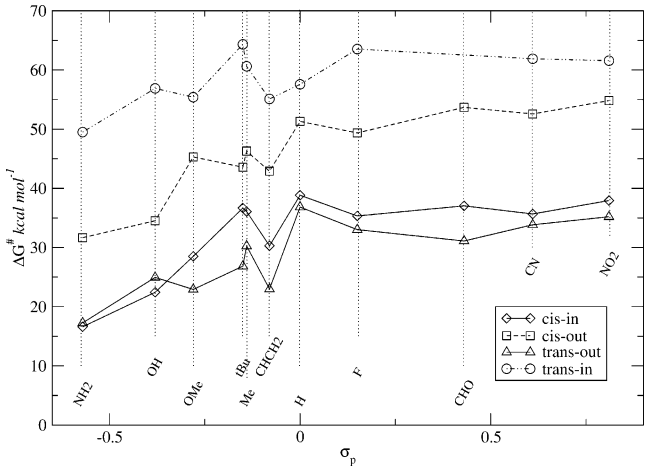


FIGURE 5. Activation energies versus Hammett's σ_p for different R groups for the two Woodward−Hoffmann-allowed ring-opening reactions of *cis*-**1x** and *trans*-**1x** (**x** = **a**−**k**).

electrocyclic opening of substituted cyclobutenes. In all cases the torquoselectivity in the ring opening of substituted cyclopropyl halides is solely determined by the configuration of the C1 center. The effect of the R group manifests itself in the raising or lowering of the activation energy depending on its size and its ability to stabilize the positive charge buildup in the system as the reaction progresses. Thus, the size of the substituent or the DePuy primary electronic effect, which do not depend on the electronic nature of the substituents on the ring, appear to be dominant or to mask other electronic effects. The smaller size of the ring that is treated here and the resulting congestion in the transition structure that tends to amplify local effects, together with the smaller orbital interaction that is expected for a disrotation, all contribute to modulate the effects described by Houk for cyclobutenes.

As can be observed in Figure 5, there is a rough correlation between the electron-donor ability of the substituents and the activation energy of the associated processes. As the correlation is independent of the inward or outward rotation, the stabilization of the incipient carbenium ion in the transition state is the key to the reactivity difference. The main deviations from the linear behavior correspond to groups that, having negligible or small resonance effects (H, Me, ^{t}Bu, and vinyl that is not conjugated with the forming π system in the transition structure), are subject to dominant steric factors in the transition structure. For example, the activation energy of of *cis*-**1b** (R= H) relative to that of **1a** (R = Me), which was expected to be lower upon inward rotation as a result of reduced steric hindrance and a better stabilization of positive charge, is 2 kcal/mol higher as a result of a more stabilized reactant.

The pattern of charge localization also supports this assumption, with positive charge accumulation on C3 when R is a donor group and on C2 otherwise. However, when looking at NBO values (Table 4), a subtle effect arises that could explain the surprisingly low barriers for the reactions of R = NH_2 or other donor groups (R = OH, F, and OMe). Although we would not expect more than a rough linear fit of free energies versus Hammett parameters (the reactions used are very different from the model, and steric factors play an important role here as well), an extrapolation of the $\Delta G^{\ddagger}$ values for the acceptor groups would predict for the donors higher activation energies than those observed. In these cases, there is a minor secondary interaction in the first stages of the IRC between a lone pair of the heteroatom and the antibonding σ^*_{C2-C3} orbital, which increases as the reaction proceeds, thus favoring the C−C bond cleavage and lowering the transition state energy.

TABLE 4. Variation in NBO Atomic Charges (ts−reactant, in e$^-$) for the Solvolytic Ring-Opening Reactions Shown in Figure 4

	cis-in			*cis-out*		
R	Δq_{C1}	Δq_{C2}	Δq_{C3}	Δq_{C1}	Δq_{C2}	Δq_{C3}
Me	0.04	0.25	0.25	0.20	0.13	0.13
H	0.04	0.33	0.17	0.20	0.16	0.14
^{t}Bu	0.03	0.23	0.29	0.21	0.13	0.10
$CHCH_2$	0.04	0.24	0.19	0.12	0.14	0.12
F	0.01	0.28	0.18	0.09	0.18	0.12
NH_2	0.05	0.03	0.14	0.13	−0.01	0.08
OH	0.04	0.09	0.19	0.16	0.02	0.10
OMe	0.03	0.17	0.19	0.10	0.06	0.10
CN	0.02	0.33	0.08	0.05	0.26	0.10
NO_2	−0.01	0.40	0.06	0.00	0.34	0.05
CHO	0.02	0.34	0.12	0.02	0.32	0.07
	trans-out			*trans-in*		
R	Δq_{C1}	Δq_{C2}	Δq_{C3}	Δq_{C1}	Δq_{C2}	Δq_{C3}
Me	0.05	0.25	0.25	0.25	0.11	0.11
H	0.05	0.32	0.16	0.21	0.20	0.12
^{t}Bu	0.05	0.24	0.26	0.27	0.09	0.11
$CHCH_2$	0.05	0.24	0.20	0.18	0.14	0.14
F	0.04	0.26	0.21	0.17	0.14	0.13
NH_2	0.03	0.07	0.16	0.10	−0.05	0.14
OH	0.05	0.15	0.21	0.17	0.05	0.12
OMe	0.06	0.14	0.20	0.16	0.04	0.13
CN	0.04	0.31	0.08	0.08	0.31	0.08
NO_2	0.02	0.35	0.06	−0.03	0.38	−0.02
CHO	0.05	0.34	0.07			

Taken collectively, the computations on the effect of the substituents on the rotational preferences do not appear to support current theoretical models of torquoselectivity. No change in the simple torquoselectivity established for the model system is observed, the reactions proceeding through TS-*cis-in* and TS-*trans-out* being favored over the alternative disrotation starting from the *cis* and *trans* diastereomers of the cyclopropyl derivatives. The disrotatory preference is attributed 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, it appears that, from the early stages of the reaction progress, 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 disrotatory movement. As a consequence, the C2−C3 breaking 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 TS). The role of the substituents seems to be secondary and is reflected in the stabilization

TABLE 5. Difference in Activation Energies (kcal/mol) in Gas Phase and in Solution for Favored and Disfavored Ring Openings of *cis*-1x and *trans*-1x (x = a−k)

	cis-**1x**		*trans*-**1x**	
R	gas	solvent	gas	solvent
Me	10.21	11.31	30.36	26.26
H	12.48	14.15	20.75	25.80
^{t}Bu	6.89	5.60	37.47	33.30
$CHCH_2$	12.60	13.87	32.12	30.18
F	14.03	15.01	30.51	32.36
NH_2	15.06	16.08	32.24	32.43
OH	12.09	12.64	31.92	33.72
OMe	19.12	18.01	32.49	35.29
CN	16.91	13.32	28.06	29.77
NO_2	16.89	13.64	26.38	*a*
CHO	16.64	13.16		

[a] The geometry optimization of *trans-out*-**1j** (R = NO_2) in solvent, using the Onsager method, presented convergence problems, so we do not include in our discussion data about this transition structure.

of the incipient carbenium ion and its distribution along the carbon skeleton, thus affecting the activation energies.

Only in the ring opening of 1-bromo-3-amino-2-methylcyclopropane (**1f**) and 1-bromo-3-hydroxy-2-methylcyclopropane (**1g**), computations predict a reversal of the reactivity, with *cis* reacting at a rate higher than that of the *trans* diastereomer. This is not due to a change in the dominant electronic interaction, since the breaking C2−C3 bond is compromised with the stabilization of the σ^*_{C1-Br} orbital. We have found that the proximity of the N−H (O−H) bond to the leaving bromide in the *cis-in* disrotation stabilizes this TS relative to the *trans-out*, the preferred pathway exhibited by the remaining groups. The difference in activation energy for the inward disrotation relative to that of the outward is modest (0.66 kcal/mol) for R = OH but significant for R = NH_2 (2.5 kcal/mol), the substituents that show a reversal of the general trend.

3.3. Solvent Effect. The effect of the solvent was estimated using full optimizations of the gas-phase structures with the Onsager method (MeOH, $\epsilon = 32.63$), using the gas phase "volume" to determine the size of the cavity.

Solvation stabilizes all structures, in particular those of the transition states, in which charge separation is greater. The combination of a small stabilization for reactants (1.07 and 0.73 kcal/mol in average for *cis*-**1x** and *trans*-**1x** structures, respectively) and a much higher solvation energy for transition structures (averages of 4.6, 5.0, 6.9 and 7.1 kcal/mol for *cis-in*, *cis-out*, *trans-out*, and *trans-in*, respectively) leads to a considerable reduction in activation energies for all processes (Table 5). The magnitude of the stabilization confidently correlates with the computed (in the gas phase) dipole moments, being therefore more important for *trans-in* and *trans-out* than for the stereisomeric *cis-in* and *cis-out* disrotations. Nevertheless, although the energy ordering of transition structures is in some cases altered, the torquoselectivity of the ring opening is not affected by solvation.

The geometries of reactants barely change when solvent is considered (the highest variation in a bond length is 0.01 Å), but transition structures are more affected, albeit not in a regular way (Supporting Information, Tables 3 and 4). In general, transition structures in MeOH are found earlier in the reaction coordinate relative to the gas phase and exhibit shorter C−C bond distances. They are also more asynchronous, with longer C−Br distances relative to the values computed in vacuo, but in both cases there are exceptions and the variations are modest (−0.1 Å for the C−C bond and 0.06 Å for the C−Br bond on average).

The inclusion of solvent effects allows for a comparison of computed and experimental values. Although the reaction conditions are quite different (AcOH versus 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*- and *trans*-1-bromo-2,3-dimethylcyclopropane, respectively, at 100 °C.[15]

3.4. Characterization of Transition State Aromaticity. One of the most used methods of characterization of pericyclic reactions is the aromaticity of the transition state. Symmetry-allowed reactions would have an aromatic transition state, whereas forbidden processes would cross antiaromatic transition structures.

Despite the ongoing intense debate on the appropriate characterization of aromaticity,[63−65] magnetic criteria are particularly suitable because they can be obtained by computations. Among them, the nucleus independent chemical shift (NICS) introduced by Schle,[66,67] computed at 1 Å above the molecular plane (to minimize diamagnetic and paramagnetic effects caused by the bonding, nonbonding pairs and delocalized electrons), provides an absolute scale for the characterization of aromaticity. In general, large negative NICS values are associated with aromatic character. In this work, the NICS of the four TSs for the disrotatory paths available to the parent 1-bromo-2,3-dimethylcyclopropane stereoisomers were computed at the B3LYP-GIAO/6-311++G** level at points located along an axis perpendicular to the ring plane that includes the geometric center (usually, it is the ring critical point that determines the center of the ring, but a topological analysis of the charge density found neither a C2−C3 bond nor RCP for the studied transition structures) of the cyclopropane ring, at distances between −3 and 3 Å.

For some reactions where substituent-induced torquoselectivity is found,[68] the destabilizing four-electron two-orbital interaction makes the NICS values for the unfavored process lower than those corresponding to the favored one, introducing at the same time a distortion in the usual shape of the NICS curve. However, despite the difference in the activation energies for the two disrotations available to each of the two studied diastereomers, there is no difference in the shapes of the corresponding NICS curves (Figure 6). This behavior of

(63) Krygowski, T. M.; Cyrañski, M. K.; Czarnocki, Z.; Häfelinger, G.; Katrizky, A. R. *Tetrahedron* **2000**, *56*, 1783−1796.
(64) Cyrañski, M. K.; Krygowski, T. M.; Katritzky, A. R.; Schleyer, P. v. R. *J. Org. Chem.* **2002**, *67*, 1333−1338.
(65) Minkin, V. I.; Glukhovtsev, M. N.; Simkin, B. Y. *Aromaticity and antiaromaticity. Electronic and structural aspects*; John Wiley & Sons: New York, 1994.
(66) Schleyer, P. v. R.; Jiao, H. *Pure Appl. Chem.* **1996**, *2*, 209−218.
(67) Schleyer, P. v. R. *Chem. Rev.* **2001**, *101*, 1115−1117.
(68) Faza, O. N.; López, C. S.; Álvarez, R. de Lera, A. R. *Chem. Eur. J.* **2004**, *10*, 4324−4333.

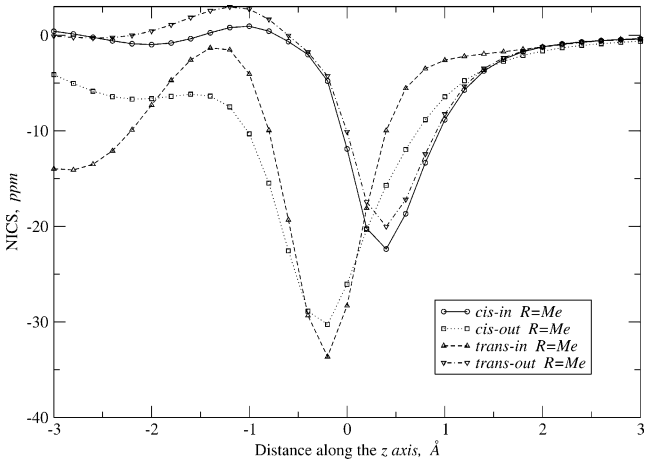


FIGURE 6. Variation of NICS along the *z* axis for the four TSs of model **1a** (R = Me). The higher values for the *cis-out* and *trans-in* systems can be attributed to the residual σ aromaticity of the reactants in these transition structures that resemble a cyclopropyl cation.

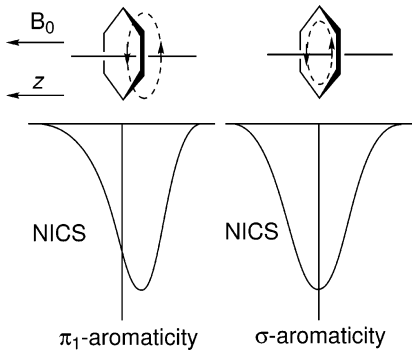


FIGURE 7. Representation of NICS along an axis normal to the molecular plane and the ring currents corresponding to each type of TS aromaticity.

the diamagnetic shielding is similarly observed for the ring opening of cyclopropyl halides with other substituents (e.g., amino group), and appears to be general (unpublished results).

For this reaction, we have found highly aromatic transition structures where the diamagnetic shielding maximum is located out of the molecular plane, to the side where the p atomic orbitals of the forming allyl cation are in close proximity during the disrotatory movement. This feature allows us (within the limitations imposed by small rings for the computations of magnetic properties)[55] to classify the TS for the disrotatory ring opening of cyclopropylbromides as having π_1 aromaticity (Figure 7).[69] The lack of effect of the orientation of the substituent on the NICS profile points again at a C1 origin of the torquoselectivity in these systems.

3.5. Dibromocyclopropanes. The effect of a second bromine on C1 was then studied for the parent system and most of the substituted cyclopropylhalides (Figure 8). Consistent with the results of the monobrominated analogues, these systems conform with the DePuy rule, and the departure of the halogen takes place in concert

(69) de Lera, A. R.; Alvarez, R.; Lecea, B.; Torrado, A.; Cossío, F. P. *Angew. Chem., Int. Ed.* **2001**, *40*, 557−561.

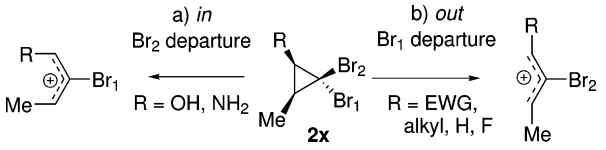


FIGURE 8. The two possible disrotatory ring-opening reactions for *cis*-1,1-dibromo-2-methyl-3R-cyclopropanes **2x** labeled *a* and *b* for inward or outward rotation of the substituents, respectively. The DePuy rule determines which bromine (arbitrarily labeled as Br_1 and Br_2) is the leaving group.

TABLE 6. Activation Energies (kcal/mol) for the Two Available Paths for Ring-Opening Reactions of *cis*-1,1-Dibromo-2-methyl-3-R-cyclopropanes[a]

	in		out			
R	$\Delta G^{\ddagger}$	$\Delta\Delta G^{\ddagger}_{m-d}$	$\Delta G^{\ddagger}$	$\Delta\Delta G^{\ddagger}_{m-d}$	diBr $\Delta\Delta G^{\ddagger}_{i-o}$	monoBr $\Delta\Delta G^{\ddagger}_{i-o}$
Me	37.52	−1.44	32.35	−2.09	5.18	5.82
H	41.25	−2.42	38.53	−1.70	2.72	2.00
$CHCH_2$	31.76	−1.47	26.92	−3.94	4.83	7.31
F	38.89	−3.56	35.13	−2.11	3.76	2.31
NH_2	15.57	1.03	16.23	1.03	−0.66	−0.66
OH	21.08	1.36	22.88	2.07	−1.80	−2.51
OMe	27.37	−1.19	23.78	−0.87	3.59	3.27
CN	38.50	−2.83	34.65	−0.81	3.85	1.83
NO_2	41.77	−3.85	38.67	−3.48	3.10	2.73
CHO	39.05	−2.01	32.36	−1.27	6.68	5.95

[a] Only the paths conforming to the DePuy rule were considered, using the arbitrary distinction between the bromine atoms, Figure 8) and differences between them and the corresponding reaction for the monobromo compounds ($\Delta G^{\ddagger}_{m-d} = \Delta G^{\ddagger}_{monoBr} - \Delta G^{\ddagger}_{diBr}$). The last two columns list the difference of the barriers for the *in* and *out* rotations in the dibromo compounds ($\Delta\Delta G^{\ddagger}_{i-o}$) and the analogue difference $\Delta G^{\ddagger}_{cis-in} - \Delta G^{\ddagger}_{trans-out}$ for the monobromo structures (Table 1).

with the C−C bond cleavage, while the outward disrotatory movement of the substituents located *trans* to the leaving group facilitates the second-order orbital interactions (as assessed by NBO analysis) previously described. For simplicity, only the reaction paths conforming to this rule will be discussed here.

The TS geometries are very similar to those of the monobrominated cyclopropanes. A slight shortening of the C−Br bond in the TS is found on the dibromo structures relative to their monobromo counterparts (variations between 0.00 and 0.12 Å, with a mean value of 0.06 Å), whereas the difference in C−C bond lengths are negligible (they can be positive or negative, with an average of 0.02 Å). The charge distribution is similar as well, with positive charge building up in C2 for acceptor groups and in C3 for donors. Charges at C1 are less negative, but the charge buildup from reactant to TS is greater for the dibromocyclopropane than for the monobrominated systems.

Table 6 lists the energies of activation of the *in* and *out* disrotatory movements of dibromocyclopropanes **2x**. Activation energies are generally higher for the geminal dibromides than for the monobromides, which could be due to the electron-withdrawing character of the bromine at C1, which destabilizes the incipient carbenium ion in the transition structure. The only exceptions are the donor groups NH_2 and OH.

The last two columns in Table 6 list the difference of the barriers for the *in* and *out* rotations in the dibromo

compounds ($\Delta\Delta G^{\ddagger}_{i-o}$) and the corresponding difference $\Delta G^{\ddagger}_{cis,in} - \Delta G^{\ddagger}_{trans,out}$ for the monobromo structures. The rotational preferences of the dibromoderivatives differ only slightly with respect to the monobromo analogues, with variations between 0.0 and 2.5 kcal/mol (1.0 kcal/mol average).

Whereas comparison of activation energies for alternative DePuy disrotations was made for diastereomeric reactants in the monobrominated cyclopropanes, stereoselectivity in the ring opening can result from competing disrotation in the 1,1-dibromoderivatives. In general, adhering to the findings in the simpler systems, the outward disrotatory ring opening and departure of bromine *trans* (Br_1 in structure **2x**) is of lower energy for *cis*-1,1-dibromo-2-methyl-3-R-cyclopropanes. As before, the preference for the outward rotation of Me and R is dominated by steric effects, and in general, the groups in Table 6 do not force the bromine *cis* to themselves to leave by a preferred inward rotation. The exception to the general rule is observed for R = NH_2 and R= OH. The formation of a hydrogen bond between the amino or hydroxyl groups and the leaving bromide explains again the inversion in the trend for these substituents.

To summarize, the solvolytic ring-opening reaction of cyclopropyl halides has been described using DFT. Transition structures for the two possible disrotatory modes of ring opening starting from diastereomeric 2,3-disubstituted cyclopropyl bromides were located. These TSs were shown to have aromatic character and show NICS maxima at a distance from the molecular plane, in the region in which the rotating p orbitals overlap, a feature of π_1 aromaticity. Comparison of activation energies and NBO analysis confirm the DePuy rule or preference for the disrotatory movement that ensures electron assistance to bromine departure by the breaking C−C bond. The effect of the substituents is only modest and primarily steric in nature. However, hydrogen bonding in amino and hydroxyl-substituted cyclopropanes overrides steric effects, and the inward disrotation was found to be of lower energy. For the 1,1-dibromocyclopropanes, these general findings are corroborated, but the presence of two geminal dibromides allows for a prediction of torquoselectivity. It was found that hydrogen bonding is again dominant in the opening of amino (hydroxy) cyclopropyl derivatives, inducing inward disrotation.

The stage is now set for extending these studies to the more complex *trans*-1,1-dibromo-2,3-disubstitutedcyclopropanes, for which the rotational preference of the substituents might operate in a synergistic or opposite sense. If a combination of substituents induced a marked rotational preference, the selective cleavage of one of the two *gem* leaving groups could be realized. Judicious choice of the R_1/R_2 combination might then result in a regio- and stereodefined preparation of alkenyl halides (see Figure 9), themselves interesting building blocks for further functionalizations (the *cis*,*trans*-allyl cation-*trans*,*trans*-allyl cation isomerization has an activation free energy of 24.0 kcal/mol, which results in a half-life of about 10 minutes at 35 °C).[59] Theoretical scrutiny and experimental verification of these predictions is in progress in our laboratories.

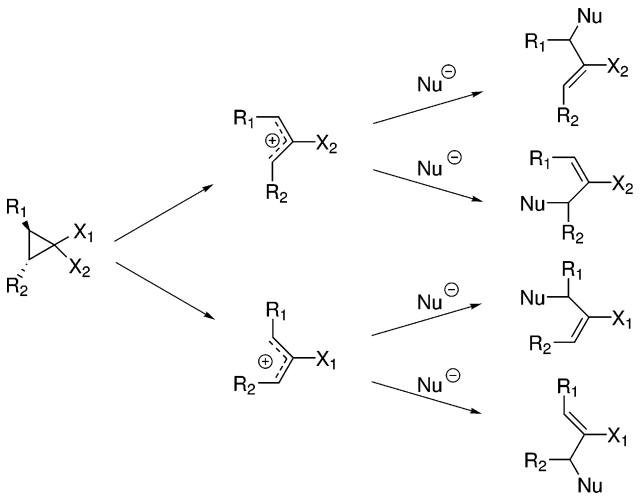


FIGURE 9. The four possible products that can be obtained through solvolysis of a *gem*-dihalocyclopropane with *trans* substituents. Provided selectivity in the ring-opening step and substituent-dependent trapping of the carbenium ion,[9] only one of the possible alkenyl halides would be obtained.

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Supporting Information Available: Complete tables with thermodynamic and geometric information along with Cartesian coordinates for all studied structures. This material is available free of charge via the Internet at http://pubs.acs.org.

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