Geometric Equivalents of Enantiomers in Studies of the Stereochemical Course of Substitution at Carbon. Electronic Effects in Nucleophilic Addition to Carbonyl Groups and to Carbocations. Virtual Proof of the Existence of σ Participation by Unstrained Carbon–Carbon Bonds†

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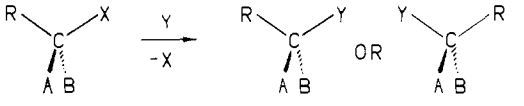
Abstract: The argument is developed that 2,5- (or 1,4-) substituted adamantanes are the geometric equivalents of enantiomers in that stereorandom reactions at the 2-position would be revealed by a 50/50 product composition. Systematic and fairly large deviations from this expectation are encountered in nucleophilic additions to the carbonyl group of 5-substituted adamantanones; electron-withdrawing substituents favor syn approach, and electron-donating groups lead to anti approach. The product distribution correlates well with the strength of the induction: $\Delta\rho = -0.39$. These findings lend strong support to Cieplak's view of electronic effects in asymmetric induction, which attributes these effects to preferential interaction of the newly developing σ^* orbital with the electron-richest anti-periplanar bonds. The equivalence objective is achieved with 5-deuterio substitution, the isomers being distinguishable by ^{13}C (and sometimes ^2H) NMR spectroscopy. This probe is then applied to determine the stereochemistry of solvolysis of 2-adamantyl substrates; predominant retention is found. Large 5-substituent effects are also described in the capture of both tertiary and secondary 2-adamantyl cations. The tertiary ions produce the same mixtures regardless of progenitor; the now very large deviations from 50/50 product distributions are again attributed to the Cieplak effect that for cations translates into σ participation. Thus, the 5-substituted tertiary 2-adamantyl cations constitute an exceedingly sensitive indicator of σ participation; no alternative interpretation is available. Secondary ions, generated from the alcohol and capture with Lucas reagent, give rise to products of largely retained configuration, more so for the *Z* than for the *E* isomers as expected. The retention in the secondary ions is almost certainly related to now stronger participation and hence more strongly σ-delocalized ions, but in this case, pyramidal cations or loose ion pairs may also contribute.

Studies of the stereochemical course of substitution at carbon traditionally are based on the use of enantiomers, in which any two of the three substituents (for example, A and B in Scheme I) serve as direction indicators defining the positions of the incoming and leaving groups. These indicators and the carbon atom lie in a plane perpendicular to that containing RCX, thus conferring upon such molecules the special characteristics of chirality. In general, this approach in such studies is technically difficult, incorporating as it does the needs for resolving both substrate and product, for determining their optical purities, and for establishing their relative configurations. Its major advantage is that by virtue of the mirror image relationship, stereorandomness is unambiguously indicated by a 50/50 composition of products (racemization and total loss of optical activity), and stereoselectivity is indicated by any deviation from this criterion; there is no need to study both enantiomeric substrates.

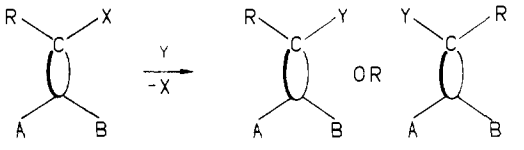
One alternative that has been applied is the use of geometric isomers in which the indicators are in the same plane as the RCX function (Scheme II). The separation of such isomers and the determination of their purities and of their relative or even absolute configurations are then much simpler, but the disadvantage of this approach is that one has no a priori information concerning product composition in the event of stereorandomness. By convention, the 50/50 level is still used as a basis for the use of terms such as stereoselectivity, but in actual fact it is necessary to study the reaction with both epimers of the substrate in order to learn whether any inherent propensity toward stereoselection exists. Thus, if a given substitution at C_4 of both (*E*)- and (*Z*)-4-halo-1-*tert*-butylcyclohexane yields the same 95:5 composition of *E* and *Z* products respectively, this obviously stereorandom reaction is said to proceed highly selectively, with retention for the (*E*)- and with inversion for the (*Z*)-halide, while the results may actually merely be a reflection of steric differences between the products (Scheme III; product development,[1] or product stability control[2]).

Some years ago, we became interested in the stereochemistry of the base-promoted and carbene-mediated substitution at C_3

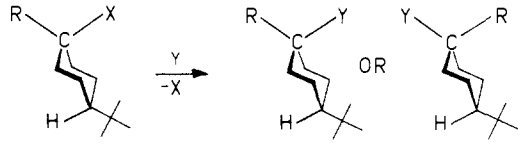
Scheme I



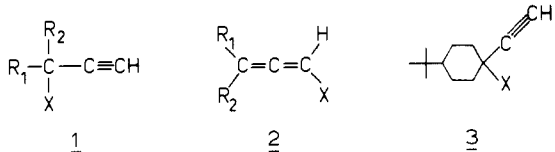
Scheme II



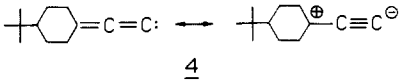
Scheme III



of tertiary propargyl halides (**1**) and their concurrent isomerization to allenes (**2**). Since the tasks of resolution and determination



1 **2** **3**



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of relative configuration then seemed forbiddingly difficult and in view of the drawback just presented, we were moved to consider

† Based in part on the M.S. thesis of L.T.T. and the Ph.D. thesis of C.K.C.

(1) Dauben, W. G.; Fonken, G. J.; Noyce, D. S. *J. Am. Chem. Soc.* **1956**, *78*, 2579.
(2) Brown, H. C.; Deck, H. R. *J. Am. Chem. Soc.* **1965**, *87*, 5620.

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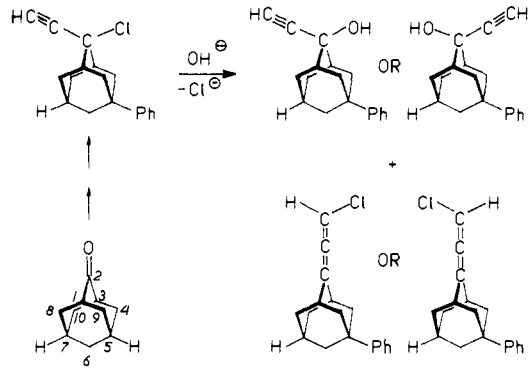
Scheme IV[a]



[a] To avoid confusion, we use the numbering as shown here throughout the article, even though this is technically wrong in some instances (thus, 2,5-dichloroadamantane is really 1,4-, etc.)

the use of (*E*)- and (*Z*)-4-*tert*-butylcyclohexyl analogues (**3**) but were discouraged by the obvious prospect of a steric predilection of equatorial over axial approach to the trigonal carbon in the intermediate **4** (steric approach,[1] or steric strain control[2]). This in turn led us to contemplate adamantane derivatives in which all of these drawbacks would seem to have been vanquished; see Scheme IV. We assumed, following a generation of chemists who have used large 4-substituents as "locks" in cyclohexanes,[3] that the phenyl group used as a direction indicator would not affect the outcome.[4]

The assumption proved to be on shaky ground, even in the initial stages of the investigation. Thus, the ethynylation of 5-phenyladamantan-2-one in liquid ammonia gave predominantly the (*E*)-alcohol rather than the expected 50/50 mixture,[5] and the methenolysis of either of the corresponding chlorides gave predominantly the (*Z*)-ether and not an equimolar mixture of both ethers.[6] The nucleophile clearly is directed by the phenyl group to the syn position in both cases. Moved by the analogous observation by Posner[7] that a phenyl substituent in a cyclic enolate conferred a stereochemical preference for syn pairing upon the lithium counterion, we tentatively proposed[6] that our results were consistent with a picture in which the nucleophile is weakly bound to the phenyl through a network of hydrogen bonds. Whatever the reason, it was clear that "locks" *can* affect the chemistry taking place at the site across the saturated six-membered ring. Since it proved possible to synthesize both stereoisomers of all three compounds in Scheme IV, the study could be carried to definite conclusions at any rate.[5] We now report a follow-up study directed at these two questions: (a) Can the directive effects of substituents at the 5-position of an adamantyl substrate with a trigonal C_2 provide useful insights into the chemistry of addition to such carbons? (b) Can the original goal of making use of the symmetry of the adamantyl system to furnish the geometric equivalents of enantiomers still be realized? In this initial report we describe our findings in nucleophilic addition to carbonyl and cationic carbons on the first question and to the stereochemistry of solvolysis of 2-adamantyl esters on the second; however, as we hope to make clear in part (c), the applicability of our conclusions goes well beyond the reactions at hand.

Results and Discussion

(a) Nucleophilic Approach to Trigonal Carbon: Adamantanones. Nitration of 5-phenyladamantan-2-one gave the *p*-nitro derivative,

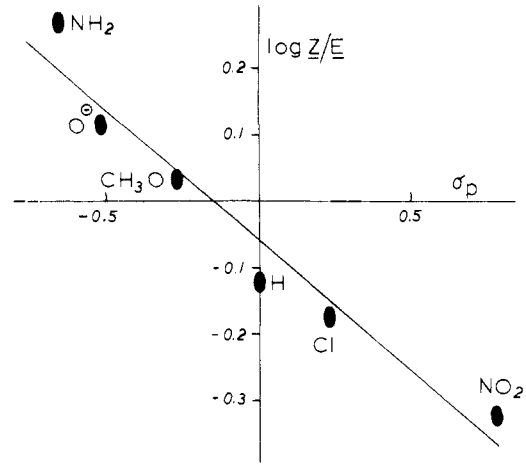


Figure 1. A plot of log [*Z*]/[*E*] vs. σ_p in the reduction of 5-*p*-phenyl-substituted adamantan-2-ones with $NaBH_4$. Note that electron-withdrawing substituents favor the formation of (*E*)-alcohols, i.e., syn approach of the hydride donor. The correlation coefficient is 0.97.

and this in turn could be converted to several other para-substituted analogues. Reduction of these ketones to mixtures of epimeric alcohols was achieved in quantitative yields with several reducing agents. The composition of these mixtures was initially assessed by means of HPLC and a ^{13}C NMR-based assignment of configuration for each of the pure isomers, but eventually we found it possible to analyze the mixtures by means of NMR (^1H and/or ^{13}C) spectroscopy alone, without separation. Similar experiments were done with 5-*tert*-butyl-, 5-fluoro-, 5-chloro-, 5-bromo-, and 5-hydroxyadamantan-2-one; the results are grouped together with a few scattered literature observations in Table I.

The data show at once that the simple picture of hydrogen-bond-mediated approach of the nucleophile syn to the 5-substituent is untenable; in most of the entries in which either the solvent is not a hydrogen-bond donor or the 5-substituent is not an acceptor, substantial deviations from a 50/50 product distribution persist. The *tert*-butyl group, the one most likely to be electronically innocuous, does indeed come closest to the ideal partition of 50/50 between epimers when the reduction is carried out with lithium aluminium hydride. A modest departure from this ratio in favor of (*Z*)-alcohol is observed with the tris-*tert*-butoxyhydride. A small steric contribution appears to be involved in the use of this bulky hydride with both the 5-phenyl- and 5-*tert*-butyl-adamantan-2-ones; however, the electronic nature of the aluminum hydride bond may also have been changed by the presence of the three *tert*-butoxy groups.[8]

The direction by the para substituent in the 5-phenyl-adamantan-2-ones suggests that the effect is electronic in nature; indeed, a plot of the logarithm of the ratio of isomers vs. σ gives a reasonably straight line, with $\Delta\rho = -0.39$ (Figure 1; correlation coefficient of 0.97). The ratio observed with *p*-hydroxy was not affected if an excess of sodium methoxide was present, hence we used the σ-value for $p\text{-}O^-$ in that case. Clearly, the preferred approach is related to the electron donating or withdrawing nature of the substituent. The same general conclusion follows from an inspection of the entries with a carbomethoxy or halogen substituent; all of these are electronegative groups, and in each case the approach is from the syn side. The effect is also more pronounced with fluoro than with chloro, and this has a larger effect than bromo.

It may be noted that the literature entries for chloro and bromo rest on tentative stereo assignments[9] that we have shown to be wrong.[10] The effect of a hydroxy group appears to go counter

(3) Winstein, S.; Holness, N. J. *J. Am. Chem. Soc.* **1955**, *77*, 5562.
(4) The phenyl group was chosen in preference to *tert*-butyl in view of the expected need of a UV-absorbing moiety (HPLC) and of the perceived greater likelihood of solid derivatives (X-ray diffraction). For a comparison of the merits of these two groups, see text.
(5) le Noble, W. J.; Chiou, D.-M.; Okaya, Y. *J. Am. Chem. Soc.* **1979**, *101*, 3244.
(6) le Noble, W. J.; Chiou, D.-M.; Okaya, Y. *Tetrahedron Lett.* **1978**, 1961.
(7) Posner, G. H.; Lentz, C. M. *Tetrahedron Lett.* **1977**, 3211.
(8) Rei, M.-H. *J. Org. Chem.* **1983**, *48*, 5386.
(9) Giddings, M. R.; Hudec, J. *Can. J. Chem.* **1981**, *59*, 459.
(10) Srivastava, S.; Cheung, C. K.; Le Noble, W. J. *Magn. Reson. Chem.* **1985**, *23*, 232. (Note: in Table I in this paper, in 2-chloroadamantane, C_5 should read 68.54 rather than 63.54.)
(11) Geluk, H. W.; Schlatmann, J. L. M. A. *Tetrahedron* **1968**, *24*, 5309. Volicka, L.; Hlavaty, J. *Collect. Czech. Chem. Commun.* **1979**, *44*, 3296.

Table I. Stereochemical Course of Nucleophilic Attack on 5-Substituted Adamantan-2-ones

5-substituent	nucleophile	conditions	alcohol % *E*	alcohol % *Z*	analysis	ref
C_6H_5	$LiAlH_4$	Et_2O, RT[a]	56	44	HPLC	this work
C_6H_5	$LiAl(O\text{-}t\text{-}Bu)_3H$	Et_2O, RT	49	51	HPLC	this work
t-Bu	$LiAlH_4$	Et_2O, RT	50	50	HPLC	this work
t-Bu	$LiAl(O\text{-}t\text{-}Bu)_3H$	Et_2O, RT	42	58	HPLC	this work
$p\text{-}C_6H_4NO_2$	$NaBH_4$	Me_2CHOH, RT	66	34	^1H NMR	this work
			64	36	^{13}C NMR	this work
$p\text{-}C_6H_4Cl$	$NaBH_4$	Me_2CHOH, RT	60	40	^1H NMR	this work
			59	41	^{13}C NMR	this work
C_6H_5	$NaBH_4$	Me_2CHOH, RT	58	42	^1H NMR	this work
			57	43	^{13}C NMR	this work
$p\text{-}C_6H_4OCH_3$	$NaBH_4$	Me_2CHOH, RT	48	52	^1H NMR	this work
			48	52	^{13}C NMR	this work
$p\text{-}C_6H_4OH$	$NaBH_4$	Me_2CHOH, RT	44	56	^1H NMR	this work
			43	57	^{13}C NMR	this work
$p\text{-}C_6H_4NH_2$	$NaBH_4$	Me_2CHOH, RT	34	66	^1H NMR	this work
			36	64	^{13}C NMR	this work
F	$NaBH_4$	Me_2CHOH, RT	62	38	^1H NMR	this work
			62	38	^{13}C NMR	this work
Cl	$NaBH_4$	Me_2CHOH, RT	59	41	^1H NMR	this work
			60	40	^{13}C NMR	this work
			54	46	^{13}C NMR	this work
F	$NaBH_4$	Me_2CHOH, 0 °C	58	42	VPC	this work
Cl	$NaBH_4$	Me_2CHOH, 0 °C	57	43	VPC	this work
F	$NaBH_4$	MeOH, 0 °C	62	38	^1H NMR	ref 9
Cl	$NaBH_4$	MeOH, 0 °C	40	60	^1H NMR	ref 9
Br	$NaBH_4$	MeOH, 0 °C	41	59	^1H NMR	ref 9
Cl	$NaBH_4$	MeOH, 0 °C	67	33	^1H NMR	this work
			67	33	^{13}C NMR	this work
Br	$NaBH_4$	MeOH, 0 °C	59	41	^1H NMR	this work
			59	41	^{13}C NMR	this work
			59	41	VPC	this work
F	MeLi	Et_2O, 0 °C	70	30	VPC	this work
OH	$NaBH_4$	MeOH, 0 °C	43	57	^1H NMR	this work
			43	57	^{13}C NMR	this work
OH	$NaBH_4$	MeOH, 0 °C	43	57	^1H NMR	ref 11
CF_3	$NaBH_4$	Me_2CHOH, 0 °C	59	41	VPC	this work
CF_3	MeLi	Et_2O, 0 °C	72	28	VPC	this work
$-COOCH_3$	$NaBH_4$	MeOH, 0 °C	61	39	VPC	ref 12

[a] Room temperature.

to all of the others, but this is again only apparent since the reaction involves the oxide anion as the substrate (carrying out this reaction in the presence of excess methoxide ion does not change the result).

If our conclusion of virtually exclusive electronic control by the substituent is accepted, the first question arising is whether the ratio reflects product stability or not. To that end, we studied the equilibration of the epimeric 5-phenyladamantan-2-ols directly. Both pure (*E*)- and (*Z*)-alcohols were treated with aluminum isopropoxide in isopropyl alcohol containing traces of acetone at 130 °C for 24 h in sealed tubes; they gave the same mixture of 56.7% (*Z*)-alcohol and 43.3% (*E*)-alcohol. Thus, the (*Z*)-alcohol is more stable by 220 cal/mol under these conditions. A similar ratio, 55/45, was encountered with the 5-*tert*-butyl alcohols. The reason for the lower free energy of the (*Z*)-alcohols is not known. It may be noted in this connection that a small distortion of the ring by these substituents has been observed by Chadwick[13] in an NMR study of the effects of lanthanide shift reagents on cyclohexanones (see further below). However, the important point is that the epimeric preference in the product is opposite to that of the borohydride reduction transition states; incipient product stability is therefore not playing the decisive role in the reactions.

Hudec[9] offered a new view on the question of stereo approach to the carbonyl group, in 1981. He proposed that the preferred direction is controlled by deviations in the "twist angle", which is the angle by which the axis of the π^* orbital of the carbonyl

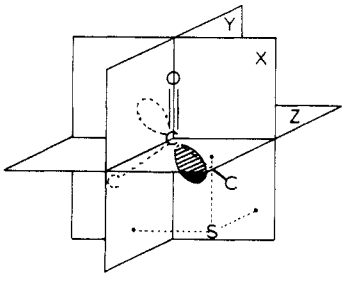


Figure 2. A ketone with the carbonyl function in the *x* plane of the paper and a substituent S in the quadrant shown. If the π^* orbital at carbon bends toward it as shown, the deviations from the *x* axis, θ_y and θ_z, are both considered to be positive.

carbon atom is twisted toward the substituent making the two faces diastereotopic. If this angle is positive, the nucleophile would preferably approach from the side of the substituent, and conversely, if the angle is negative, attack would predominantly come from the opposite direction (Figure 2). These small twist angles were evaluated by means of a CNDO/2 calculation. Impressive support was mustered in support of this proposition; thus, a changeover was said to occur in both the calculated twist angle and in the preferred direction of a hydride reducing agent in both the 4- and 5-haloadamantan-2-ones between fluorine and chlorine. However, as noted,[10] the tentative assignments made in the configuration of both 5-chloro and 5-bromo alcohols were wrong, and hence this part of the support in fact presents a problem. Furthermore, the same thoery[14] predicts anti approach (hence

(12) Lantvoev, V. I. *J. Org. Chem. USSR (Engl. Transl.)* **1980**, *16*, 1409. For a recent discussion of solvent effects in these reductions, see: Soai, K.; Oki, K. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 1601.

(13) Abraham, R. J.; Bergen, H. A.; Chadwick, D. J. *Tetrahedron Lett.* **1981**, *22*, 2807 and earlier work quoted there.

(14) Hudec, J., private communication.

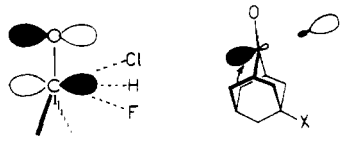


Figure 3. (a) Variations in Hudec's twist angle, induced by 5-halo substituents. (b) Delocalization of neighboring σ bonds into the incipient C–Nu σ^* orbital.

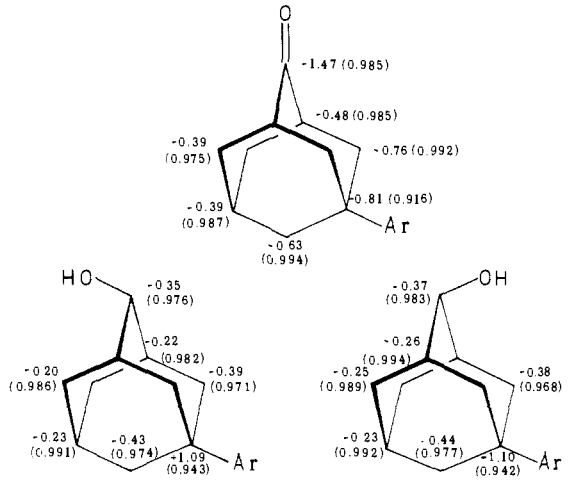
formation of (*Z*)-alcohol) for 5-phenyladamantanone, in contrast to what is observed.

A somewhat related but in practice more successful qualitative theory was devised by Cieplak[15] on the basis of the delocalization of neighboring-group electrons in the σ^* orbital of the incipient C–Nu bond (Figure 3). Whether the approach of the nucleophile is syn or anti to the substituent is now controlled by the electron density of the parallel bonds at the atom neighboring the carbonyl group. Thus, all 5-halogen substituents should cause greater electron density in the 1,8 and 3,10 bonds than in the 1,9 and 3,4 bonds; hence, the opportunity for delocalization will be greatest in the syn approach (*E* transition state). Cieplak's view accounts simply and elegantly for the well-known, pronounced preference of nucleophiles to approach axially in locked cyclohexanones; it is a consequence of the fact that C–H bonds are better electron donors than C–C bonds.[16] In the case of our adamantanones, there are of course only C–C bonds on both sides; nevertheless, the 5-substituent produces differences in their ability to function as donors, and this leads to substantial deviations from 50/50 product distributions. Cieplak's notions neatly explain all of the data in Table I.

Perhaps the principal difference between Cieplak's and Hudec's views is in the stress that the former places on the transition state and the latter on the initial state. The main problem with the assessment of the initial-state differences is that the size and even sign of the twist angles are not intuitively obvious, and only a quantum mechanical calculation can reveal it; by contrast, the transition-state approach of Cieplak only uses the well-known gradations in electronegativity of various substituents.

While a full-scale review[17] of the widely investigated topic of stereo approach of nucleophiles to carbonyl carbon is inappropriate, a few of the principal contributions may be singled out here in the light of our results. Cram,[18] Karabatsos,[19] Noyce,[1] Brown,[2] and Felkin[20] all have stressed the steric aspects of this reaction, and while there can be hardly any doubt that steric factors can be important and even overriding, the results recorded here show clearly that electronic effects of even a rather distant substituent can exert a substantial influence. At least in the cyclohexyl system, Klein[21] has emphasized the importance of electronic effects in both nucleophilic and electrophilic addition. Anh[22] stressed the importance of the antiperiplanarity of the newly forming bond and one of the three bonds originating at the two neighboring carbons. He suggested that the stereo preference was related to the ordering of the antibonding levels of these bonds, but the idea does not permit predictions on a qualitative basis. Both of these theories view the interaction of the π^* orbital with the neighboring bonds as the important one as the new bond begins to form. The principal advantage of Cieplak's proposal is that it recommends the very simple device of electron withdrawal or donation to predict preferred directions, and it appears to do so with success, at least

Scheme V



in the cases reported here. Furthermore, it appears to be capable of extension to such additional features as the nucleophilicity of the reagent group, solvent effects, and the direction of approach in electrophilic addition of carbocations, carbenes, and alkylating agents to olefins and enolates. All of these aspects can be studied by means of the same basic adamantane structures, and we are engaged in a program of this sort. Thus, much larger effects may be anticipated in the collapse of nucleophilic solvent with 5-substituent 2-adamantyl cations; indeed as noted in part (c), the ratios then reach magnitudes clearly of importance to the synthetic chemist, rivalling those, for example, on which A-values are based.

Other items worth noting in Table I include the facts that methyllithium produces somewhat higher ratios than do the metal hydrides, as might be expected on the basis of its greater nucleophilicity, and that the fluoro substituent is as effective a syn director as trifluoromethyl. The latter fact contracts with many cases in the literature in which π back-donation by fluorine unshared pairs largely negates the inductive effect.[23] The small temperature and solvent effects that have been discussed also by Lantvoev[12] requires that the comparison of ratios be restricted to experiments involving common conditions.

We close this section with some comments on our NMR results. One of these concerns the use of the two most bulky groups most commonly used as "locking groups" in cyclohexanes. After the initial experiments by Winstein and Holness,[3] *tert*-butyl was the group most often used, especially in the efforts to measure the A-values of various substituents.[24] In our carbene study, we used the phenyl group instead, for the experimental reasons mentioned earlier. After it became clear that phenyl had a substantial directing effect, we became interested in a report[25] that, in fact, *tert*-butyl may be inferior to phenyl as a locking device. This conclusion was based on a study of the effect of shift reagents on the proton and ^{13}C resonances in cyclohexanone and 4-*tert*-butyl- and 4-phenylcyclohexanone; a sophisticated computer search for the best structure suggested that the phenyl group caused less flattening of the ring than the *tert*-butyl group. Our hopes to get an insight with the corresponding solid adamantanones foundered on crystal disorder problems limiting refinement to 30%; however, a shift reagent study similar to that reported[13] does allow the conclusion that qualitatively similar distortions (Figure 2) are apparently present in the two adamantanones. As noted, they may be related to the similar small departures of the reduction product equilibrium ratios from unity. However, these effects are limited to the small distortions of the six-membered rings. As the product ratios in the reduction experiments show, phenyl clearly has a substantial directive effect, and *tert*-butyl does not.

(15) Cieplak, A. S. *J. Am. Chem. Soc.* **1981**, *103*, 4540.
(16) de la Mare, P. B. D. *Pure Appl. Chem.* **1984**, *56*, 1755. See also ref 15, footnotes 34–36.
(17) A useful summary of reviews and leading papers: Wigfield, D. C. *Tetrahedron* **1979**, *35*, 449.
(18) Cram, D. J.; Abd Elfahez, F. A. *J. Am. Chem. Soc.* **1952**, *74*, 5828. Cram, D. J.; Leitereg, T. J. *J. Am. Chem. Soc.* **1968**, *90*, 4011, 4019.
(19) Karabatsos, G. J. *J. Am. Chem. Soc.* **1967**, *89*, 1367.
(20) Cherest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 2199. Cherest, M.; Felkin, H. *Tetrahedron Lett.* **1968**, 2205.
(21) Klein, J. *Tetrahedron Lett.* **1973**, 4307. *Tetrahedron* **1974**, *30*, 3349.
(22) Anh, N. T.; Eisenstein, O. *Tetrahedron Lett.* **1976**, 155. Anh, N. T. *Top. Curr. Chem.* **1980**, *88*, 145.
(23) For a spectacular example, see: Paprott, G.; Seppelt, K. *J. Am. Chem. Soc.* **1984**, *106*, 4059.
(24) Eliel, E. L. *Angew. Chem., Int. Ed. Engl.* **1965**, *4*, 761.
(25) Abraham, R. J.; Chadwick, D. J.; Griffith, L. *Tetrahedron Lett.* **1979**, 4691. Abraham, R. J.; Chadwick, D. J.; Sancassan, F. *Tetrahedron* **1982**, *38*, 1485.

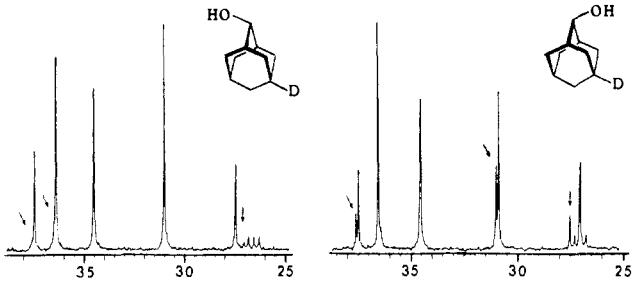
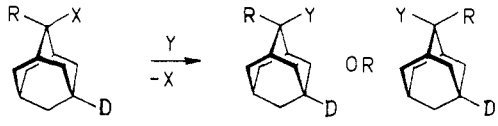


Figure 4. ^{13}C NMR spectra of (*E*)- and (*Z*)-5-deuterioadamantan-2-ol. The arrows point to peaks or shoulders revealing contamination by the natural abundance alcohol (6% in the *E* and 24% in the *Z* isomer. The shielding effects of D-substitution and of a *syn*-2-OH group clearly lead to maximum separation of C_5 and C_7 in the *E* and to isochronous signals in the *Z* isomer.

Scheme VI



The detailed results of the shift reagent study may be published elsewhere.

Finally, we take note of some peculiar features of the ^{13}C NMR spectra of the para-substituted 5-phenyladamantan-2-ones and -ols. The chemical shifts of all adamantane carbons were ascertained on the basis of simple additivity considerations; they were plotted in ppm against σ, and the slopes and correlation coefficients are recorded in Scheme V. Negative slopes imply increased shielding with increasing electron-withdrawing power. Perhaps naively, we had expected that all of the slopes would be positive, but this is actually true only of the benzylic bridgehead carbons in the alcohols. The same feature had been noted by Reynolds et al.[26] in the chemical shifts of the α-carbons in ethyl- and cyclopropylbenzenes. They interpreted this in terms of hyperconjugation, but it is not obvious how this explanation can be extended to more complex carbon skeletons. Another interesting fact is that the carbonyl carbon is affected more than any other by the phenyl substituent, even though no other carbon atom in the system is located further away. Such a large interaction between an sp^2 carbon with the distant bridgeheads in adamantyl skeletons is not without precedent; thus, Nelsen et al.[27] reported large proton hyperfine splittings at these sites in the adamantylideneadamantane radical cation.

(b) The 5-Deuterio-2-adamantyl System as a Stereochemical Probe. When the large prejudices that 5-substituents can impart against syn/anti equivalence at C_2 became known to us, we deduced that one could be certain of such equivalence in a variety of reactions only with deuterium substitution. Accordingly, we prepared both (*E*)- and (*Z*)-2-adamantanol-5d_1 by means of lithium aluminum deuteride (LAD) reduction of appropriately protected 5-chloro compounds. The ^{13}C and ^2H NMR spectra have been described and analyzed elsewhere,[10] but the following aspects are pertinent here. The C_5 and C_7 resonances in the natural abundance alcohol differ by about 0.5 ppm, with C_5 (the syn bridgehead carbon) the more deshielded. Superimposed upon this shift difference is the α-deuterium isotope shift that is of about the same magnitude. As a result, the sharp C_7 singlet and the C_5 triplet ($J_{^{13}C^2H}$ = 20.1 Hz) are well separated in the *E* isomer, where the singlet is superimposed upon the centerpeak of the triplet in the *Z* epimer. These two spectra are therefore very different in this region (Figure 4), and they should not merely permit the assignment of configuration but the analysis of mixtures as well.

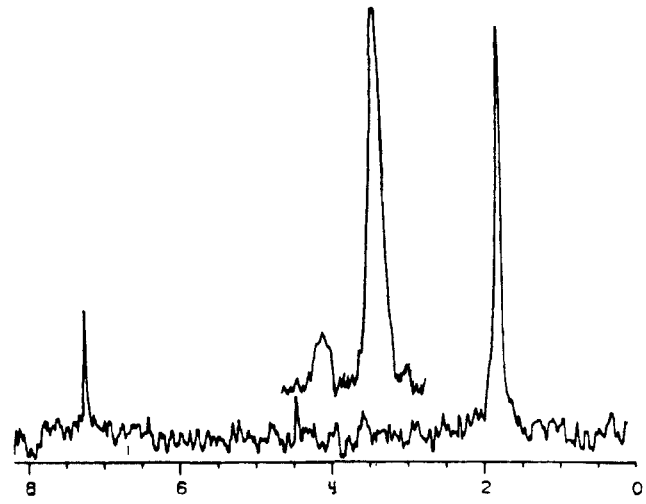


Figure 5. ^2H NMR spectra of the hydrolysis product of (*E*)-5-deuterio-2-adamantyl tosylate in $CDCl_3$ alone and in the presence of $Eu(fod)_3$ (inset).

The magnitude of the δC_5–δC_7 difference varies somewhat with the 2-substituent; however, these variations do not offer a serious complication.[28] Moreover, when the 2-substituent contains an atom capable of complexing with a paramagnetic shift reagent, analysis is greatly facilitated by the possibility of using ^2H NMR. Thus, H_5 and H_7 in 2-adamantanol are very differently affected by the presence of $Eu(fod)_3$,[29] and the same is of course true for deuterium atoms in those positions. As an example of how these considerations work out in practice, we now discuss an experiment that establishes the stereochemistry of solvolysis of "unsubstituted" (except for the deuterium) 2-adamantyl tosylate; as Figure 5 clearly shows, the (*E*,*Z*) product ratio deviates far from unity, and retention dominates inversion in the solvolysis in 40% aqueous acetone at 60 °C by a ratio of 92/8. Even in 97% aqueous hexafluoro-2-propanol at 25 °C, retention is still dominant at 65/35.

These results confirm and extend information developed by Whiting et al.,[30] who observed predominant retention in the solvolyses of both 5-methyl- and 2,5-dimethyl-2-adamantyl tosylates. These facts seem perhaps surprising because these esters have been proposed to be *the* outstanding example of limiting solvolysis of secondary substrates,[31] occurring with minimal anchimeric and/or solvent assistance. Indeed, there is much support for the position that this is a pure k_c process; thus, the rates correlate well with those of tertiary systems such as 1-adamantyl and 1-bicyclo[2.2.2]octyl,[32] azide ion does not capture the cation,[33] and α-deuterium substitution leads to the large effects typical of limiting solvolysis.[34] The argument is that the four axial γ-hy-

(26) Reynolds, W. F.; Kohler, R. H.; Hamer, G. K. *Tetrahedron Lett.* **1976**, 4671. For a recent study of substituent effects on ^{13}C chemical shifts showing a similar lack of correlation with electronegativity, see: Adcock, W.; Butt, G.; Kole, G. B.; Marriott, S.; Topsom, R. D. *J. Org. Chem.* **1985**, *50*, 2551.

(27) Nelsen, S. F.; Kessel, C. R. *J. Am. Chem. Soc.* **1979**, *101*, 2503.

(28) The complication most likely to arise with two 2-substituents with very nearly the *same* effects; these would then cancel the chemical shift differential. This is the case with 2-ethynyl-2-adamantanol, which has only one signal in the C_5–C_7 region. Even then, the problem in principle is soluble by means of ^{13}C NMR spectroscopy, e.g., by converting the hydroxy moiety into (trimethylsilyl)oxy (Basak, S. unpublished work) or by reduction of the ethynyl group.

(29) (a) Duddeck, H.; Dietrich, W. *Tetrahedron Lett.* **1975**, 2925. (b) Berger, S.; Zeller, K. P. *J. Chem. Soc., Chem. Commun.* **1976**, 649.

(30) Bone, J. A.; Whiting, M. C. *J. Chem. Soc., Chem. Commun.* **1970**, 115. Sinnott, M. L.; Whiting, M. C. *J. Chem. Soc., Perkin Trans. 2* **1975**, 1446. Storegund, H. J.; Whiting, M. C. *J. Chem. Soc., Perkin. Trans. 2* **1975**, 1452. Their discussions of the behavior of the (*E*)- and (*Z*)-5-methyl- and 2,5-dimethyl-2-adamantyl esters are difficult to follow since they apparently changed conclusions about the configuration of these compounds since their original communication and referred to them in later papers as "cis" and "trans" for both pairs of derivatives.

(31) Fry, J. L.; Lancelot, C. J.; Lam, L. K. M.; Harris, J. M.; Bingham, R. C.; Raber, D. J.; Hall, R. E.; Schleyer, P. v. R.; *J. Am. Chem. Soc.* **1970**, *92*, 2538; Schleyer, P. v. R.; Fry, J. L.; Lam, L. K. M.; Lancelot, C. J. **1970**, *92*, 2542.

(32) Schleyer, P. v. R.; Woodworth, C. W. *J. Am. Chem. Soc.* **1968**, *90*, 6528.

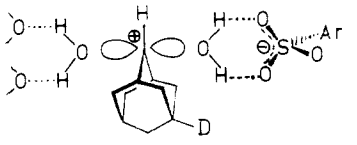
(33) Raber, D. J.; Harris, J. M.; Hall, R. E.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1971**, *93*, 4821.

Table II. Stereochemical Course of Nucleophilic Capture of the Carbocations Produced from 2-Adamantyl Substrates

2-substitutents	5-substituent	nucleophile	conditions	alcohol % *E*	alcohol % *Z*	analysis	ref
(*E*)-Me, OH	F	Cl^-	HCL/CH_2Cl_2; 0 °C	17	83	VPC	this work
(*Z*)-Me, OH	F	Cl^-	HCl/CH_2Cl_2; 0 °C	19	81	VPC	this work
(*E*)-Me, OH	CF_3	Cl^-	HCl/CH_2Cl_2; 0 °C	24	76	VPC	this work
(*Z*)-Me, OH	CF_3	Cl^-	HCl/CH_2Cl_2; 0 °C	26	74	VPC	this work
(*E*)-C≡CH, Cl	C_6H_5	MeOH	0 °C	25	75	HPLC	6
(*Z*)-C≡CH, Cl	C_6H_5	MeOH	0 °C	25	75	HPLC	6
(*E*)-Me, $O(C_6H_3N_2O_4)$	Me	AcOH	76 °C	44	56	VPC	30
(*Z*)-Me, $O(C_6H_3N_2O_4)$	Me	AcOH	76 °C	33	67	VPC	30
(*E*)-H, OTs	Me	AcOH	100 °C	45	55	VPC	30
(*Z*)-H, OTs	Me	AcOH	100 °C	19	81	VPC	30
(*E*)-H, OTs	C_6H_5	H_2O	40% aq Me_2CO; 60 °C	75	25	HPLC	this work
(*Z*)-H, OTs	C_6H_5	H_2O	40% aq Me_2CO; 60 °C	0	100	HPLC	this work
(*E*)-H, OH	Cl	Lucas	115 °C	50	50	VPC	this work
(*Z*)-H, OH	Cl	Lucas	50 °C	2	98	VPC	this work

drogen atoms shield the cationic site; furthermore, elimination and rearrangement are not important complications. On this basis, one might have anticipated stereorandom product formation. Yet another surprise was contributed to Bunnett,[35] however, who showed that oxygen scrambling occurs, indicating that return competes very effectively with solvolysis, and hence, that an ion pair is unexpectedly[36] an important intermediate.

Whiting discussed his result in terms of three possible explanations: buttressing of the axial hydrogens neighboring the 5-methyl group, the enhanced nucleophilicity of solvent trapped between the ions as in **5**, and weak anchimeric assistance. Yet



5

a fourth possibility mentioned later by Sunko[37] is that of a pyramidal (and nonequilibrating) trigonal carbon. The first possibility is ruled out by the fact that retention persists with a 5-label as innocent as deuterio. The second is consistent with the fact that we observe less retention in the more polar solvent (more extensive ion separation), but so is the third (according to the Born equation, solvation free energies are proportional to $q^2(D-1)/rD$, so that delocalization is less beneficial from a solvation standpoint in highly polar media). But before concluding, we need to describe additional results pertaining to the capture of both secondary and tertiary 2-adamantyl cations; these results are closely related to those described in part (a).

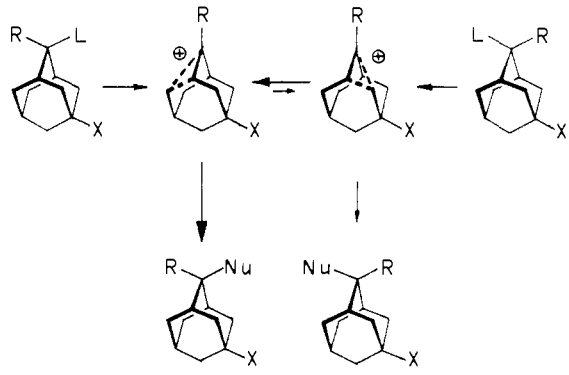
(c) Nucleophilic Approach to Trigonal Carbon: 2-Adamantyl Cations. The following two points need to be made before the results are analyzed. First, since some of the reactions had to be carried out under biphasic conditions, it was not convenient for us to study the relative rates of disappearance of epimeric substrates, which is the approach most often followed, and instead we measured the ratios of epimeric products. This is a perfectly valid tactic; as especially Brown[38] has reminded us, on the basis of the Goering–Schewene diagram,[39] the formation and capture of carbocations are essentially one another's reverse, and microscopic reversibility requires that whatever factors are responsible for unusual ratios in the one will also be the cause of similar ratios in the other. Thus, in 2-norbornyl substrates, high exo/endo rate ratios *imply* high exo/endo product ratios, and observation of the latter is not an independent argument for anything.

Second, there is a close connection between Cieplak's view[15] of nucleophilic approach to carbonyl carbon and Winstein's concept[40] of σ participation in the formation and hence capture of carbocations. The only distinguishing feature is that in the former theory, the delocalization of the neighboring σ electrons is into the σ^* orbital arising out of the combination of the high energy carbonyl π^* orbital and the unshared-pair orbital of the nucleophile; in Winstein's description of carbocations, these electrons are delocalized into the vacant p-orbital. As the bond formation progresses, the difference becomes smaller and finally vanishes as the carbonyl electrons become oxygen unshared electrons. It will be clear that the stabilization for carbocations will be greatest before the nucleophile begins to bind, whereas with the carbonyl compound, stabilization is more prominent in the transition state. We now turn to the data presented in Table II.

In striking agreement with the foreging discussion, the inductively withdrawing fluoro substituent in the 5-position powerfully directs chloride ion to the syn 2-position when the alcohols are allowed to react with HCl in methylene chloride. Since this epimeric precursor alcohols give the same mixture, the two reactions involve a common intermediate or common mixture of rapidly equilibrating intermediates. It was shown in separate experiments that the two epimeric products were stable under the reaction conditions and hence the product ratio reflects kinetic control. Hindrance in this sterically nearly C_{2v} symmetry system can obviously not account for this observation, and while both loose and tight ion pairs must at some stage be involved, the common product ratio precludes any rate controlling influence by them. The same may be said for pyramidal cations. We conclude that this observation is uniquely traceable to sigma participation. The same result is obtained with a 5-trifluoromethyl substituent, though it is a little less strong. A 5-phenyl substituent also serves as an inductively withdrawing group in the methanolysis of the tertiary 2-ethynyl tosylates as reported earlier;[6] in all three cases, common mixtures were obtained from both epimeric substrates. Even 5-methyl has a noticeable effect;[30] as expected (see above[16]), it retards the rate slightly, and while the mixtures obtained from the (*E*)- and (*Z*)-tosylates were not quite the same, they both approach the common geometric mean *E*/*Z* ratio of about 2/3. With secondary substrates, common mixtures are no longer obtained as retention begins to dominate; however, the geometric means suggest that the participation is stronger now. With 5-methyl, Whiting finds an averaged *E*/*Z* product ratio of about

(34) Harris, J. M.; Hall, R. E.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1971**, *93*, 2551. Shiner, V. J.; Fischer, R. D. *J. Am. Chem. Soc.* **1971**, *93*, 2553.
(35) Paradisi, C.; Bunnett, J. F. *J. Am. Chem. Soc.* **1981**, *103*, 946.
(36) Schadt, F. L.; Bentley, T. W.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1976**, *98*, 7667. Raber, D. J.; Harris, J. M.; Schleyer, P. v. R. In "Ions and Ion Pairs in Organic Reactions"; Szwarc, M., Ed.; Wiley: New York, 1974; Vol. 2, p 279.
(37) Sunko, D. E.; Szele, I.; Hebre, W. J. *J. Am. Chem. Soc.* **1977**, *99*, 5000.
(38) Brown, H. C. "The Nonclassical Ion Problem", with comments by Schleyer, P. v. R. Plenum: New York, 1977. In this final paper on the subject, Brown once again asserts that "... the tertiary ions are classical...-.". Rei, M.-H.; Chandrasekharan, J.; Somayaji, V.; Brown, H. C. *J. Org. Chem.* **1985**, *50*, 0000; a similar comment ("There is no controversy over the classical structure of the 2-Ph-norbornyl cation....") appears in Stirling's recent review: Stirling, C. J. M. *Tetrahedron* **1985**, *41*, 1613. Such statements tend to equate the occurrence of σ participation with that of *symmetrically* bridged ions.
(39) Goering, H. L.; Schewene, C. B. *J. Am. Chem. Soc.* **1965**, *87*, 3516.
(40) Winstein, S.; Trifan, D. *J. Am. Chem. Soc.* **1952**, *74*, 1147, 1154.

Scheme VII



1/2, and with 5-chloro, we find an averaged ratio of 1/7 upon treatment of the alcohols with Lucas reagent. With 5-phenyl, retention becomes so potent that we cannot compute an average for the still clearly present preference for syn approach. The inductive strength of the phenyl group is clear from the fact that we find the tosylates to solvolyze about 10 times more slowly than the parent compound. Our results are accommodated by the steps shown in Scheme VII, where R is H, Me, or C≡CH, L the leaving group, X an electron-withdrawing group, and Nu the nucleophile. The tertiary ions are formed and captured with σ participation, but the bridging is weak, and they equilibrate fully before the product-forming step. The secondary ions do not reach equilibrium, possibly because the bridging is stronger, or because their life time is shorter. While we have concerned ourselves primarily with products, even Whiting's results with the relatively mild directing effect of a 5-methyl group show that the *Z* substrates also produce the cations faster, and this agrees with qualitative observations in our own work. Thus, while the secondary (*Z*)-chloro alcohol gave the (*Z*)-dichloride with Lucas reagent at 50 °C, prolonged treatment at 115 °C was necessary to convert the epimeric alcohol. These observations may well be helpful in facilitating the sometimes difficult separations of such *E* and *Z* isomers; work on such applications is in progress.

It is a surprising development that bridging and σ participation should be found in tertiary ions, since such ions were adopted long ago as standards for limiting k_c behavior, and since especially Brown[38] has frequently used them as models against which to judge the possibility of σ participation in secondary substrates. However, it is conceivable that the presence of a third alkyl group does not quench the need for such participation so fully as is often supposed; likewise, it is possible that such suppression is much more effective with bridging than with σ participation. We have further experiments under way to test how effectively such donors as phenyl and even alkoxy substituents diminish σ participation; should this diminution be moderate or even absent, this would be an obvious weakness in Brown's long search to find large differences in exo/endo rate ratios of secondary and tertiary 2-norbornyl substrates. The problem in the search for experimental proof of σ participation may have been not that it is so rare but that it is so common!

It is equally unexpected that after decades of research on the 2-norbornyl ion that the 2-adamantyl ion should provide the better measuring stick. The main problem with the 2-norbornyl ion has been that the exo and endo faces are diastereotopically so different, leaving one free to assign anyone of a number of reasons to the differential effects observed. The long drawn-out and inconclusive debates over the possible intrusion of strain relief and steric hindrance testify to this. By contrast, the C_{2v} symmetry of the unstrained 2-adamantyl ion is virtually undisturbed by the 5-substituent in our C_s models, thus allowing, in effect, the operation of σ participation to be determined not merely in carbocationic processes but even in the nucleophilic addition to the carbonyl group. While the product ratios reported here may not seem impressive compared to, say, those in the 2-norbornyl cation, it must be remembered that they reflect only the *difference* in ability to participate between two carbon–carbon bonds that are distinguished only by a single atom located four bonds from the reactive center. Our compounds should be seen as sensitive *probes* of σ participation, and not as historic examples of its potential magnitude.

It is pertinent at this point to mention the following related recent studies. Grob[41] has, on the basis of extensive substituent effect studies, concluded that 2-methyl-*exo*-2-norbornyl ester solvolyzes with carbon σ participation; likewise, he has recently noted[42] that such participation must be occurring in the solvolysis of 2-adamantyl esters to account for the effect of 4-substituents on the rates. In agreement with our findings, it was also learned that in the anti series of 4-substituted 2-adamantyl esters, retention was favored over inversion when the 4-substituent is methyl but not when it is cyano. Finally, it should be recalled that Schleyer et al.[43] in 1980 published NMR evidence that the 1,3,5,7-tetramethyl-2-adamantyl cation is a rapidly equilibrating mixture of four ions; in other words, in this fairly "loaded" case, bridging occurs, but it involves only one bond at a time.

We close this section with a comment on the thought that perhaps the effects observed should be attributed to hyperconjugation, i.e., the ability of antiperiplanar bonds to delocalize charge *without* bridging. The main argument against it is that there is not precedent for the proposition that differential hyperrconjugation might have *stereochemical* consequences. In other words, while in a planar 2-methyl-5-fluoro-2-adamantyl cation the distal antiperiplanar bonds may be better able to interact with the p-orbital than the proximate ones, this would not constitute an obvious reason for preferred nucleophilic approach on the fluoro side. However, the difference between σ participation and hyperconjugation is not fundamental, if it exists at all, and since it is in any case not possible to gauge the position of C_2 and C_4 in the cations (and hence the degree of bridging), further discussion of this "alternative" is not profitable at this time.

Conclusion

The experiments described herein show that 5-substituted adamantan-2-ones and their derivatives are useful strereochemical probes. They permit quantitative assessment of the electronic effect of cross-ring substituents in nucleophilic attack upon the carbonyl carbon of cyclohexanone, providing a way to avoid the steric (axial *or* equatorial) complication. Nucleophilic approach syn to electron-withdrawing substituents is clearly favored, as is anti approach in the case of electron-donating substituents. Extensions to other kinds of chemistry and stereochemistry of trigonal carbon are readily envisioned.

In addition, the 5-deuterioadamantan-2-ols and their derivatives provide a tool for the assessment of stereoselection in substitution at saturated carbon that combines the advantages of geometric isomers and enantiomers. In the first application, the retention characterizing solvolysis of 2-adamantyl esters has been firmly established.

Finally, consideration of our results with tertiary 2-adamantyl cations bearing an inductively withdrawing substituent in the 5-position leads inescapably to the conclusion that they are stabilized by σ delocalization.

Experimental Section

Materials. The synthesis of 5-*tert*-butyladamantan-2-one has been described,[44] as has that of 5-phenyladamantan-2-one.[45] Nitration of the latter compound (procedure of Nelson and Brown)[46] gave the *p*-nitro derivative alone, 50% mp 127–128 °C; reduction with zinc dust and ammonium chloride in refluxing aqueous ethanol[47] gave the *p*-aminophenyl analogue, 53%, mp 126–130 °C. Diazotation with nitrous acid in methanol[48] gave the corresponding anisyl derivative, 55%, mp 72–75

(41) Grob, C. A.; Waldner, A. *Helv. Chim. Acta.*, 1983, *66*, 2481.
(42) Grob, C. A.; Wittwer, G.; Rao, K. R. *Helv. Chim. Acta* **1985**, *68*, 651.
(43) Schleyer, P. von R.; Lenoir, D.; Mison, P.; Liang, G.; Prakash, G. K. S.; Olah, G. A. *J. Am. Chem. Soc.* **1980**, *102*, 683.
(44) le Noble, W. J.; Srivastava, S.; Cheung, C. K. *J. Org. Chem.* **1983**, *48*, 1099.
(45) Geluk, H. W. *Synthesis* **1972**, 374.
(46) Nelson, K. L.; Brown, H. C. *J. Am. Chem. Soc.* **1951**, *73*, 5605.
(47) Morgan, G. T.; Middethwait, F. M. G. *Trans. Chem. Soc.* **1912**, *101*, 151.
(48) Remsen, I.; Orndorff, W. R. *Am. Chem. J.* **1887**, *9*, 395.

°C, and in water it gave the phenol, 70%, mp 190–191 °C. Sandmeyer reaction with CuCl gave the *p*-chloro ketone, 60%, mp 80–83 °C; this substance was also obtained by means of the Friedl-Crafts reaction of 5-bromoadamantan-2-one (activated as the ethylene glycol ketal) with chlorobenzene.

Sodium borohydride reduction of the phenyl ketone followed by HPLC separation gave the (*E*)- and (*Z*)-alcohols, mp 109 °C and 126 °C, respectively. The 5-*tert*-butyl alcohols were similarly obtained: mp 135 °C and 145 °C, respectively.

5-Hydroxy-,[45,49] 5-chloro-,[45] 5-bromo-,[50] and 5-fluoroadamantan-2-ones[51] have all been described: the 5-fluoro ketone was obtained by the adaptation of a procedure given by Schleyer for 1-fluoroadamantane[52] (refluxing a mixture of 20 mL of the bromo ketone in 150 mL of cyclohexane with 50 mM anhydrous silver fluoride). This method, giving a 96% yield, is much superior to that given by Tabushi.[51] Our fluoro ketone and that reported by Tabushi differed somewhat in their ^{1}H NMR spectra, though both gave satisfactory analyses; ours melted about 100 °C higher (276 °C vs. 170 °C). Our ^{13}C NMR spectrum is quantitatively in agreement with that calculated on the basis of the additivity method. Treatment of this ketone with methyllithium gave the tertiary fluoro alcohols that were quantitatively separated with GC (Carbowax) and crystallized from pentane; (*E*)-alcohol, mp 223–224 °C (*Z*)-alcohol, mp 143–144 °C. Reduction of the ketone with sodium borohydride gave the secondary fluoro alcohols that were similarly separated; (*E*)-alcohol, mp 242 °C, (*Z*)-alcohol, mp 218 °C. The secondary bromo and chloro alcohols were obtained in the same way; bromo alcohols, mp (*E*), 141–142 °C, (*Z*), 126–127 °C; chloro alcohol, (*E*), 194–196 °C, (*Z*), 176–179 °C. The trimethylsilyl ethers of the bromo and chloro alcohols were obtained by reaction with trimethylchlorosilane triethylamine, for purposes of GC separation and purification; chloro ethers, mp (*E*)-, 33–36 °C ((*Z*) is a liquid); bromo ethers, mp (*E*), 67–68 °C, (*Z*), 42–43 °C. The reduction of the chloro ethers with lithium aluminum deuteride to the 5-deuterio ethers has been described previously.[53] 1-(Trifluoromethyl)adamantane[54] was oxidized with sulfuric acid (chromium trioxide does not work) according to the procedure used by Geluk[55] to give a 15% yield of 5-(trifluoromethyl)adamantan-2-one, which was purified by flash column chromatography, as well as a trace of 1-(trifluoromethyl)-adamantan-2-one and a 65% yield of 3-(trifluoromethyl)adamantan-1-ol (mp 77–78 °C). The main ketone was reduced with sodium borohydride to the secondary alcohols and treated with methyllithium to give the tertiary alcohols ((*E*) mp 87 °C); both mixtures were separable by GLC. The tertiary alcohols were treated with HCl dissolved in methylene chloride over $CaCl_2$ to give a common mixture of chlorides. The tertiary fluoro alcohols under these conditions also gave a common mixture of fluoro chlorides. The secondary fluoro alcohols did not react with HCl; when they were treated with Lucas reagent they were immediately converted into the 5-chloroadamantan-2-ols. Independently obtained pure samples of the (*Z*)-chloro alcohol when treated with Lucas reagent for longer periods at 50 °C gave the (*Z*)-dichloride with virtually complete retention; the (*E*)-alcohol required a sealed tube and 115 °C to react, giving a 50/50 mixture of stereoisomers. Essentially the same results were obtained if the reaction was carried out homogeneously, in THF. Control experiments established that the products were essentially stable under these conditons. The tosylates of the 5-phenyl-adamantan-2-ols were prepared by treating ether solutions of the alcohols with a 10% excess of *tert*-butyllithium in hexane at 0 °C and then with the equivalent amount of *p*-toluenesulfonyl chloride dissolved in ether; the crude products were purified by column chromatography. Compelte listings of the IR, ^{1}H NMR, ^{13}C NMR, and mass spectral data as well as elemental analyses of these compounds are given in the supplementary material; the assignment of configuration of the *E* and *Z* isomers on the basis of ^{13}C NMR spectroscopy is described elsewhere.[10]

Product distributions in the reduction experiments were determined by means of standard NMR, VPC, and/or HPLC procedures; calibrations with known mixtures were carried out with the latter. The equilibration of the (*E*)- and (*Z*)-5-phenyl- and 5-*tert*-butyladamantan-2-ols was carried out in sealed tubes in 2-propanol containing a trace of acetone with aluminum 2-propoxide a 130 °C until the same mixture was obtained from either isomer (several days).

The configurations for the 5-substituted 2-methyladamantan-2-ols were determined by the additivity scheme[10] based on 2-methyladamantan-2-ol; the ^{13}C NMR signals in this parent were assigned on the basis of signal intensities, chemical shifts, and bound shifts with $Eu(fod)_3$: $C_2 \gg CH_3 \gg C_{4,9} > C_{1,3} > C_5 > C_7 > C_{8,10} > C_6$.

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Registry No. 5-Phenyladamantan-2-one, 38584-33-7; (*E*)-5-phenyladamantan-2-ol, 94062-20-1; (*Z*)-5-phenyladamantan-2-ol, 93965-96-9; 5-*tert*-butyladamantan-2-one, 84454-67-1; (*E*)-5-*tert*-butyladamantan-2-ol, 99766-80-0; (*Z*)-5-*tert*-butyladamantan-2-ol, 99827-58-4; 5-(4-nitrophenyl)adamantan-2-one, 99766-75-3; (*E*)-5-(4-nitrophenyl)-adamantan-2-ol, 99766-81-1; (*Z*)-5-(4-nitrophenyl)adamantan-2-ol, 99827-59-5; 5-(4-chlorophenyl)adamantan-2-one, 99766-76-4; (*E*)-5-(4-chlorophenyl)adamantan-2-ol, 99766-82-2; (*Z*)-5-(4-chlorophenyl)-adamantan-2-ol, 99827-60-8; 5-(4-methoxyphenyl)adamantan-2-one, 99766-77-5; (*E*)-5-(4-methoxyphenyl)adamantan-2-ol, 99766-83-3; (*Z*)-5-(4-methoxyphenyl)adamantan-2-ol, 99827-61-9; 5-(4-hydroxyphenyl)adamantan-2-one, 99766-78-6; (*E*)-5-(4-hydroxyphenyl)-adamantan-2-ol, 99766-84-4; (*Z*)-5-(4-hydroxyphenyl)adamantan-2-ol, 99827-62-0; 5-(4-aminophenyl)adamantan-2-one, 99766-79-7; (*E*)-5-(4-aminophenyl)adamantan-2-ol, 99766-85-5; (*Z*)-5-(4-aminophenyl)-adamantan-2-ol, 99827-63-1; 5-fluoroadamantan-2-one, 41171-83-9; (*E*)-5-fluoroadamantan-2-ol, 41163-73-9; (*Z*)-5-fluoroadamantan-2-ol, 41163-72-8; 5-chloroadamantan-2-one, 20098-17-3; (*E*)-5-chloroadamantan-2-ol, 98463-98-0; (*Z*)-5-chloroadamantan-2-ol, 98463-97-9; 5-bromoadamantan-2-one, 20098-20-8; (*E*)-5-bromoadamantan-2-ol, 58241-08-0; (*Z*)-5-bromoadamantan-2-ol, 58267-57-5; 5-hydroxyadamantan-2-one, 20098-14-0; (*E*)-adamantane-2,5-diol, 73346-81-3; (*Z*)-adamantane-2,5-diol, 73346-82-4; 5-(trifluoromethyl)adamantan-2-one, 80859-73-0; (*E*)-5-(trifluoromethyl)adamantan-2-ol, 99766-86-6; (*Z*)-5-(trifluoromethyl)adamantan-2-ol, 99827-64-2; (*E*)-5-fluoro-2-methyladamantan-2-ol, 99766-87-7; (*Z*)-5-fluoro-2-methyladamantan-2-ol, 99827-65-3; (*E*)-2-chloro-5-fluoro-2-methyladamantane, 99766-90-2; (*Z*)-2-chloro-5-fluoro-2-methyladamantane, 99827-67-5; (*E*)-2-methyl-5-trifluoromethyladamantan-2-ol, 99766-88-8; (*E*)-2-chloro-2-methyl-5-trifluoromethyladamantane, 99766-91-3; (*Z*)-2-chloro-2-methyl-5-trifluoromethyladamantane, 99827-68-6; (*E*)-5-phenyl-2-adamantyl tosylate, 99766-89-9; (*Z*)-5-phenyl-2-adamantyl tosylate, 99827-66-4; (*E*)-2,5-dichloroadamantane, 39646-69-0; (*Z*)-2,5-dichloroadamantane, 39646-70-3; (*E*)-5-deuterio-2-adamantanol, 98464-02-9; (*Z*)-5-deuterio-2-adamantanol, 98389-97-0; (*E*)-5-deuterio-2-adamantyl tosylate, 99766-92-4; (*Z*)-2-methyl-5-trifluoromethyl-adamantan-2-ol, 99827-69-7.

Supplementary Material Available: Analytical and spectral data of all new compounds (15 pages). Ordering information is given on any current masthead page.

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