Search for a Supraannular Effect

Bradford P. Mundy* and Timothy R. Schwartz

Department of Chemistry, Montana State University, Bozeman, Montana 59717

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In a series of papers published in the mid 1960s, the suggested preferential axial conformation for electronwithdrawing substituents [Z = C = N, C(0)OR, C(0)R] in the 4-position of cyclohexene derivatives (1) was attributed



to a supraannular effect.¹ This interpretation requires that electrons from the π bond of the alkene be delocalized to the electron-withdrawing substituent, as represented by 2. A necessary ramification of this, aside from the preferential axial conformation of the substituent, is a reduced reactivity of the alkene bond toward electrophilic reagents.

Although there is a paucity of experimental or theoretical support for the concept, there has also been no direct questioning of its importance. Research data are available to put the concept in doubt. For example, an NMR study of the equilibrium $3 \rightleftharpoons 4$ demonstrated a

significant preference for the diequatorial conformation.² Also, electron-withdrawing groups at the 4-position are not required for reduction of alkene reactivity. For example, in reactions with bromine, cyclohexene is 17 times more reactive than 4.4-dimethylcyclohexene where one methyl group must always occupy the axial position.³ Similar rate reductions (relative to cyclohexene = 1.00) have been noted for the Simmons-Smith reaction $(0.91)^4$ and epoxidation $(0.81)^5$ of 4-methylcyclohexene. In these examples it should be noted that rate reduction is observed even though the methyl group is neither electron withdrawing nor preferentially axial.

We reasoned that if the supraannular effect was operative, the reduction of alkene reactivity should find a parallel expression in the response of the Z group to reactions. Thus, a resistance of the alkene π bond to react with electrophilic agents (the electrons are delocalized to the Z group) should be matched by a reduction in the reactivity of the Z group (Z = >C=0) to nucleophilic agents (the carbonyl carbon is scready accepting electrons from the alkene). A well-exclaimed probe of carbonyl reactivity is found in sodiu borohydride reduction. Unlike lithium aluminum hydride, this reagent does not become less reactive as it sequentially delivers hydride;⁶ thus, problems of having a reagent alter reactivity and selectivity during a reaction are minimized. This reagent has already proven to be useful in examining ring-size



effects of cycloalkanones⁷ and steric effects in the methylcyclohexanones.⁸ This reagent was then selected to examine the carbonyl reactivities of 5 and 6.

Me	\bigcap		
5	6 8		

Equimolar amounts of the two ketones were allowed to compete for limiting sodium borohydride in 2-propanol such that there was about a 10-fold excess of carbonyl compound to hydride. Quantitative GLC, with electronic integration of peak areas, was used to evaluate the concentration of unreacted ketone. A series of dilutions of each reactant with 2-propanol to which an aliquot of an internal standard (o-dibromobenzene) was added provided a standard graph. From this linear response of moles of reactant to integrated peak area (correlation coefficients for each standard graph were 0.999) we could directly ascertain the number of moles of reactant. After each reaction of the ketone mixture, quantitative GLC was utilized to determine the amount of unreacted ketone. All data were collected within the portion of the standard curve for which there were actual data points. Each experiment was run in duplicate, and the relative reactivities were calculated according to the eq 1.9

$$RR = \frac{\ln (fraction of 5 remaining)}{\ln (fraction of 6 remaining)}$$
$$= \frac{k_5}{k_6}$$
$$= 0.76 \pm 0.04$$
(1)

The role of a supraannular effect is readily dismissed by examining these reactivities. The saturated system, incapable of a supraannular interaction, is less reactive than its unsaturated counterpart.

As a consequence of our interests in the stereoselectivity of reactions at the carbonyl carbon of 7, which after me-

thylation followed by borohydride reduction has been used in a synthesis of brevicomin (8),¹⁰ we required an unambiguous assessment of the importance of the supraannular effect in molecules also containing a heteroatom. In our first examination of this question, we competitively reacted 7 with 6 with the result shown in eq 2. These results

$$RR = k_7 / k_6 = 0.45 \pm 0.003 \tag{2}$$

demonstrate a retarding effect of the adjacent oxygen; however, the origins of this retardation are not readily

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Notes

Table I.	l. Normalize	d Relative .	Reactivities	
compd	5	6	7	12
normalized RR	1.00	1.26	0.57	0.33

rationalized. With the recent report¹¹ that neighboring oxygen markedly affects the stereoselectivity of sodium borohydride reductions, coupled with the well-established body of knowledge demonstrating the importance of cations in determining the regioselectivity of enolate formation,¹² we decided to examine whether these same effects could be found in reductions of 7 (Table I).

Results from this study, although not repeated for statistical validity, seem to show a very small trend; however, even a very modest 5% error would reduce the difference appreciably. With these data it is difficult to ascribe a strong coordinating effect of the heteroatom.

The next obvious experiment was the comparison of reactivity of 7 to its alkene-reduced counterpart, 12. The preparation of 12 proved to be considerably more difficult than anticipated. Under a variety of reduction conditions. the alkene bond of 7 was found to be quite resistant to reduction. A more circuitous route was required. In a previous study of ketals 9 and 10^{13} we found that catalytic reduction converted them to 11. Accordingly, we prepared the ketals by established methods, reduced them to 11, and then oxidized the alcohol mixture to 12 (eq 3).

9+10
$$\xrightarrow{c_{H_1}} \xrightarrow{o_{H_1}} \xrightarrow{c_{H_1}} \xrightarrow{c_{H_2}} \xrightarrow{c_{H_3}} (3)$$

At this juncture we decided to also test whether our experimental technique and approach were sufficiently sensitive and reproducible to accurately measure the small changes found. According to the theory of competitive reactions, all that is required is that neither substrate be limiting relative to the common reactive species. In our previous experiments we have maintained the substrates at essentially equimolar ratios. For the duplicate runs of 7 vs. 12 we decided to run one competition with equimolar ratios and the second competition with a 2-fold excess of 7. The results are shown below. These results demon-

> expt 1 RR = $k_{12}/k_7 = 0.58$ expt 2 RR = 0.61 $avg = 0.59 \pm 0.02$

strate, without doubt, the accuracy of our experimental approach and further redemonstrate a trend in reversal of that required for an operative supraannular effect. The results for the combined experiments, normalized to 5 are shown in Table II.

As a result of the reactivity measurements, we find no support for the supraannular concept. Are other tests possible? The use of ¹³C NMR spectroscopy has been thought to be a useful probe of electron-density changes about carbon. Accordingly, we examined the carbon chemical shifts of the carbonyl carbon and the α -carbon in the ring. There is absolutely no correlation of carbonyl carbon chemical shifts with reactivity; however, a trend for the α -carbon can be seen (Figure 1). Unfortunately, attempts to extend this to other systems are not possible. If we compare the reactivities of 13 and 14 (RR = k_{13}/k_{14}



Figure 1. Comparison of reactivity with chemical shift.

= 1.29 ± 0.02) with the observed chemical shift data, a reverse correlation is noted (Figure 1).

At this juncture we are left with serious doubt as to the validity of the supraannular effect. Although changes in reactivity of the carbonyl groups of several ketones and aldehydes can be noted, no trends can be found, and it appears that adjacent heteroatoms influence reactivity to as great an extent as the presence (or absence) of remote π bonds. At this time we cannot justify the reactivity differences by any general electronic argument.

Experimental Section

Compounds used in this study have been previously characterized. Our products compared with those previously reported. The standard curves for GLC analysis and the competitive kinetic technique utilized are described for a typical example.

Standard Curve. To 0.50 g of each component in a 10.0-mL volumetric was added sufficient 2-propanol to bring the total volume to mark. A 5.0-mL sample of this solution was mixed with 1.0 mL of a standard o-dibromobenzene solution and the total volume adjusted to 10.0 mL. Two $5-\mu L$ injections of this sample into the GLC apparatus and the electronic integration of peak areas (area of ketone/area of GLC standard) provided the first calibration points to determine the moles/area. The remaining 5.0 mL was adjusted to 10.0 mL, and the procedure was repeated. Five such sequential dilutions resulted in the standard graph.

Kinetic Experiment. To about 0.50 g of each of two ketones was added sufficient 2-propanol to bring the volume to 25.0 mL. Five milliliters of this solution was mixed with 1.0 mL of the o-dibromobenzene standard stock solution, and GLC analysis of this solution (area of ketone peak compared to area of o-dibromobenzene peak) provided the data for graphical determination of the number of moles of unreacted ketone. To the

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^{1976, 41, 371.}

remaining 20 mL of solution was added a limiting amount of borohydride (about 3 mol of ketone/mole of hydride), and the mixture was allowed to react at room temperature. After the reaction was quenched with water, most of the solvent was removed by rotary evaporation, and the residue was made up to 20.0 mL with 2-propanol. Five milliliters of this solution was withdrawn and added to 1.0 mL of the o-dibromobenzene stock solution. GLC analysis of this sample provide data to establish the number of moles of ketone remaining. Each GLC analysis was performed in duplicate, and each experiment was run in duplicate. Relative reactivities were calculated by eq 4 with the GLC areas and standard curves to establish concentrations of ketone before and after the reaction.

rel rate =
$$k_{\rm A}/k_{\rm B} = (\ln [{\rm A}]_t/[{\rm A}]_0)/(\ln [{\rm B}]_t/[{\rm B}]_0)$$
 (4)

Preparation of 2-(1-Hydroxyethyl)-6-methyltetrahydropyran (11). An ethanolic solution containing 27.2 g of 9 + 10and 0.13 g of 5% Pd/C was hydrogenated. After the uptake of hydrogen had ceased, the reaction mixture was filtered, and the filtrate was reduced in volume to give the alcohol mixture. GLC (15% Carbowax) demonstrated very high conversion to the desired product. An analytical sample was obtained by GLC. Anal. Calcd for C₈H₁₆O₂: C, 66.67; H, 11.11. Found: C, 66.50; H, 10.98. **Preparation of 2-Acetyl-6-methyltetrahydropyran** (12). To 2.1 g of 11 in 20 mL of Et₂O was added, dropwise, 1 equiv of Jones reagent. After being stirred for 2 h at 25 °C, the reaction mixture was neutralized with bicarbonate, and the ether layer was dried and reduced in volume to give the desired ketone. An

analytical sample was obtained by GLC. Anal. Calcd for $C_8H_{14}O_2$: C, 67.61; H, 9.86. Found: C, 67.61; H, 10.07. **Acknowledgment.** Partial support by the NSF (Grant No. ISP-8011449) is acknowledged. The gift of a generous supply of methyl vinyl ketone from Pfizer is greatly appreciated. The support of the NSF toward acquisition of the 250-MHz NMR spectrometer used in examining ma-

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Condensation of Naphthoquinones with Polar Ethylenes. A Reexamination

Marshall Gates

Department of Chemistry, University of Rochester, Rochester, New York 14627

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Some years ago I described¹ the condensation of naphthoquinones with polar ethylenes such as 1,1-bis[p-(dimethylamino)phenyl]ethylene and 1,1-di-p-anisylethylene. The products in the case of the condensation of 1,1-bis-[p-(dimethylamino)phenyl]ethylene with α -naphthoquinone and β -naphthoquinone, respectively, were formulated as 1 and 2, resulting from nucleophilic attack of the ethylene on the quinone followed by protolytic and redox equilibration. Structures analogous to 1 were proposed for the condensation products of naphthazarin with 1,1-bis[p-(dimethylamino)phenyl]ethylene and of α naphthoquinone with 1,1-di-p-anisylethylene.

A reexamination of these substances with the aid of instrumental techniques unavailable at the time of the original work has para-disubstituted phenyl certain of the



structural assignments are incorrect. Thus the mass spectrum of the condensation product of 1,1-bis[p-(dimethylamino)phenyl]ethylene with α -naphthoquinone shows a parent ion of m/e 420; structure 1 requires 422. Similarly, the condensation product of 1,1-di-p-anisylethylene and α -naphthoquinone has a parent ion of m/e394, two less than that required by a structure analogous to 1.

The 400-MHz NMR spectra of these two condensation products show only one AB pattern of the type expected from the para-substituted (dimethylamino)phenyl residues; structure 1 requires two. The second phenyl derived from the ethylene has acquired an additional substituent and appears as an unsymmetrical trisubstituted aromatic ring exhibiting the expected coupling ($J_{\text{para}} = 0$ Hz, $J_{\text{ortho}} = 9.3-10$ Hz, $J_{\text{meta}} = 2.4-2.9$ Hz).

In addition, syntheses of the hydroquinone dimethyl ethers corresponding to structure 1 and its analogue from 1,1-di-*p*-anisylethylene by alternate and unambiguous routes (see Scheme I) gave substances (6 and 7) not identical with those produced by reductive methylations of the corresponding quinone condensation products. The NMR spectra of these substances do show two AB patterns.

The condensation products of α -naphthoquinone with 1,1-bis[*p*-(dimethylamino)phenyl]ethylene and with 1,1-di-*p*-anisylethylene must thus be reformulated as 8 and 9, respectively,³ consistent with their mass spectra and their 400-MHz NMR spectra.

Likewise the product derived from naphthazarin and 1,1-bis[p-(dimethylamino)phenyl]ethylene must be reformulated as 10 since its mass spectrum shows a parent ion of m/e 452, and its 400-MHz NMR also exhibits the single AB quartet and trisubstituted aromatic pattern characteristic of 8 and 9.

⁽¹⁾ Gates, M. J. Am. Chem. Soc. 1944, 66, 124.

⁽²⁾ Some quinones show parent ions corresponding to their hydroquinones (Aplin, R. T.; Pike, W. T. *Chem. Ind.* 1966, 2009, and private communication from Mr. Joseph Wright of the Eastman Kodak Research Laboratories).

⁽³⁾ That these substances might be the result of additions of the Diels-Alder type was first suggested to me by Dr. George Fawaz, then of the American University in Beirut, in 1946.