Bridgehead Substituents Effect on the Reactivity of Bicyclobutane in its Reactions with Nucleophiles. A Comparison with Olefinic Systems.

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Abstract: The reactivity of bridgehead substituted bicyclobutanes towards nucleophilic attack was compared with that of the analogous vinylic compounds. *Ab initio* calculations suggest that the substituents exert nearly the same energetic effects on the ground state of the two systems. The observed difference in the reactivity of the two systems stems, therefore, from the different nature of corresponding transition states.

INTRODUCTION

The high p character (96%) and the pronounced bend (30.8°-45°) of the central bond in bicyclobutane[1-3] cause its reactivity to largely resemble that of a π bond in olefins. The similarity is indeed remarkable. Bicyclobutane undergoes practically all the reactions that typify the chemistry of carbon-carbon double bonds. It undergoes electrophilic additions,[1,4] radical additions,[5] polymerization reactions[6] and, when properly activated by an electron withdrawing group (EWG) at a bridgehead position, it also undergoes nucleophilic addition analogous to the Michael reaction.[7-10]

In the absence of quantitative data, it is not clear whether the similarity between bicyclobutane and vinylic systems is merely qualitative in nature or whether it can be extended into the quantitative domain of reactivity. The proclivity of bicyclobutane to undergo nucleophilic reactions provides an opportunity to study the effect of an EWG at the bridgehead position on the kinetics of this process in comparison with data for the analogous olefinic substrates.

RESULTS

Rate constants for the addition of MeO$^-$ in MeOH to the three substrates (EWG= COPh, SO$_2$Tol and COOMe, eq 1) were determined at several temperatures.

$$(1)$$
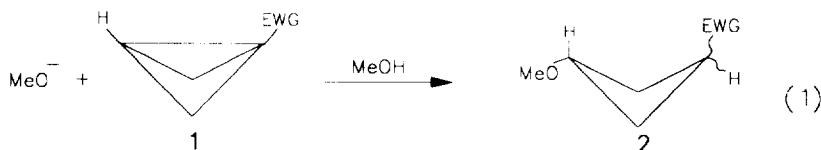
The reactions of the ketone (**1k**) and the sulfone (**1s**) derivatives gave a quantitative yield of a mixture of a *cis* and *trans* addition products. The ester compound (**1e**) gave mainly the addition products. However, these were accompanied by some unidentified compounds which appeared only at the later part of the reaction.

Therefore, for the reaction of **1e**, the rate constants are based on data from the first 30% of the reaction where

no by products were observed. At each temperature, between two to four independent determinations of the rate constant were performed and in general the error in the determined rate constant is less than ±5% (error estimated on the basis of reproducibility and the error in the regression line used to calculate the rate constants). The second order rate constants and activation parameters are given in Table 1. Table 2 shows as a typical example detailed results for the kinetics of MeO$^-$ addition to 1s.

Table 1: Second Order Rate Constants and Activation Parameters for the Addition of MeO$^-$ in MeOH to Bicyclobutane-EWG.

EWG	10^5k $(M^{-1}s^{-1})$ [a]	$\Delta H^{\ddagger}$ kcal/mol	$\Delta S^{\ddagger}$ e.u.
SO$_2$Tol	2.6 (30) 35.4 (60)	17.7	-23.2
COOMe	3.3 (30) 61.6 (60)	19.1	-16.2
CN[b]	5.9 (30)	18.5	-15.9
COPh	1260 (0) 9780 (25)	12.7	-20.4

[a] temperatures are give in parentheses

[b] data from ref. 10

Table 2: Kinetic data for the addition of MeO⁻/MeOH to 1s.

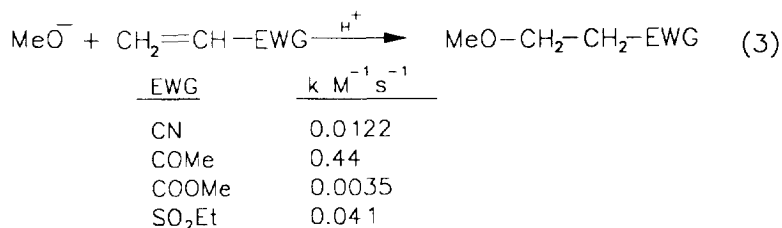| [1s]	[MeO⁻]	T °C	k_{add}	r
M	M		$M^{-1}, sec^{-1}*10^5$	
0.031	0.29	30	2.59	0.9984
0.032	0.29	30	2.55	0.9988
0.031	0.132	40	6.2	0.9964
0.031	0.132	40	5.9	0.9965
0.032	0.132	60	37.6	0.9993
0.028	0.132	60	36.7	0.9940
0.031	0.29	60	33.7	0.9920
0.031	0.29	60	33.5	0.9970

DISCUSSION

Nucleophilic attacks on bicyclobutane derivatives have been thoroughly examined in the past.[7-10] These, like the Michael addition reactions,[11] were found to be two step reactions with the nucleophilic step being rate determining (eq. 2)
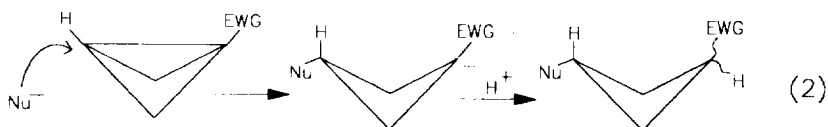
The activation order of the bicyclobutane molecule by bridgehead substituents towards nucleophilic attack (see Table 1) is as follows:

$$COPh >> CN > CO_2Me > SO_2Tol$$
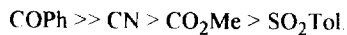
In spite of the aforementioned similarity between olefinic systems and bicyclobutane, the observed activation order does not parallel that found for the addition of MeO⁻ to the analogous vinylic derivatives (eq 3).[12]

$$MeO^- + CH_2 = CH - EWG \xrightarrow{\ \ H^+\ \ } MeO - CH_2 - CH_2 - EWG \quad (3)$$

EWG	$k\ M^{-1}s^{-1}$
CN	0.0122
COMe	0.44
COOMe	0.0035
SO$_2$Et	0.041

A plot of log k for the addition of MeO⁻ to bicyclobutane vs. that for the addition to the corresponding olefins (Fig. 1) shows the absence of any correlation between the two. The reactivity in the bicyclobutane reactions spans a nearly 4 log units range as compared with only two for the olefinic system. However, while in the latter system the data points are relatively equally spaced over this range, in the case of bicyclobutane, the data points for three of the four substituents (CN, CO$_2$Me and SO$_2$Tol) are confined to a 0.4 log unit range only. The COPh derivative is significantly more reactive than the three other substrates.
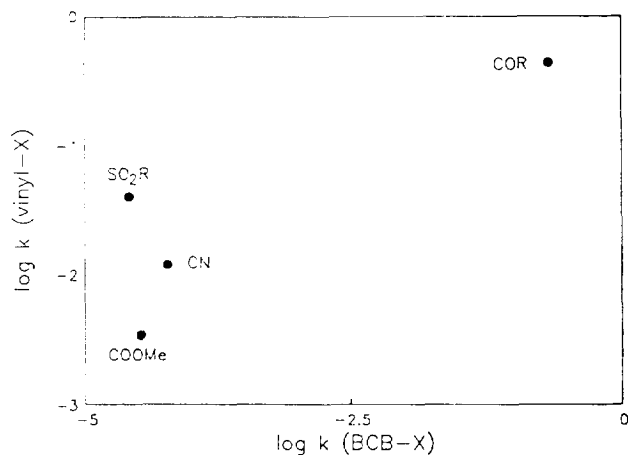

Figure 1: A plot of log k for MeO⁻ addition to olefins vs. log k for MeO⁻ addition to bicyclobutanes.

In a detailed study of the parameters affecting the activation of olefins Rappoport *et al.* found that, for the addition of morpholine, the activation order is governed by the enthalpy of activation whereas the activation entropy remains essentially constant along the series.[13] However, in the present system no correlation is obtained between log k and $\Delta H^{\ddagger}$ or $\Delta S^{\ddagger}$ (Fig. 2). Therefore it is not surprising that no significant correlation is apparent between the observed rates and the various types of σ values[14] for these activating groups (in some cases in the absence of σ values for SO$_2$Tol and COPh, σ values for SO$_2$Me and COMe were used). Since an incipient negative charge is developed on C1 in the course of the reaction, a correlation of the data with the pKa of the corresponding carbon acids (H-CH$_2$-EWG) was sought for. Unfortunately, we were unable to find reliable data for the pKa of the whole series in MeOH. The data for aqueous solutions are based mainly on

estimates.[15] Data are available for the pKa of PhCOMe (24.7), $MeSO_2Me$ (31.1) and MeCN (31.3) in DMSO.[16] However, it is impossible to base any conclusion on three data points two of which are very close in value.
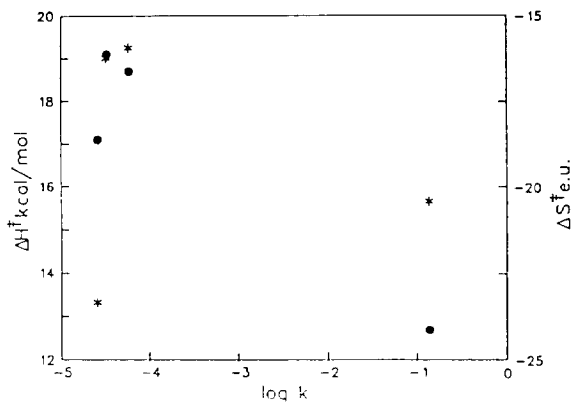

Figure 2 A plot of activation parameters *vs.* log k for MeO⁻ addition to bicyclobutanes.

The difference between the activating effect of the substituents in the bicyclobutane and the olefinic series may result from either a difference in the stabilization of the ground states or the transition states or both. In order to examine the effect of the substituents on the ground states of bicyclobutane and the olefin, the two isodesmic reactions (eq. 4 and 5) were evaluated computationally using the Gaussian 92 program with a 6-31G* basis set.[17]


$$\text{(4)}$$

$$\text{(5)}$$

The energies and the main geometrical parameters of both systems are given in Table 2.

Figure 3 shows a plot of the stabilization energy, relative to CH_3, of the bicyclobutane derivatives *vs.* the corresponding vinylic systems. The correlation is remarkably linear with a slope of 0.96 and a correlation coefficient of 0.9880. It seems highly likely therefore that the substituents effect on the energy of the ground states are not the cause for the absence of correlation in the reactivity between the two series. This absence of correlation stems most probably from a differential effect on the transition state.

Table 3: Energies and Major Geometrical Parameters Computed at the 6-31g* Level for Substituted Bicyclobutane, Ethylene and Methane.
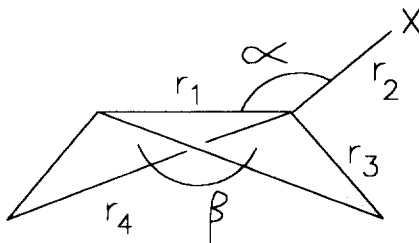
X	Ea.u.	r1	r2	r3	r4	α	β
CN	-246.609079	1.477	1.428	1.495	1.495	130.57	122
COOMe	-381.521864	1.487	1.468	1.491	1.493	127.2	122.9
SO$_2$H	-702.018565	1.469	1.735	1.49	1.494	129.6	122.4
CHO	-267.603518	1.492	1.466	1.497	1.49	126.5	123.1
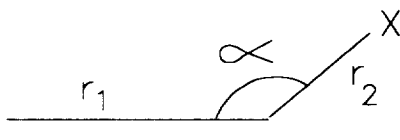
X	Ea.u	r1	r2	α
CN	-169.768015	1.32	1.433	122.2
COOMe	-304.679773	1.319	1.485	124.3
SO$_2$H	-625.177407	1.316	1.755	120.7
CHO	-190.762424	1.321	1.478	121.3

Me $\xrightarrow{\ r_1\ }$ X
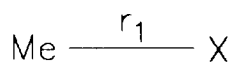
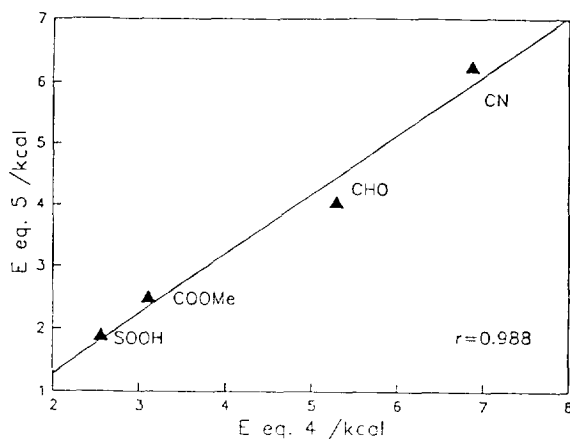| X	Ea.u	r1
CN	-131.927534	1.468
COOMe	-266.836829	1.505
SO$_2$H	-587.337879	1.767
CHO	-152.915965	1.504

Figure 3: Substituent Stabilization Effect on Olefins *vs.* Bicyclobutanes as Derived from the Isodesmic Reactions in Equations 4 and 5.

As was pointed out before, the data points for the olefin reactions were spread evenly over the whole reactivity range. Whereas, in the bicyclobutane series, while the overall change in rate constants is ca. 5000 fold, the rate constants for the weakly activating groups differ by a factor of 2 only. This is consistent with the assumption that the olefinic system comprises a family of substrates and therefore their transition states are of similar structures. On the other hand, the bicyclobutane do not comprise a family in LFER terms. Further support for this assumption can be obtained from examination of the plots of log k or $\Delta H^{\ddagger}$ *vs.* the LUMO energies. In spite of the limitations of the Koopmans theorem,[18] a rather reasonable correlation is obtained between log k and the corresponding LUMO energies for the olefinic system. On the other hand, no such correlation is obtained between $\Delta H^{\ddagger}$ and the LUMO energies for the bicyclobutane series (Fig. 4).
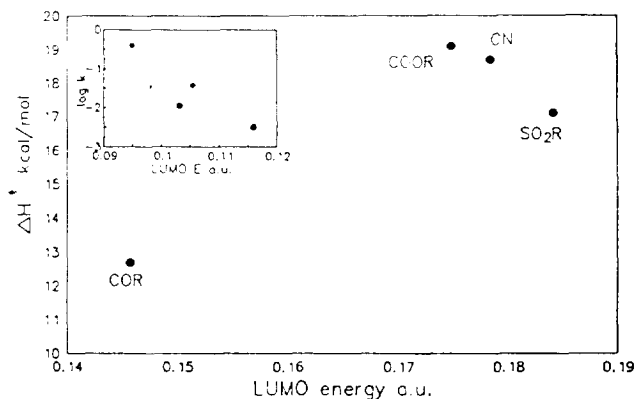

Figure 4: Activation Enthalpy as a Function of the LUMO Energies of Bicyclobutane Derivatives. In the Inset; Log k *vs.* the LUMO Energies for the Corresponding Olefins.

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According to the Hammond postulate[19] it would be expected that the transition state is rather late for the ester, sulfone and nitrile derivatives of bicyclobutane and early for the COPh derivative.   The good correlation obtained for the energetic effects of the various substituents on the ground state energies of the olefinic and the bicyclobutane derivatives (Fig. 3) suggests that the absence of correlation in the reactivity of the two substrate types stems from a TS effect. In a "well behaved" series, all the effects, for example, parameters such as the degree of bonding with the nucleophile, cleavage of the central bond, strain release and incipient charge stabilization by the EWG progress at a proportional rate toward the TS. A referee raised the question "Why is the reaction (of the COPh derivative) so much faster?" In fact, we don't know that it is indeed so much faster. It is possible that, in Fig. 1, a line should be drawn through the points of COOMe and COPh. In this case, the two charge localizing substituents, CN and SO_2Ph, deviate by displaying an exceptionally low reactivity. On the other hand, it is possible that for all the weakly activated bicyclobutanes, factors such as strain relief, which are less substituent dependent, control the reactivity whereas, for the COPh substrates the enhanced capability to stabilize the negative charge may, in accord with the Hammond postulate, lead to a much earlier TS.

It is possible that, since the central bond of bicyclobutane resembles in part a Π and in part a σ C-C bond, a better correlation would have been obtained if the comparison would have been made with a four parameter equation presenting a combination of data for Michael and a SN2 reaction. Unfortunately, SN2 reactions with substituents of the type CH_3-CH_2-EWG, whose σ C-C bond is cleaved, are not known at present.

SUMMARY AND CONCLUSIONS

There is no linear correlation between the reactivity of the bicyclobutane system and analogous vinyl derivatives. For the three weakly activating groups, ester, sulfone and nitrile, the olefinic system is more reactive than the bicyclobutane system by ca. three orders of magnitude. This difference practically disappears for the more reactive keton derivatives. The absence of a correlation may be explained assuming that the four derivative of the bicyclobutane series do not comprise a single family of substrates. *Ab initio* calculations suggest that the substituents effect on the energies of the ground states are similar for the two series. Assuming the vinylic system is "well behaved", the data suggests that the transition states for the nucleophilic attacks on the three weakly activated derivatives of bicyclobutane have a transition state which significantly differs from that of the phenylketone derivative. The latter probably has a much earlier transition state.

EXPERIMENTAL SECTION

General. NMR spectra were recorded on a Bruker AM-300 spectrometer and measured in $CDCl_3$ solution. Mass spectra were taken with a Finnigan 4021 mass spectrometer. For analytical purposes, a Packard Model

878 (FI detector) gas chromatograph was used whereas for preparative separations a Varian 920 gas chromatograph (TC detector) was used.

Reactants and products. bicyclobutyl-tolylsulfone (**1s**) was obtained from Prof. Y.Gaoni[20] and is known in the literature. Methylbicyclobutanecarboxylate (**1e**) was prepared according to a literature procedure[6] with the difference that the two steps - hydrolysis of the nitrile function and esterification of the resulting acid derivative were combined into a single step according to the following procedure. A heterogeneous mixture of 2.8 g (0.024 mol) 3-chloro-bicyclobutanecarbonitrile and 21 mL of conc. HCl were vigorously stirred under gentle reflux for 1 hr. 40 ml of MeOH were added and the reflux was continued for 22 hrs. The reaction mixture was treated with methylene chloride and aq. NaHCO$_3$. The organic phase was dried over MgSO$_4$ filtered and evaporated yielding 3.53 g (95% yield) of yellow liquid composed mainly of the two isomers of methyl-3-chloro-cyclobutanecarboxylate. The mixture was then subjected to elimination and the product, methyl bicyclobutanecarboxylate, was kept in ethereal solution at -25°C. Before each kinetic experiment the product was separated and purified by preparative gas chromatography (5% XE 60 on Chromosorb W, 50°C). Bicyclobutyl phenylketone (**1k**) was prepared according to literature procedure[21] and purified by preparative GC (0.5% XE 60 on Chromosorb W, non-acid washed, 95°C).

The methoxy adducts of the three substrates were independently prepared according to published procedures.[8,20,21] The two isomers of 3-Methoxycyclobutyl p-tolylsulfone (**2s**) were separated on a GC column (0.5% XE 60 on Chromosorb W, non-acid washed, 170°); ^{1}H NMR of the *cis* isomer; 2.2-2.8 (m, 4H), 2.44 (s, 3H) 3.0-3.4 (m, 1H), 3.22 (s, 3H), 3.77 (qn, J=7) 7.34, 7.35(4H); ^{1}H NMR of the trans isomer; 2.44 (s, 3H), 2.05-2.4, 2.6-3.05 (m, 4H), 3.22 (s, 1H) 3.5-3.8 (m, 1H), 4.15 (qn, J=6) 7.34, 7.79 (4H). The two isomers of methyl-3-methoxy cyclobutylcarboxylate (**2e**) were separated and their geometry was assigned according to Razin *et al*.[8] The two isomers of 3-methoxycyclobutyl phenylketone (**2k**) were obtained as a mixture after column chromatography with methylene chloride. ^{1}H NMR of the *cis* isomer; 2.24-2.37, 2.53-2.65 (m, 4H), 3.25 (s, 3H), 3.49 (tt, J=10,8), 3.97 (tt, J=7,8), 7.45-7.91 (5H); ^{1}H NMR of the *trans* isomer; 2.27-2.4, 2.59-2.7 (m, 4H), 3.27 (s, 3H), 3.91-4.05 (m, 2H), 7.46-7.9 (5H). (The geometrical assignment was based, as before, on the difference in the H nmr chemical shift of the hydrogen atoms on C1 and C3. The chemical shifts of these hydrogens is shifted down field when they are syn to an electronegative group such as MeO- or one of the activating groups).

General procedure for the kinetic experiments. Solutions of MeONa in MeOH were prepared from Na and MeOH under nitrogen. The solutions at the appropriate concentration (0.002 - 0.3M) were incubated in a temperature bath (0 - 60°C, the lowest temperature and nucleophile concentration were used in the reactions of **1k** whereas the high temperature and nucleophile concentration were employed in the reactions of the more sluggish substrates). For each substrate, rate constants were measured over a temperature range of at least 25°

C. The MeO⁻ solutions were either added to the previously weighed substrate in the reaction flask placed in the temperature bath or a 5 μL methylenechloride solution of the substrate was injected into 2 mL of the methoxide solution at the appropriate concentration. The reactions were carried out under pseudo first order conditions (excess MeO⁻). In several runs, fluorene or naphthalene were added to the reaction mixture as an internal standard. Aliquots 0.2 -0.25 mL were periodically removed. The reactions of 1s and 1k were quenched by aq. NaCl solution and extracted with ether. In the case of 1e, quenching was done with AcOH. Care was taken to assure that the quenched solutions were neutral since under either basic or acidic conditions the composition of the samples did not remain constant after several days. A 2% XE-60 on chromosorb W column was used for the GC analysis of the reactions of 1e whereas a 0.5% XE-60 on chromosorb W (non- acid washed) column was used for the GC analysis of the reactions of 1s and 1k.

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