Mechanism and Stereochemistry of General Acid Catalyzed Additions to Bicyclobutane[1]

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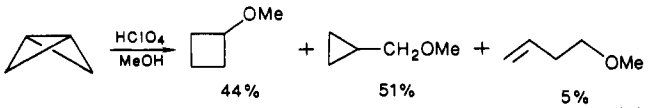
The electrophilic addition of MeOH across the central bond of 3-X-bicyclobutanecarbonitriles (X = H, Me, Cl) was found to be a general acid catalyzed reaction with Brønsted $\alpha = 0.96$. The ρ^+ value of these reactions is -7.1 ± 1.3. These two coefficients are interpreted as an indication of an unbalanced transition state. In the case of X = H and Me, the addition reaction is of syn stereochemistry. This is probably also the stereochemistry in the case of X = Cl. However, the initially formed adduct in this case reacts further to give ketal **3a**. In the presence of $NaClO_4$, anti addition products are also observed and reaction rates increase linearly with the concentration of the salt. Ab initio calculations (3-21G) show that protonated bicyclobutane has two stable geometries (C_s symmetry), one highly puckered and the other nearly planar. The first structure is more stable by 9.5 kcal/mol (6-31G*/3-21G). It is concluded that with strong nucleophiles, the syn stereochemistry results from a concerted attack by the proton and the nucleophile from the equatorial directions. With weaker nucleophiles, the first step is protonation of the substrate which is followed by nucleophilic attack on the puckered cation. Both attacks take place from an equatorial direction leading therefore ultimately to the observed stereospecificity.

In a fashion similar to many highly strained systems, bicyclobutane and its derivatives undergo a facile reaction with a variety of electrophilic agents.[2-4] As exemplified by the acid-catalyzed addition of MeOH to bicyclobutane,[5] three types of products are usually obtained. These are the cyclobutyl, the cyclopropylcarbinyl, and the allylcarbinyl derivatives (eq 1). In most cases the latter class



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of products is obtained either in minute amounts or is completely absent from the reaction mixture.

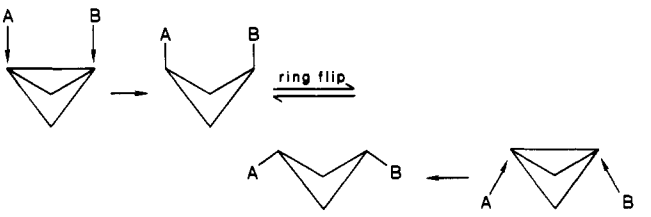
This paper will focus on two major aspects involved in the acid-catalyzed additions to bicyclobutane. Namely, the stereochemistry and the reaction mechanism. We will concentrate mainly on the reactions in which the cyclobutane framework is retained.

The addition of the proton and its nucleophilic counterpart to bicyclobutane could, in principle, be either a syn or an anti addition. In the majority of the cases, only cis addition products are observed.[3a,6] The cis addition can occur via two different routes, diequatorial or diaxial (Scheme I), both of which lead essentially to the formation of the same product.

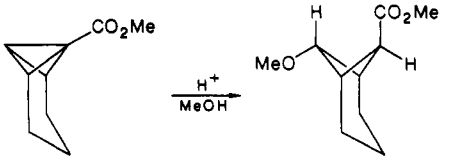
In order to distinguish experimentally between these two possibilities, the bicyclobutane moiety must be first confined in a rigid system to prevent ring flipping which equilibrates the two primary products of these attacks.

Unfortunately, despite the many reported acid-catalyzed additions to bicyclobutane, there is only one relevant experiment.[6c] However, in this experiment the 1,3 addition

Scheme I



product, in which the cyclobutane framework is retained, was obtained in only 0.8% yield (eq 2). Nevertheless, the



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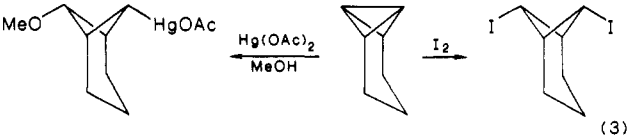
reactions of the parent hydrocarbon with other electrophiles such as I_2[7] and $Hg(OAc)_2$[8] clearly shows that the addition is diequatorial (eq 3).



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A priori, two alternative explanations may be suggested for the preference of the cis diequatorial addition mode. It has already been shown that both nucleophilic[9] and electrophilic[10] attacks on bicyclobutane occur preferentially from the equatorial direction. Therefore, if the reaction is concerted, then the sum total of the two attacks will yield a diequatorial addition product. However, the reaction may be a stepwise process in which case the initially formed bent carbocation is trapped by the nucleophile before it undergoes planarization or ring flip to its isomeric bent form.

The mechanistic study reported here is aimed to shed some light on this yet unanswered problem.

(1) This is part 11 in the series "cyclobutane–Bicyclobutane System". For the previous paper in the series, see: Hoz, S.; Levy, R. J. *Mol. Struct. (Theochem).* **1985**, *121*, 93.

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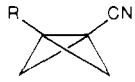
Results

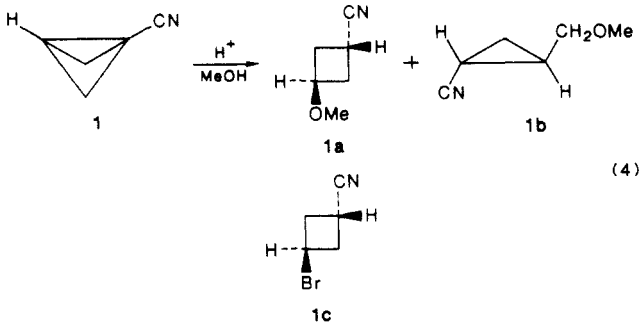
The kinetics and product distribution of the acid-catalyzed addition of MeOH to a series of substituted bicyclobutanes (1–3) were investigated. The reactions were



1, R = H
2, R = Me
3, R = Cl

followed by analytical gas chromatography with an internal standard and found to proceed to completion. Most of the work was performed on the methyl derivative **2** whose reactivity was found to be most suitable for a study with a wide range of catalyzing acids.

Reactions of 1. The reaction of this substrate is the only case in which the formation of the cyclobutyl derivative (**1a**) was accompanied by a ca. equal amount of the cyclopropylcarbinyl product (**1b**). The two products together account for at least 98% of the reaction products (eq 4). In the reactions of the two other substrates, no



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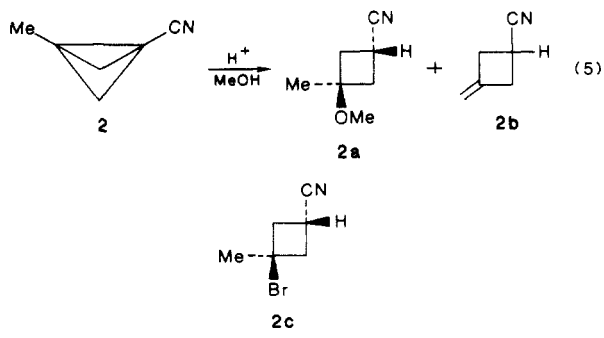
cyclopropylcarbinyl derivatives were obtained. In the presence of NaBr, small quantities (less than 5%) of **1c** were obtained. The amounts of the latter product were dependent on the concentration of NaBr in the reaction mixture.

Reaction rate constants were determined at 35 and 50 °C with TsOH–TsONa (1:1 ratio) buffer varying over the range of 0.11–0.56 M. The reaction was found to be general acid catalyzed and the first-order rate constants are given in Table I. In general, each rate constant in the following tables (I–VI) is based on the average on 8 data points. With a buffer concentration of 0.225 M, addition of $NaClO_4$ (0.3 M) induced a 30% increase in the reaction rate constant at 35 °C. This rate increase was accompanied by the formation of 18% of the trans (with respect to MeO–H) isomer of **1a** (**1a′**). The ratio **1a**:**1b** (not **1a** + **1a**:**1b**) has not been significantly affected by the presence of $NaClO_4$.

Reactions of 2. The main product (85%) of the acid-catalyzed reaction of **2** in MeOH is **2a** which results from a cis addition of MeOH (eq 5). This is accompanied by



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minor quantities (1–2%) of the trans addition product **2a′**.

Table I. First-Order Rate Constants for the Acid-Catalyzed Methanolysis of 1 in the Presence of a 1:1 TsOH–TsONa Buffer

[buffer], M	10^5k, s^{-1} (35 °C)	10^4k, s^{-1} (50 °C)
0.113	1.67	0.99
0.225	2.73	1.86
0.338	4.47	2.34
0.563	6.86	3.56
0.225[a]	3.57	

[a] In the presence of 0.3 M $NaClO_4$.

Table II. First-Order Rate Constants for the Acid-Catalyzed Methanolysis of 2 in the Presence of a 1:1 TsOH–TsONa Buffer

[buffer], M	10^3k, s^{-1} (25 °C)	[buffer], M	10^2k, 2^{-1} (50 °C)
0.0049	0.164	0.0051	0.11
0.0098	0.311	0.0102	0.22
0.0196	0.676	0.0205	0.51
0.0392	1.25	0.0410	1.03
0.0588	1.62	0.0615	1.36
0.0788	2.04	0.0819	1.82
0.0980	2.4	0.0902	2.06

Table III. First-Order Rate Constants for the Acid-Catalyzed Methanolysis of 2 in the Presence of 1:1 Cl_3CCO_2H–Cl_3CCO_2Na Buffer

[buffer], M	10^6k, s^{-1} (25 °C)	10^5k, s^{-1} (50 °C)
0.006	1.20	0.53
0.012	2.30	0.90
0.024	3.56	2.19
0.048	6.55	4.59
0.072	9.06	7.48
0.096	14.0	10.9
0.12	14.9	11.7

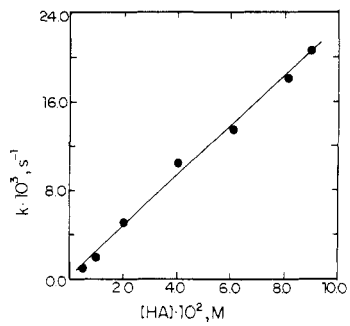


Figure 1. Plot of first-order rate constants for the TsOH-catalyzed addition of MeOH to **2** vs. [TsOH] at 50 °C (r = 0.998).

In addition, **2b** is obtained in 10–15% yield. The larger amounts are obtained at the higher temperature (50 °C). The latter product is inert under the reaction conditions and does not transform to any of the other products.

The kinetics of the addition reactions were determined in buffered solutions (buffer ratios 1:1). With buffers of tosyl alcohol (TsOH) and trichloroacetic (TCA) acid, reactions were performed at 25 and 50 °C. With the weaker acids, dichloroacetic (DCA), *p*-nitrobenzoic (pNB), and benzoic (Bz), the reactions were followed only at 50 °C. Due to the slowness of the reactions in the presence of the two benzoic acids, rate-constant determinations in these cases are based on the first 15% of the reaction. The reactions were found to be general acid catalyzed and the relevant data are given in Tables II–IV. An example of the linear dependence of the rate constants on the buffer concentration is given in Figure 1. A Bronsted plot of log k (50 °C) vs. the pK_a of the catalyzing acids gives a straight line (Figure 2, r = 0.9988) with α = 0.96.

Table IV. First-Order Rate Constants for the Acid-Catalyzed Methanolysis of 2 at 50 °C in the Presence of 1:1 Buffers of Cl_2HCCO_2H–Cl_2HCO_2Na, p-$O_2NC_6H_4CO_2H$–p-$O_2NC_6H_4CO_2Na$, and $C_6H_5CO_2H$–$C_6H_5CO_2Na$

acid	[buffer], M	10^7k, s^{-1}
Cl_2CHCO_2H	0.103	39.1
	0.206	76.5
	0.309	103.0
	0.515	185.5
	0.206[a]	161.0
p-$O_2NC_6H_4CO_2H$	0.076	0.67
	0.113	0.88
	0.189	1.57
	0.076[a]	1.26
$C_6H_5CO_2H$	0.152	0.105
	0.304	0.223
	0.455	0.316
	0.759	0.579
	0.304[a]	0.47

[a] In the presence of 0.6 M $NaClO_4$.

Table V. First-Order Rate Constants for the Acid-Catalyzed Methanolysis of 2 in the Presence of Variable Concentrations of $NaClO_4$

$[NaClO_4]$, M	10^3k, s^{-1} [a]	**2a**/**2a′** [a]	10^3k, s^{-1} [b]
0	3.71	~58	0.62
0.0012	3.83	40.4	
0.024	4.22	14.6	
0.06	4.31	10.35	0.72
0.12	5.16	7.32	0.92
0.24			1.16
0.36	8.2	3.91	1.35
0.48			1.68

[a] Reactions were performed in the presence of 0.1 M TsOH. [b] Reactions in the presence of 0.0238 M 1:1 TsOH–TsONa buffer.

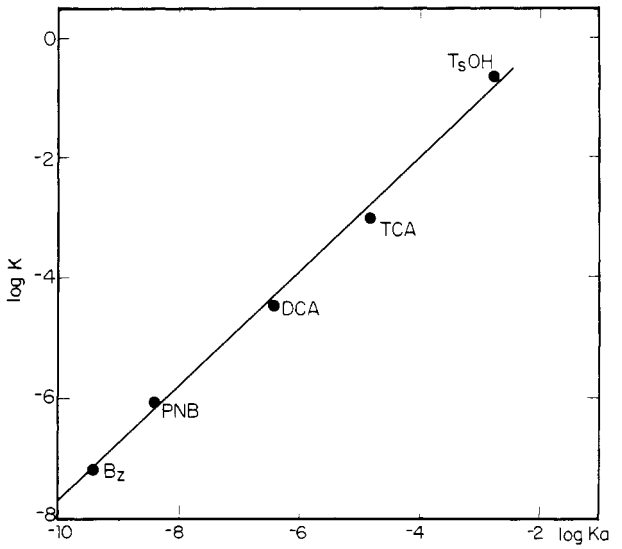


Figure 2. Brønsted-type plot for the acid-catalyzed methanolysis of **2** at 50 °C (r = 0.998).

Addition of NaBr induced the formation of **2c**, the amount of which is linearly dependent on the concentration of the salt.

The effect of added $NaClO_4$ on the kinetics and stereochemistry of the reaction was studied in the presence of TsOH and its buffer (Table V). The data shows that the rate constants increase linearly with the perchlorate concentration (see Figure 3 for the reactions in buffered medium). These results can be correlated by eq 6 with b = 3.5 ± 0.2.

$$k = k_0(1 + b[NaClO_4]) \quad (6)$$

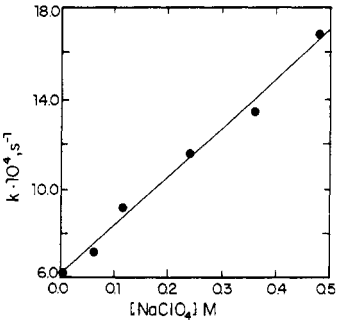


Figure 3. Effect of $[NaClO_4]$ on the rate constants for the methanolysis of **2** at 50 °C (r = 0.996).

Table VI. First-Order Rate Constants for the Acid-Catalyzed Methanolysis of 3 in the Presence of 1:1 TsOH–TsONa Buffer

[buffer], M	10^5k, s^{-1} (35 °C)	[buffer], M	10^5k, s^{-1} (50 °C)
0.111	1.12	0.117	7.37
0.223	1.97	0.234	10.8
0.334	2.76	0.350	14.7
0.446	3.41	0.467	18.1
0.111[a]	1.26	0.584	22.7
		0.117[a]	9.62

[a] In the presence of 0.36 M $NaClO_4$.

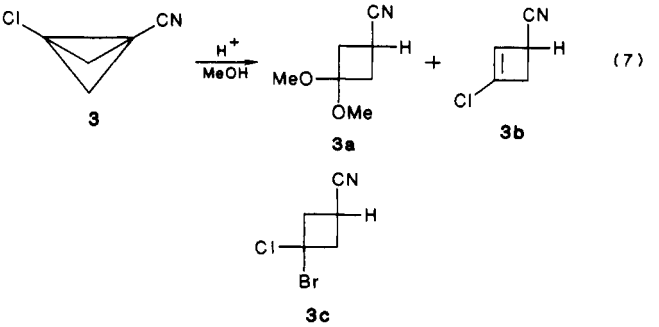
Table VII. Second-Order Rate Constants for the Acid-Catalyzed Methanolysis of 1, 2, and 3

substr	acid	pKa[a]	10^4k_{HA}, M^{-1} s^{-1} (25 °C)[b]	10^5k_{HA}, M^{-1} s^{-1} (50 °C)[b]
1	TsOH	2.75[c]	1.18[d]	55.8
2	TsOH	2.75[c]	240	22400
2	TCA	4.98[e]	1.26	106.0
2	DCA	6.41[e]		3.52
2	pNB	8.35[f]		0.0813
2	Bz	9.42[f]		0.0078
3	TsOH	2.75[c]	0.686[d]	32.5

[a] At 25 °C. [b] Obtained from the slope of k vs. [buffer]. The standard deviation of the slope does not exceed 5%. [c] Perrin, D. D.; Dempsy, B. *Buffers for pH and Metal Ion Control*; Chapman and Hall: London 1979. [d] At 35 °C. [e] Ritchie, C. D.; Virtanen, P. O. I. *J. Am. Chem. Soc.* **1972**, *94*, 1589. [f] Elliott, J. H.; Kilpatrick, M. *J. Phys. Chem.* **1941**, *45*, 454.

The added perchlorate has an immense effect on the stereochemistry of the reaction as well. Its presence gives rise to the formation of large quantities of the trans addition product **2a′** (Table V). The overall rate constant for the disappearance of **2** can be disected into the individual rate constants for the formation of **2a** and **2a′**. Implementing the two sets of data into eq 6 gives b values of 1.5 and 30 for the formation of **2a** and **2a′**, respectively.

Reactions of 3. In the reaction catalyzed by TsOH, the major product is the ketal **3a** which is accompanied by small quantities of **3b** (eq 7). In the presence of NaBr,



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3c (stereochemistry not known) is also obtained in quantities dependent on the NaBr concentration. The kinetics

Table VIII. Activation Parameters for the General Acid Catalyzed Methanolysis for 1, 2, and 3

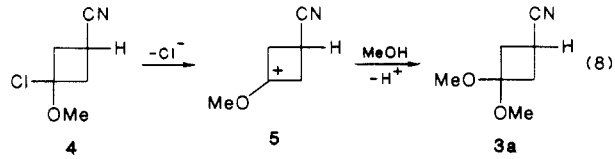
substr	acid	$\Delta H^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$, eu	$\Delta F^{\ddagger}$(25 °C), kcal/mol
1	TsOH	19	−14	24
2	TsOH	16	−12	20
2	TCA	15	−25	23
3	TsOH	19	−15	24

of the reactions were followed in a buffered solution at 35 and 50 °C. The results are given in Table VI.

General. The second-order rate constants for the three substrates are given in Table VII. Rate constants for their reactions with $MeOH_2^+$ (k_H) were obtained from the intercepts of plots of k vs. the buffer concentration and are of low accuracy. For substrates 1 and 3, k_H (35 °C) is ca. 0.002 M^{-1} s^{-1} and at 50 °C it is around 0.02 M^{-1} s^{-1}. For 2, k_H was determined in several experiments with different acids and its value is therefore more reliable. It is 0.07 ± 0.01 and 0.15 ± 0.25 M^{-1} s^{-1} at 25 and 50 °C, respectively. The activation parameters are given in Table VIII. In the presence of 0.3 M NaBr the ratios of HBr to MeOH addition products are 0.33, 0.09, and 0.13 for 1, 2, and 3, respectively. The ρ^+ value for the reactions with TsOH is −7.1 ± 1.3 at 50 °C.

Discussion

Stereochemistry and Salt Effect. NMR analysis of the addition reaction products clearly confirms previous notions that acid-catalyzed addition of water[6a] and alcohols[3a,6b,c,10] to bicyclobutanes are largely syn stereoselective. In the case of the chloro derivative 3, the stereochemistry of the primary addition product cannot be recognized due to consecutive steps as shown in eq 8. In this series of



4 5 3a (8)

steps, the α-halo ether moiety in 4 undergoes as expected a very fast solvolysis to give the oxocarbonium 5. The latter traps another solvent molecule, yielding the final ketal 3a. These two steps are in fact also common to the previously reported formation of the ionic bicyclobutane.[11,12]

It is interesting to examine the effect of the added salts on the course of the reactions. The addition of up to 0.3 M of NaBr, depending on the substrate, leads to the formation of up to 33% of the corresponding bromide with a syn (Br–H) stereochemistry. However, the presence of this salt has no effect on the reaction rate. This clearly indicates that the reaction is stepwise rather than concerted and that the incorporation of the nucleophile occurs in a post-rate-determining step. The contrasting behavior of the reactions in the presence of $NaClO_4$ is noteworthy. In this case, reaction rate constants are significantly increased (see Table V) and the stereochemistry is drastically altered to give relatively large proportions of the trans addition product 2a′. Addition of a salt to a reaction medium may enhance reactions in which charges are formed at the transition state. In the present case, the cation of the salt can interact with the acid function, stabilizing this way the incipient negative charge. Alternatively, the anion of the salt can stabilize the developing positive charge on C3. The pronounced effect of the perchlorate ion on the stereochemistry of the reaction (see Table V) clearly indicates that the second interaction mechanism is the operative one in this case. The initially formed cation is most probably trapped by the perchlorate anion from the equatorial direction, namely, cis to the entering proton similar to other nucleophiles. The intermediate formed, be it an ion pair or a covalent compound, undergoes a second nucleophilic attack by a methanol molecule with a second inversion of configuration on C3, giving largely the trans addition product 2a′. The oriented interaction of the perchlorate anion with the substrate is largely supported by the differential effect it has on the b factor in eq 6 (1.5 for the formation of 2a as opposed to 30 for the formation of 2a′).

The differences in the interaction mechanism of anions such as Br and ClO_4^- with various substrates has long been recognized. This is exhibited for example by the inability of Br^-, as opposed to the perchlorate anion, to denature proteins.[13] Another example is the micellar deamination of 2-aminooctane. In the presence of small ions such as Cl^- or Br^-, no stereochemical changes were seen. Large anions such as perchlorate and fluoroborate were required for stereochemical control.[14] It is generally believed that the difference in the behavior between the two anions stems from the large difference in their solvation requirements. Thus, the relatively small and therefore highly solvated bromide anion is less reactive since it has to undergo an energetically unfavored desolvation process before it can interact with the reaction center. On the other hand, the poorly solvated large perchlorate anion can much more efficiently interact with it at a small energy cost.[15]

Acid Catalysis. The linear correlation of the first-order rate constants for the three substrates with the buffer concentrations at a constant pH show that the methanolyses of bicyclobutanes 1–3 are general acid catalyzed reactions. In other words, the transfer of the proton from the acid to the substrate is rate-determining. This in fact is not entirely unexpected since this mechanism is typical also of the two highly related systems, olefins[16] and substituted cyclopropanes.[17-19] Yet exceptions are known in the chemistry of both systems. Kresge[20] has recently shown that some olefins undergo specific acid-catalyzed reactions. Results obtained for the electrophilic cleavage of unsubstituted cyclopropane indicate that proton transfer is only partly rate-determining.[17,21]

In general, a high value of α (>0.8) is believed to be unreliable due to the masking effect of the H^+ reaction.[22] Using the pK_a of methoxonium ion (−1.43) in combination with the observed Bronsted correlation ($\log k = 1.88 + 0.96 \log K_a$) results in a value of 1800 M^{-1} s^{-1} for the reaction rate constant of $MeOH_2^+$ with 2. The fact that the observed rate constant (0.15 M^{-1} s^{-1}) is significantly lower

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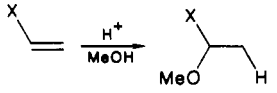
than the calculated value permits the reliable determination of the Bronsted coefficient α.

The magnitude of α can be used to estimate the degree of proton transfer at the transition state.[23] The value of 0.96 indicates that at the transition state, the proton is almost completely transferred from the acid to the substrate.

Substituent Effect. An additional criterion for determining the location of the transition state on the reaction coordinate is provided by the effect of the substituents at position 3. Unfortunately, for experimental reasons, the range of substituents at this position is limited. One cannot employ substituents of large electron-withdrawing power since the reactions are likely to be too slow to enable convenient rate determination. On the other hand, electron-releasing substituents such as amines and alkoxides are not available as bridgehead substituents in stable bicyclobutanes.[2] Therefore, measurements could be performed with substituents covering the middle range of the σ^+ scale only.

In order to estimate the amount of charge developed on C3 at the transition state, one would like to compare the observed ρ^+ value to that corresponding to a full charge unit. In the absence of data for equilibrium reactions in which a unit positive charge interacts with substituents directly bound to the carbon bearing the charge (in the absence of any other substituents which can stabilize that positive charge, e.g., Ph), one has to turn to kinetic data. Probably the most relevant example for this is the acid-catalyzed addition of MeOH to a series of olefins (eq 9).



(9)

The ρ^+ value reported by Tidwell and co-workers[24] for this reaction is −12.3. Being much larger than the value reported here for the same reaction in the bicyclobutane system, it suggests that at the transition state of the present reaction, the charge on C3 is only partly developed. Thus, as can be judged from the Bronsted α value and the ρ^+ value, the transition state of the reactions at hand is highly unbalanced.[25,26] While the proton is almost completely transferred to C1 at the transition state, its charge is only partly transferred to C3. We will return to this point in the discussion regarding the structure of the intermediate.

Nature of the Intermediate and the Nucleophilic Step. The absence of any contribution of the bromide concentration to the overall reaction rate shows that nucleophilic attack by Br^- (and also by MeOH which is even a weaker nucleophile) is not coupled with the proton transfer at the rate-determining step. Therefore, in order to enable the observed syn stereospecificity, the cation must be in a bent geometry, thereby allowing the nucleophile to approach from the preferred equatorial direction. A highly puckered cation in which there is a short separation and therefore a large interaction between C1 and C3 was first realized by semiempirical calculations.[27,28] This cation was invoked in order to explain the large rate differences (10^6–10^8) observed[29] in the solvolyses of the tosylates **6** and **7**. The results of later calculations reported in the literature can be divided into three different categories. The first group includes calculations supporting the highly puckered structure with a short (ca. 1.7 Å) C1–C3 separation.[10b,30,31] To the second group belong calculations[32,33] in which minimum in energy was found only for a nearly planar structure with a long C1–C3 distance (ca. 2.1 Å). The last group consists of the work of Hehre et al.[34] claiming that the observed minimum for the bent cation is in fact a saddel point rather than a minimum. In other words, this is an illusive minimum resulting from the imposed constraint of a C_s symmetry in the calculations. However, in a perpendicular direction, it is the transition state for the conversion of the cyclobutyl into the cyclopropylcarbinyl cation. Since this report focuses on reactions where no such rearrangement takes place, this third possibility will not be considered here. In order to decide between the two former alternatives, namely, the highly puckered or the nearly planar cyclobutyl cations, we have scanned the potential surface in a cross section along the C_s symmetry plane of the cation (Scheme II) in the range of β from 115° to 175° using the 3-21G basis set.[35]

Scheme II

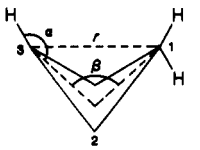
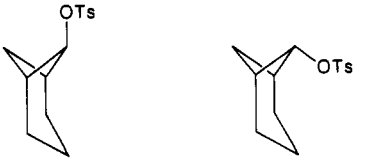


Table IX. Total Energies and Geometrical Parameters of Protonated Bicyclobutane as a Function of Variations in β° [a]

β°	α°	r_{C1-C3}, Å	r_{C1-C2}, Å	r_{C2-C3}, Å	E, au
175	178.8	2.148	1.485	1.578	−154.33529
166.92	176.9	2.140	1.485	1.581	−154.33542
					−155.20833[b]
165	176.1	2.136	1.484	1.582	−154.33541
155	171.6	2.106	1.483	1.591	−154.33499
150	167.7	2.078	1.480	1.600	−154.33462
145	161.3	2.032	1.474	1.614	−154.33452
140	151.4	1.949	1.460	1.636	−154.33545
135	147.3	1.884	1.451	1.652	−154.33733
130	147.2	1.840	1.444	1.664	−154.33904
125	148.5	1.802	1.439	1.676	−154.34014
120.17	150.5	1.770	1.434	1.687	−154.34047
					−155.22382[b]
120	150.9	1.768	1.433	1.689	−154.34047
115	153.7	1.736	1.429	1.703	−154.33990

[a] Calculations were performed with a 3-21G basis set. [b] 6-31G* calculation on the 3-21G optimized geometry.



6 **7**

(23) This interpretation of α was criticized in cases where the variable acids were highly delocalized carbon acids. To the best of our knowledge, this interpretation was never challenged for a case where the proton was transfered from a series of normal acids to a common substrate.

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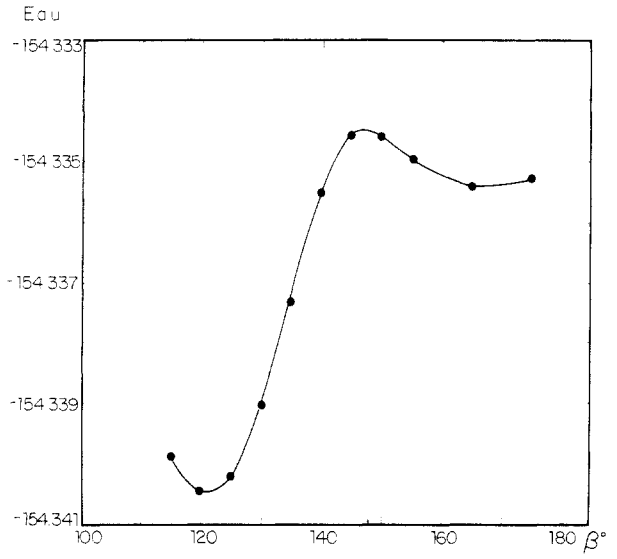

Figure 4. Energy of protonated bicyclobutane as a function of the puckering angle β.

For each of the β values in this range (Table IX), the structure of the cation was fully optimized. Our calculations support both the first as well as the second aforementioned theoretical predictions as we found two minima along this coordinate. The structures at these points was reoptimized with respect to all the parameters including β. The first minimum belongs to the highly puckered cation with β = 120.17° and r = 1.770 Å, while the second minimum has a nearly planar structure (β = 166.92° and r = 2.14A, Figure 4). The main geometrical parameters and the energies of these structures are given in Table IX.

The formation of the cis addition product can be explained as suggested by a nucleophilic attack on the bent cation from the equatorial direction. Flattening of the puckered cation to the nearly planar geometry will permit trans addition either by a direct nucleophilic attack on this cation or on the cation formed by a flip of the ring. The latter process is likely to be of a relatively small activation energy since the reacting species is already in a nearly planar geometry.

In order to obtain a high stereospecificity, the bent cation must have a relatively long lifetime so that the nucleophilic reactions will be able to compete successfully with planarization or inversion of the cation. The selectivity in the nucleophilic step as evidenced by the bromide to methanol incorporation ratio clearly indicates that this step is not diffusion-controlled. Therefore, the barrier for the ring flattening process must be larger than 3 kcal/mol. Since the 3-21G basis set calculations are not expected to furnish reliable energy data for strained systems, we have recalculated the energies of the two 3-21G minima at the recommended[36,37] 6-31G* level.[38] According to these calculations, the energy differences between the two minima is 9.5 kcal/mol, which is more in line with the mechanistic explanation we have suggested above to the high stereospecificity observed.

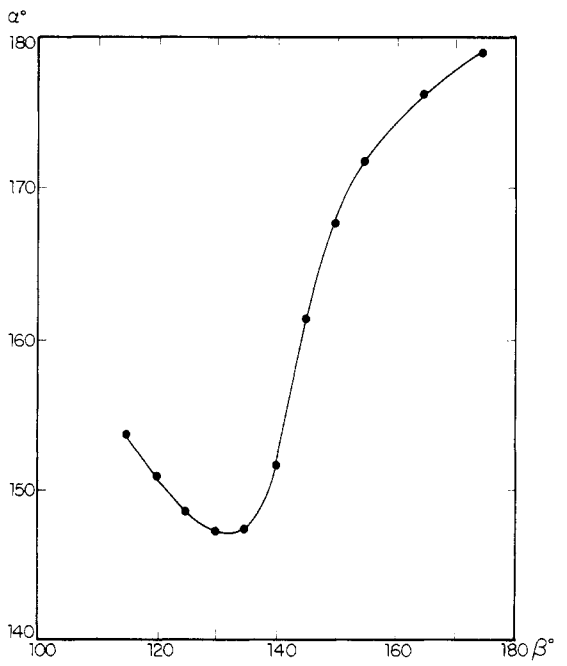

Figure 5. Variations in α as a function of the puckering angle β.

It is interesting to note the absence of synchronousness between the motion of the hydrogen on C3 and the expansion of β. As β increases this hydrogen moves first in and then around β = 135°, it starts moving rapidly out (Figure 5). This phenomenon was noticed experimentally as well as theoretically by several groups[39-44] for bicyclobutane and some of its derivatives. To the best of our knowledge, this is the first time that such a nonsynchronousness has been observed for the cation of bicyclobutane. The motions of this bridgehead hydrogen are probably governed by two factors, namely, the "directionality" of the vacant orbital toward C1 and its "size" in the bonding zone. An inward motion of the hydrogen improves the "directionality" of the vacant orbital but at the expense of "squeezing" it out toward the equatorial side. At short distances, "directionality" seems to be the important factor. However, in the nearly planar structure where the cross ring interaction ceases to exist, an sp_2 geometry purterbed somewhat as a result of the inner ring angle is favored.[45]

At this stage, on the basis of the experimental and computational results the following conclusions can be derived. In the case of a highly reactive nucleophile—with reactivity higher or similar to that of perchlorate ion but with capability to form a stable bond with the substrate—the syn addition mode results from a concerted approach of the proton donor and the nucleophile from the equatorial directions. In the case of less reactive nucleophile, the reaction takes place in two stages with protonation being the first and rate-determining step. In the second step, the incorporation of the nucleophile has

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(45) Inverting the geometry around C3 (α = 209.5°) while maintaining the conformation of the first minimum, raises the energy by 48 kcal/mol for the first case. On the other hand, using the geometry of the second minimum with an α of 183.1° (inversion around C3) raises the energy by only by 0.5 kcal/mol which is in line with the suggested explanation.

to compete effectively with the flattening of the initially formed bent cation in order to maintain the syn stereospecificity. The 6-31G* calculations (Table IX) show that the bent cation has indeed a sufficient lifetime to undergo nucleophilic attack prior to other conformational changes.

The short C1–C3 distance points to an intensive interaction between these two carbon atoms.[46] This interaction which was realized by theoretical calculations has been previously utilized to explain experimental results such as the rates of solvolysis of the tosylates **6** and **7** (see above) and has further utilized in the present paper to rationalize the syn stereospecificity in electrophilic addition reactions. However, this interaction has never been experimentally verified. We believe that the imbalance transition state which has been discussed earlier provides the first experimental support to this theoretical prediction. The large Bronsted α value observed (0.96) shows that at the transition state, the proton has in fact been completely transferred from the acid to the substrate. In the absence of any cross ring interaction, one would expect that the positive charge will be largely transferred to C3. Yet the ρ^+ value (even after adding to it the error margin) suggests that the charge is only partly transferred to this carbon. This is in agreement with the previous suggestions[10b,27,28,30,31] that in the puckered structure there is some bonding between C1 and C3 which renders C1 a nonclassical pentacovalent carbon and reduces the positive charge on C3.

Experimental Section

General Methods. ^{1}H NMR spectra (in $CDCl_3$) were recorded on a Varian EM 360A(60MH) or a Bruker AM-300 (300MH) spectrometer. 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 separation, a Varian 920 gas chromatograph (TC detector) was employed. In both cases, the column was 5–15% Xe60 on Chromosorb W.

Solvents and Starting Materials. Methanol (Frutarom analytical) was dried by the magnesium method.[47] **Bicyclobutanecarbonitrile** (**1**) was prepared according to a published procedure.[48] The literature procedure[6a] for the synthesis of **3-methylbicyclobutanecarbonitrile** (**2**) involves addition of HI to 3-methylenecyclobutanecarbonitrile followed by 1,3-elimination of HI using NaH in ether. We found that the yields and reaction times can be improved by replacing HI by HBr and inducing the elimination reaction by *t*-BuOK–*t*-BuOH. Thus the following procedure was employed. A mixture of 10 g (0.13 mol) of 3-methylenecyclobutanecarbonitrile and 30 g of 48% HBr was vigorously stirred at room temperature for 24 h. This was followed by treatment with water and ether, phase separation, and washing the aqueous layer with ether. The combined ethereal solution was first washed with a 10% $NaHCO_3$ and then with a saturated salt solution. After drying over magnesium sulfate and evaporation of the ether, 18 g (90% yield) of the HBr adduct are obtained as a yellow liquid. To a solution of 9.2 g of this liquid in 25 mL of *t*-BuOH was added a solution of 6.5 g (0.058 mol) of *t*-BuOK in 25 mL of *t*-BuOH dropwise. The reaction was followed by GC and when completed was washed by water and ether. Evaporation of the ethereal phase gave 4.5 g (91% yield) of **2**. Its purification to 99% was achieved by preparative gas chromatography.

3-Chlorobicyclobutanecarbonitrile (**3**) was prepared according to a published procedure.[48] All three substrates were purified by preparative gas chromatography to at least 99% purity and stored at −70 °C. All the acids employed in this study were of analytical grade and were used without further purification.

Preparation of Products. 3-Methoxycyclobutanecarbonitrile (1a) and 1-Cyano-2-(methoxymethyl)cyclopropane (1b). To a solution of 1.9 g (0.01 mol) of TsOH in 10 mL of MeOH were injected 200 μL of **1**, and the solution was stirred at room temperature for 24 h. GC analysis showed that **1** was converted (95%) to **1a** and **1b** in a 5:4 ratio, respectively. The reaction mixture was treated with ether and a 10% aqueous solution of sodium bicarbonate. After phase separation and evaporation of the solvent, the two products were separated by preparative gas chromatography. The product **1a** is a known compound.[48] Basic isomerization of **1a** in MeOH–MeONa gave a mixture of the two isomers from which the trans (H, MeO) isomer **1a′** was isolated by preparative GC: ^{1}H NMR δ 2.2–2.8 (m, 5 H), 3.21 (s, 3 H), 3.7–4.0 (m, 1 H); ^{1}H NMR of **1b**: δ 3.32 (m, 5 H), 0.9–2 (m, 4 H); MS(CI), *m/z* 112, 82, 80. Satisfactory C, H, N analyses were obtained.

3-Bromocyclobutanecarbonitrile (1c). This compound was isolated by preparative gas chromatography from the reaction of **1** with TsOH in MeOH (see preparation of **1a**) in the presence of NaBr (0.6 M solution): ^{1}H NMR δ 2.4–3.7 (m, 5 H), 4.3–4.9 (m, 1 H); MS(CI), *m/z* 162, 160, 82, 80. Satisfactory C, H, N analyses were obtained.

3-Methoxy-3-methylcyclobutanecarbonitrile (2a and 2a′). To a 0.1 M solution of TsOH in methanol was added 0.5 g (5.4 mM) of **2** at room temperature. The reaction was followed by GC. After completion, the reaction mixture was treated with water and ether. The organic layer was washed with a 10% $NaHCO_3$ solution, dried over magnesium sulfate, and evaporated. The residue (0.65 g) contained 83% **2a**: ^{1}H NMR δ 3.14 (s, 3 H), 1.45 (s, 3 H), 2.25–2.9 (m, 5 H); MS, *m/z* 126, 99, 94, 72. Satisfactory C, H, N analyses were obtained. **2a′** was obtained in 2% yield: ^{1}H NMR δ 3.16 (s, 3 H), 1.35 (s, 3 H), 2.2–2.8 (m, 4 H); MS, *m/z* 126, 99, 94, 72. Satisfactory C, H, N analyses were obtained. **2b**[6a] was obtained in 15% yield. Products were separated by preparative gas chromatography. The trans (H, MeO) isomer (**2a′**) which in this reaction was obtained in a minute amount was obtained in larger quantities by isomerization of **2a** in MeOH–MeONa solution in a manner similar to the preparation of **1a′** described above.

3,3-Dimethoxycyclobutanecarbonitrile (3a), 1-chloro-3-cyanobutene (3b), and 3-bromo-3-chlorocyclobutanecarbonitrile (3c) were obtained in the reaction of 0.25 g (2.2 mM) of **3** in a 0.25 M solution of TsOH in MeOH containing NaBr (0.6M solution). The products were obtained in 75, 10, and 15% yields, respectively, and separated by preparative gas chromatography. **3a** is a known compound;[11] **3b**: ^{1}H NMR δ 3.05–3.25 (m, 2 H), 3.52–3.58 (m, 1 H), 5.92 (m, 1 H); MS, *m/z* 116, 114, 87, 78. The compound is unstable and develops a yellow color upon standing at room temperature. The stereochemistry of **3c** is not known; its ^{1}H NMR spectrum consists of a multiplet at δ 3.05–3.75. MS: *m/z* 198, 197, 196, 194, 161, 160, 159, 158, 117, 116, 115, 114, 113.

Kinetic Procedure. Buffer solutions were prepared by titrating acid solutions with a precalibrated solution of MeONa in MeOH. The solutions to which NaBr or $NaClO_4$ were added when needed were preincubated in a thermostated bath. after reaching the desired temperature (25, 35, or 50 °C) the substrate was introduced by microsyringe. Samples (0.1 mL) were periodically removed and quenched with a 10% $NaHCO_3$ solution.

(46) This interaction was originally interpreted by Wiberg (ref 10a) as a transfer of charge from the back lobe of the C1–H bond to the vacant orbital on C3. In order not to clutter the paper we continue the use of the term 1,3 interaction; however, we prefer to interpret this term in a broader sense so that it will include C–C hyperconjugation as well. Such an interaction is evidenced by the observed elongation of the C1–C2 and C1–C4 bonds.

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(49) The stereochemical assignment of **1a** and **1a′** is based on the ^{1}H NMR spectra and the relative stability of the two isomers[50] (the isomer with the two bulky groups syn (diequatorial) to each other is more stable). In the ^{1}H NMR spectrum, the field effect of the CN group induces a larger downfield shift on the group at C3 when located syn to the CN group than when anti. This effect is largest for an H bonded directly to C3 and is gradually reduced upon going to Me and further to MeO. This last point is nicely exemplified in the behavior of **2a** and **2a′** where the chemical shifts of the Me and the OMe groups move in opposite directions. Thus, going from **2a** to **2a′**, the Me peak is shifted upfield (from δ 1.45 to 1.35) whereas the OMe peak moves downfield by a smaller increment (from δ 3.14 to 3.16). In addition, we have recently studied the reactions of the same series of substrates with Br_2 in MeOH. Some of the products in these reactions are solid and their X-ray analyses unambiguously support our conclusion that electrophilic additions to bicyclobutane are syn stereospecific.

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The reactions were followed by analytical GC using biphenyl as an internal standard.

Registry No. 1, 16955-35-4; **1a**, 30628-83-2; **1a'**, 30628-82-1; **16**, 104575-05-5; **1c**, 104575-06-6; **2**, 694-25-7; **2a**, 4839-76-3; **2a'**, 4839-75-2; **2b**, 15760-35-7; **3**, 23745-75-7; **3a**, 87712-21-8; **3b**, 104598-35-8; **3c**, 104575-07-7; T_5OH, 104-15-4; Cl_3CCO_2H, 76-03-9; Cl_2CHCO_2H, 79-43-6; p-$O_2NC_6H_4CO_2H$, 62-23-7; $C_6H_5CO_2H$, 65-85-0; 3-bromo-3-methylcyclobutanecarbonitrile, 104575-04-4; protonated bicyclobutane, 20671-12-9.

Substituent Effects on Intramolecular Selectivity and Free Energy Relationships in Anodic and Metal Ion Oxidations of 5-X-1,2,3-trimethylbenzenes

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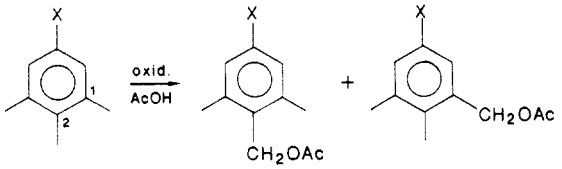
Side-chain oxidations, promoted electrochemically or chemically, by cerium(IV) ammonium nitrate (CAN) or cobalt(III) acetate, of 5-substituted-1,2,3-trimethylbenzenes have been investigated, and the relative reactivity of the 2- and 1-methyl group (k_2/k_1) has been determined. In CAN-promoted and electrochemical reactions, very similar substituent effects on the k_2/k_1 ratio are observed and a strictly linear relationship, extending to electron-withdrawing substituents such as the CO_2Me group, exists between the log k_2/k_1 values of the two processes, which should therefore occur by the same mechanism, i.e., with the formation of an alkylaromatic radical cation which is then deprotonated to benzyl radicals in the selectivity determining step. With +R substituents large k_2/k_1 ratios are observed, which indicates that in the deprotonation of the radical cation the effect of the substituent on the rate exceeds that on the equilibrium, a situation which closely resembles the "nitroalkane anomaly". A plot of log k_2/k_1 vs. $\sigma^+_p - \sigma_m$ values of substituent is also linear. In reactions of $Co(OAc)_3$ k_2/k_1 values are much less sensitive to the nature of the substituents than in the above reactions and are very close to those which, for comparison purpose, have been determined for the side-chain bromination of the same substrates by *N*-bromosuccinimide (NBS). The only exception is the result for 5-methoxyhemimellitene which with $Co(OAc)_3$ exhibits a k_2/k_1 ratio much larger than that with NBS and comparable to those determined in the anodic and CAN-promoted oxidations. It is suggested that the presence of the methoxy group induces an electron-transfer mechanism also in the reaction of $Co(OAc)_3$.

In a recent paper some of us have determined the intramolecular selectivity of the side-chain acetoxylation of hemimellitene, isodurene, and 5-*tert*-butylhemimellitene (eq 1, X = H, Me, *t*-Bu) promoted either anodically or by one-electron oxidants such as cerium(IV) ammonium nitrate (CAN) and $Co(OAc)_3$.[2]



(1)

Results of interest with respect to the reaction mechanism have been obtained. Thus, the observation that the effect of the nature of X on the relative reactivity of the 2- and 1-methyl group (k_2/k_1) was very similar for electrochemical and CAN-promoted reactions was considered to support the hypothesis that CAN reactions occur by a one electron transfer mechanism (eq 2–4) equivalent to the ECE mechanism of organic electrochemistry.[3]

$$ArCH_3 + Ce^{IV} \rightleftharpoons ArCH_3^{+\bullet} + Ce^{III} \quad (2)$$

$$ArCH_3^{+\bullet} \rightarrow ArCH_2^{\bullet} + H^+ \quad (3)$$

$$ArCH_2^{\bullet} + Ce^{IV} \rightarrow \text{products} + Ce^{III} \quad (4)$$

Conversely, the finding that the selectivity of $Co(OAc)_3$-promoted reactions was much lower than that of anodic oxidations led us to suggest that an electron-transfer mechanism might not hold for the reactions of this complex. Interestingly, this suggestion was fully supported by later work.[4]

We felt it worthwhile to expand the study of the intramolecular selectivity of reaction 1 by investigating additional substituents X for the following two reasons:

First, in the previous investigation only two and very similar (Me and *t*-Bu) substituents were considered. It is therefore of interest to check whether the observed correlation between the selectivity of anodic and CAN-promoted oxidations extend also to substituents which span a much larger range of electronic effects. A breakdown in such a correlation might be indicative of a change in the reaction mechanism induced by a change of the substituent.

Second, in side-chain oxidations which take place by an electron-transfer mechanism, intramolecular selectivity is

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