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STEREOSELECTIVITY OF CYCLOPROPYLCHLOROCARBENE

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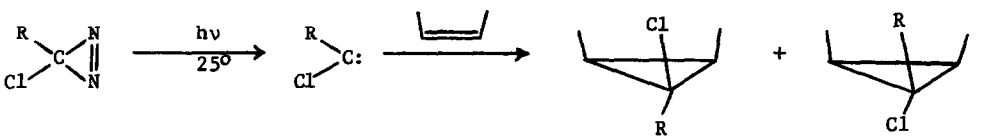
Summary. Cyclopropylchlorocarbene adds to cis-butene (25°) with a 4.6:1 preference for the syn-Cl/-anti-cyclopropyl mode of addition, more than twice the stereoselectivity of phenylchlorocarbene in the analogous reaction.

Isomeric cyclopropanes are formed when an unsymmetrically substituted carbene adds to an alkene lacking both a center of symmetry and a two-fold rotational axis coincident with the double bond. The kinetically-controlled product ratio is taken as the carbene's stereoselectivity, and can be analyzed in terms of electrostatic attraction/repulsion in the addition reaction transition states.[1,2] Additions of methylchlorocarbene[3] or phenylchlorocarbene[4] to cis-butene, for example, yield syn-chloro and anti-chloro adduct pairs; the syn-chloro isomer dominates in each case; cf., eq. (1).

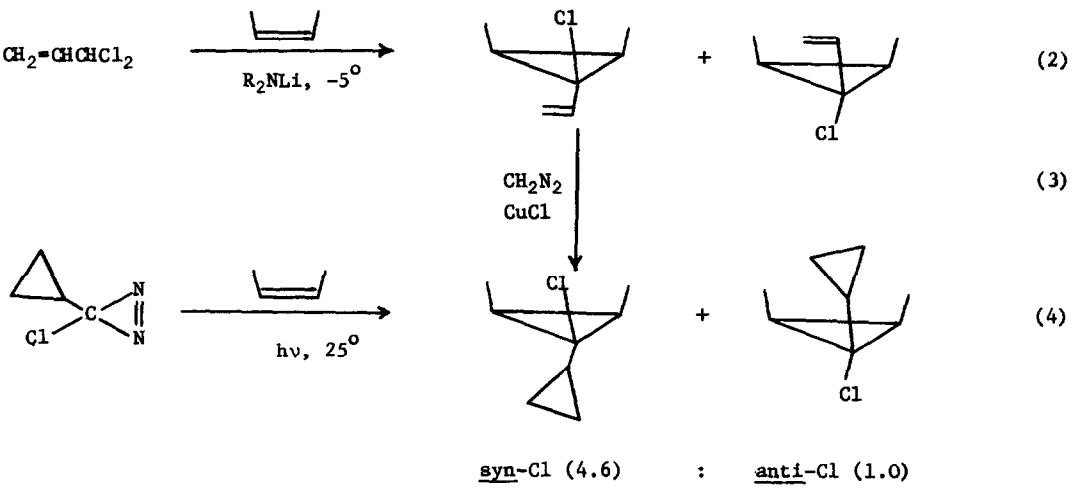


(1)

	syn-Cl	anti-Cl
R = C_6H_5	1.97	1.00
R = CH_3	2.84	1.00

More recently, cyclopropylchlorocarbene (CyCCl) was reported to yield syn- and anti-chloro adducts with cis-butene. A rather large isomer ratio (8:1 at -20°) was observed, but, unfortunately, the configurations of the products could not be readily assigned from their nmr spectra.[5] Accordingly, the direction and significance of the expressed stereoselectivity were unclear. We now describe an independent synthesis of the syn-chloro adduct, which permits the necessary configurational assignments and clarifies the stereoselectivity of the CyCCl/cis-butene reaction. The results are found to be consonant with recently advanced ideas concerning the conformational preferences of CyCCl.[6]

The action of lithium 2,2,6,6-tetramethylpiperidide on 3,3-dichloropropene generated chlorovinylcarbenoid, which reacted with cis-butene to afford an approximately 1:1 mixture of the anticipated isomeric syn-Cl and anti-Cl chlorovinylcyclopropanes; eq. (2).[7] The isomers



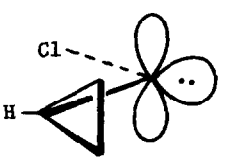
syn-Cl (4.6) : anti-Cl (1.0)

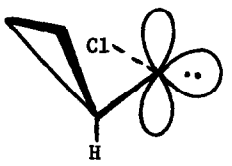
were separated by preparative gc (15' x 0.25" 16% QF-1 on 80/100 Chromosorb W column at 70°; 50 ml/min He flow rate; retn. times 14 and 18 min). The earlier-eluted product was identified as the syn-Cl isomer by nmr spectroscopy, which revealed its six methyl and two cyclopropyl ring protons as a degenerate singlet at $\delta^{TMS}_{CCl_4}$ 1.13.[7] In contrast, the syn-vinyl adduct exhibited distinct methyl (m, δ1.00-1.13) and ring proton resonances (m, δ1.47-1.83). These configurational assignments are made in analogy to those of the corresponding phenylbromo-[8] and phenylchlorocyclopropane[4] isomer pairs, for which similar chemical shift degeneracies were observed for protons of the anti-π substituent isomers.

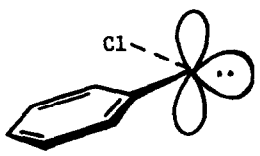
We were unable to cyclopropanate the vinyl group of 1-syn-Cl,1-anti-vinyl-2,3-cis-dimethylcyclopropane using various modifications of the Simmons-Smith reaction,[9] or with CH_2 photogenerated from CH_2I_2.[10] However, excess CH_2N_2/CuCl (Gaspar-Roth procedure)[11] accomplished the desired conversion; eq. (3). Only one product was produced in this reaction. It was shown by nmr and gc comparisons to be identical to the major adduct of the CyCCl/cis-butene reaction, which must therefore be the syn-Cl/anti-cyclopropyl isomer; cf., eq. (4).

The stereoselectivity of the CyCCl/cis-butene reaction, eq. (4), was carefully determined at 25°, where the syn-Cl/anti-Cl isomer ratio was found to be 4.6 ± 0.1 by gc analysis[13] of three separate experiments. This stereoselectivity is more than twice as large as the syn-Cl/anti-Cl preference ($1.97 \pm 0.06_3$) observed for similarly generated phenylchlorocarbene (PhCCl), cf., eq. (1).[4] That is, in the addition of CyCCl to cis-butene, the cyclopropyl group resists introduction syn to the two methyl groups at least twice as strongly as does the phenyl group in the comparable reaction of PhCCl. Why is this so?

In order to maximize favorable cyclopropyl-σ/carbene-p orbital interactions, CyCCl prefers bisected conformation lb over "twisted" conformation lt by ~9.5 kcal/mole (cf., the ab initio calculations in ref. 6). However, molecular models indicate that lb encounters substantial steric hindrance from two cyclopropyl/methyl interactions in the syn-cyclopropyl mode of addition to cis-butene. This hindrance is largely absent in the anti-cyclopropyl (syn-Cl) addition mode (opposition only by vinyl protons), which is therefore sterically preferred. Of course, the syn-cyclopropyl addition mode would not be as sterically unfavorable if the carbene







1b 1t 2

adopted conformation 1t (or a rotamer intermediate between 1b and 1t), but such torsional alternatives are unattractive due to the higher energies of the twisted carbenes.

The energetically preferred conformation of PhCCl is 2, in which the phenyl ring remains coplanar with the C_1-C-Cl plane in order to maximize π-p overlap. Addition to cis-butene in the syn-phenyl mode is not as sterically disfavored as it is in the analogous CyCCl case, so that the syn-Cl/anti-Cl preference is smaller.[14] Formulated another way, the electronically-determined, least energy conformations of PhCCl and CyCCl differ by a 90° rotation of R about the R-C bond. In the syn-R addition mode, it is CyCCl which is electronically "constrained" to approach cis-butene in the sterically worst arrangement, whereas PhCCl is electronically constrained to approach in the sterically best arrangement. Although not exclusively demanded by our observations, the foregoing rationale derives by natural extension from independently reached conclusions concerning the conformational preferences of CyCCl.[6] In this sense, the present work is a further illustration of the importance of a combined experimental and theoretical approach to the analysis of carbenic reactivity.[15]

Acknowledgments. We are grateful to the National Science Foundation and to the National Cancer Institute (research grant CA-14912) for financial support.

REFERENCES AND NOTES

(1) Review: R.A. Moss in "Selective Organic Transformations," Vol. I, B.S. Thyagarajan, Ed., Wiley, New York, N.Y., 1970, pp. 35ff. We consider only singlet carbene additions, which preserve the relative configurations of the alkenic substituents in the product cyclopropanes.

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(7) R.A. Moss and R.C. Munjal, Synthesis, 425 (1979).

(8) R.A. Moss and R. Gerstl, Tetrahedron, 22, 2637 (1966). Anti-π substituent (phenyl, vinyl) isomers adopt conformations in which the π substituents' planes bisect the cyclopropyl rings, deshielding cis-ring protons, whose chemical shifts become fortuitously equal to those of the trans-CH_3 groups. Cf., G.L. Closs and H.B. Klinger, J. Am. Chem. Soc., 87,

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(10) N.J. Pienta and P.J. Kropp, J. Am. Chem. Soc., 100, 655 (1978).

(11) W.v.E. Doering and W.R. Roth, Tetrahedron, 19, 715 (1963). We used 100 mmol of CH_2N_2, generated from Diazald (Aldrich),[12a] carried by a nitrogen stream into a solution of 1.2 mmol of substrate in 10 ml of pentane containing 100 mg of freshly prepared CuCl.[12b] The conversion to product was ~40%.

(12) (a) L.F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Vol. 1, Wiley, New York, 1967, p. 191. (b) R.N. Keller and H.D. Wyckoff, Inorg. Syn., W.C. Fernelius, Ed., 2, 1 (1946).

(13) The QF-1 column (see text) was used at 85°; detector temperature 200°; He flow rate 30 ml/min. Due to product instability, the syn-Cl/anti-Cl isomer ratio appears to increase when gc injector temperatures >130° are employed; viz., 5.4 at 140°, 5.9 at 150°, and 6.3 at 185°. Control experiments indicated no thermal dependence of gc product ratios below injector temperatures of 130°. This was established very carefully in the range 90-125°, where our final data was obtained.

(14) Attractive electrostatic interactions between phenyl π electrons and the (δ^+) syn-CH_3 groups may also be operative.[1,3,4]

(15) A referee has requested that we comment further on the observed stereoselectivities of the carbenes. In terms of syn-R/anti-R stereoselectivity toward cis-butene, PhCCl (ratio 1:1.97),[4] CH_3CCl (ratio 1:2.84),[3] and CyCCl (ratio 1:4.6) form a series of decreasing syn-R stereoselectivity. These results are consistent with simple steric preferences in the alternative syn-R/anti-R addition transition states. The spherical CH_3 group (van der Waals radius = 2.0 Å [16]) is "larger" than a phenyl ring restricted to the flat conformation of 2 (π-cloud half-thickness or van der Waals radius = 1.7 Å [16]) and lacks the π-electron polarizability (with resultant favorable electrostatic interactions[14]) of the phenyl group. Both factors should make syn-CH_3 addition of CH_3CCl to cis-butene less favorable than syn-Ph addition of PhCCl. It is harder to estimate the effective van der Waals radius of the cyclopropyl group in 1b, but we measure ~2.2 Å (including the ring protons) from a Dreiding model. The cyclopropyl substituent is thus "larger" than CH_3, and syn-Cy addition of bisected CyCCl to cis-butene should be less favorable than syn-CH_3 addition of CH_3CCl. PhCCl and CyCCl stereoselectivities are compared in detail in the text.

(16) A.J. Gordon and R.A. Ford, "The Chemist's Companion," Wiley, New York, N.Y., 1972, p. 109.

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