

agreement with the *exo/endo* distribution of 4 at 100° for 2-norbornanol⁶ (8 at 25°, extrapolated from data at 100 and 116°), and 5 at 50°⁷ (estimated as 5.6 at 25°) for 2-methylnorbornane.

Let us consider possible explanations for the high *exo/endo* rate ratios in tertiary norbornyl derivatives in the light of the present results.

(1) The high tertiary *exo/endo* ratios are due to differences in ground-state energies.^{2,8} Since the present data reveal that the *exo* and *endo* tertiary isomers start at the same ground-state energy,⁹ this possibility is no longer tenable.

(2) The *exo* and *endo* tertiary ground states are comparable in energy, but both are quite strained. This strain is relieved more effectively by departure of an *exo* leaving group, rather than an *endo*. This possibility is refuted by the present observation that the secondary derivative, 1-methyl-2-norbornanol, which should be an essentially strain-free material as far as the substituent groups are concerned, is only slightly more stable than either of the tertiary isomers.

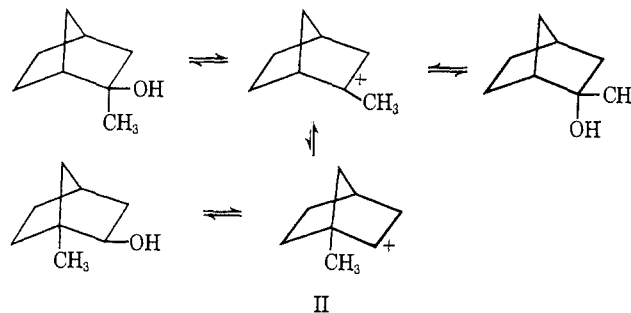
(3) The high *exo/endo* rate ratios in the tertiary norbornyl derivatives are due to participation in the *exo* isomer. This seems unlikely even to nonclassical supporters,⁸ and is rendered highly questionable both by the earlier failure to observe any significant effect of a 1-methyl substituent in the tertiary derivatives¹¹ and by the excellent correlation of the substituted 2-arylnorbornyl derivatives with the σ^+ constants.¹²

(4) The high *exo/endo* rate ratios in these tertiary derivatives are due to steric hindrance to *endo* ionization. Unless we wish to have recourse to some new explanation or some new effect not yet available, this would appear to be the sole remaining possibility.

In the acid-catalyzed treatment of 2-methyl-*exo*-norbornanol, the carbonium ion intermediate must be formed and reconverted back to the *exo* tertiary alcohol many times before the ion is finally captured by the solvent molecules to form the less reactive *endo* tertiary or *exo* secondary alcohols.⁴ Nonclassical σ bridging was postulated in the norbornyl cation primarily to account for its remarkable retention of *exo* stereochemistry.^{13,14} Consequently, it appears difficult to rationalize the more rapid substitution of the solvent at the *endo* tertiary position in terms of a σ -bridged structure for the intermediate (I).¹⁵

On the other hand, the transformations are readily rationalized in terms of a classical 2-methylnorbornyl

cation in mobile equilibrium with a small concentration of the less stable secondary 1-methylnorbornyl cation (II).



Secondary and tertiary norbornyl derivatives exhibit a remarkable similarity in their behavior, including their rates relative to an external standard, their *exo/endo* rate ratios, and their preference for *exo* substitution.¹⁶ The present results establish that the ground-state energies for the *exo* and *endo* tertiary isomers examined are quite similar and render untenable explanations based on an assumed or estimated higher ground-state energy for the tertiary *exo*-norbornyl derivatives.^{2,8}

(16) For a summary of the data, with references, see H. C. Brown, *Chem. Brit.*, 199 (1966).

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Solvolysis of Substituted 2-Aryl-*exo*-norbornyl Chlorides. Application of the Hammett Correlation as a Test for σ Participation in the Norbornyl System

Sir:

We wish to report that the rates of solvolysis of substituted 1-arylcyclopentyl and 2-aryl-*exo*-norbornyl chlorides both yield excellent linear plots *vs.* the σ^+ constants. Consequently, there is no evidence for significant participation by the 1,6-electron pair of the norbornyl system over a range of reactivity of the carbonium ion center of 10⁷.

The Goering-Schewene diagram¹ makes it clear that the factor responsible for the difference in energy between the *exo* and *endo* transition states must likewise be responsible for the stereoselectivity resulting in the almost exclusive formation of *exo* product. This factor might be (1) stabilization of the *exo* transition state by bridging, (2) destabilization of the *endo* transition state by steric strain, (3) a combination of (1) and (2), or (4) some new phenomenon not yet recognized in theory.^{2,3}

The heart of the norbornyl problem appears to involve either the demonstration of nonclassical resonance stabilization of the *exo* transition state or the demon-

(1) H. L. Goering and C. B. Schewene, *J. Am. Chem. Soc.*, **87**, 3516 (1965).

(2) For an excellent discussion of the implications of the Goering-Schewene diagram, see B. Capon, M. J. Perkins, and C. W. Rees, "Organic Reaction Mechanisms," 1965, Interscience Publishers, Inc., New York, N. Y., 1966, Chapter I.

(3) H. C. Brown, *Chem. Brit.*, 199 (1966).

(6) F. Wilcox, Jr., M. Sexton, and M. F. Wilcox, *J. Org. Chem.*, **28**, 1079 (1963).

(7) N. A. Belikova, A. F. Platé, and K. E. Sterin, *Zh. Obshch. Khim.*, **34**, 126 (1964).

(8) G. D. Sargent, *Quart. Rev. (London)*, **20**, 301 (1966).

(9) We are assuming that the steric requirements of the acyloxy and hydroxy groups are very similar in this system. This is supported by the similarity in the results for the equilibration of 2-norbornyl acetate¹⁰ with those for 2-norbornanol.⁶

(10) H. L. Goering and C. B. Schewene, *J. Am. Chem. Soc.*, **87**, 3516 (1965).

(11) H. C. Brown and M.-H. Rei, *ibid.*, **86**, 5004 (1964).

(12) H. C. Brown and K. Takeuchi, *ibid.*, **88**, 5337 (1966).

(13) T. P. Nevell, E. de Salas, and C. L. Wilson, *J. Chem. Soc.*, 1188 (1939).

(14) J. A. Berson in "Molecular Rearrangements," Part I, P. de Mayo, Ed., Interscience Publishers, Inc., New York, N. Y., 1963, p 130.

(15) The present phenomena are remarkably similar to the transformations observed by Cristol and his co-workers [*J. Am. Chem. Soc.*, **87**, 2870, 2879 (1965)] in the dibenzobicyclic [2.2.2]- and [3.2.1]octadienyl cations which led them to conclude that they were dealing with classical intermediates. See also J. Paasivirta, *Ann.*, **686**, 1 (1965).

stration of steric hindrance of ionization, adequate to account for the observed difference in energy of the two transition states.

Ideally, it should be possible to utilize the Foote-Schleyer correlation⁴ to calculate the rate for the presumed "normal" case, *endo*-norbornyl tosylate. Then the faster rate for the *exo* isomer must be the result of σ participation and the problem would be resolved. The Schleyer correlation utilizes the infrared carbonyl frequency as an estimate of bond angle and includes corrective terms for torsional effects, inductive effects, and differences in steric nonbonded strains involving the leaving group in the ground and transition states (GS-TS). In principle this last term should be capable of handling both steric assistance to ionization (GS > TS) and steric hindrance to ionization (GS < TS). However, in actual fact, in the six model compounds used to fix the correlation line and in all of the published examples, including *endo*-norbornyl tosylate, the latter term, TS, was always assumed to be negligible. We now have a number of cases where the assumption that TS \approx 0 fails to hold.⁵ Consequently, until it is possible to verify the validity of this assumption in the model compounds and in *endo*-norbornyl derivatives, it would be dangerous to rely on the correlation to provide a definitive answer to the factor or factors responsible for the high *exo/endo* rate ratios in the solvolysis of norbornyl derivatives.

Alternatively, we might utilize the well-tried tool of the organic chemist, the introduction of substituents at appropriate positions, to test for the presence of nonclassical resonance energy in the *exo* transition state, with accompanying charge delocalization from the 2 to the 1 and 6 positions. However, all such attempts have yielded negative answers in norbornyl derivatives which undergo solvolysis without rearrangement to more stable structures.³

Previous studies have also indicated the essential absence of participation in comparing the rates of solvolysis of norbornyl, 2-methylnorbornyl, and 2-phenylnorbornyl derivatives.⁶ However, it has been argued that the results are not conclusive because of a possible fortuitous cancelation of increasing steric assistance with decreasing participation.⁷

The Hammett approach provides a well-tested technique for varying the electron demand of an electron-deficient center over a tremendous range while maintaining the steric requirements constant. Consequently, we undertook to prepare 2-aryl-2-propyl, 1-aryl-1-cyclopentyl, and 2-aryl-*exo*-norbornyl chlorides, with *p*-methoxy, *p*-hydrogen, and *p*-nitro substituents, and to determine their rates of ethanolsolysis.

The *t*-cumyl chlorides⁸ and the 1-phenylcyclopentyl and 2-phenylnorbornyl chlorides⁶ were prepared as previously reported. The remaining chlorides were

(4) P. von R. Schleyer, *J. Am. Chem. Soc.*, **86**, 1854, 1856 (1964).

(5) For example, the rates for *endo*-5,6-trimethylene-*endo*-2-norbornyl tosylate and *endo*-5,6-trimethylene-*endo*-8-norbornyl tosylate, calculated with the aid of the Foote-Schleyer correlation with the usual assumption of TS \approx 0, are 10,000 to 100,000 times greater than the observed rates. For a detailed discussion, see H. C. Brown, I. Rothberg, P. von R. Schleyer, M. M. Donaldson, and J. J. Harper, *Proc. Natl. Acad. Sci. U. S.*, in press.

(6) H. C. Brown, F. J. Chloupek, and M.-H. Rei, *J. Am. Chem. Soc.*, **86**, 1246, 1247, 1248 (1964).

(7) P. von R. Schleyer, Symposium on Linear Free Energy Correlations, U. S. Army Research Office, Durham, N. C., Oct 19-21, 1964.

(8) Y. Okamoto and H. C. Brown, *J. Am. Chem. Soc.*, **79**, 1909 (1957).

prepared by treating the corresponding olefin or alcohol with hydrogen chloride by the automatic hydrochlorination technique previously described.⁹ The 2-arylnorbornyl chlorides thus obtained appeared to consist of essentially one isomer, as shown by the kinetic data over 80-90% reaction. Consequently, these were assigned the structure of 2-aryl-*exo*-norbornyl chlorides in accordance with all previous experience with such reactions in the norbornyl system.

The rates of solvolysis of the unsubstituted compounds and the *p*-nitro derivatives were determined in absolute alcohol. The *p*-methoxy compounds were too reactive to be determined in this solvent. Accordingly, the rates for the *p*-methoxy and the parent compounds were determined in 10% ethanol-90% ether (by weight) and the rate constants for the *p*-methoxy derivatives in absolute ethanol were calculated by multiplying the rate constants for the unsubstituted derivatives in absolute ethanol by the rate ratio, $k_{p\text{-OCH}_3}/k_{\text{H}}$, in 10% ethanol-90% ether.^{10,11}

The rate constants for the nine compounds under examination are summarized in Table I.

Table I. Rates of Ethanolsolysis of 2-Aryl-*exo*-norbornyl Chloride and Related Derivatives at 25.0°

| Substituent | 2-Aryl-2-propyl | $k_1 \times 10^6 \text{ sec}^{-1}$ | |
|--------------------|----------------------|------------------------------------|-------------------------------|
| | | 1-Aryl-cyclopentyl | 2-Aryl- <i>exo</i> -norbornyl |
| <i>p</i> -Methoxy | 294,000 ^a | 6,330,000 ^{a,d} | 25,500,000 ^{a,e} |
| <i>p</i> -Hydrogen | 36.9 | 1880 ^{b,c} | 20,500 ^{b,c} |
| <i>p</i> -Nitro | 0.00677 ^b | 0.776 ^f | 7.08 ^a |

^a Estimated from the rate constants in 10% ethanol-90% ether.

^b Extrapolated from rate constants at other temperatures. ^c Previously observed:⁶ 2100 and 15,800, respectively. These involve very fast reactions with long extrapolations from low temperatures.

^d Very unstable liquid. ^e Mp 54.0-54.8°. ^f Mp 58.0-58.5°. ^g Mp 87.0-87.2°.

First, it is of interest to point out that whereas a 1-*p*-anisyl group increases the rate of solvolysis of the parent *exo*-norbornyl derivative by a factor of 7.7,¹² a 2-anisyl group has an enormously greater effect, a rate enhancement of 500,000,000. Clearly the two transition states cannot both resemble the proposed nonclassical intermediate if one is formed in these solvolyses.⁶

All three sets of data give excellent linear plots against the σ^+ constants (Figure 1). The reaction constants (ρ) are: *t*-cumyl, -4.9; 1-phenylcyclopentyl, -4.5; 2-phenyl-*exo*-norbornyl, -4.3. There is no evidence for the curvature to be anticipated in the plot of the 2-arylnorbornyl data for increasing participation by the 1,6-electron pair as we proceed over this

(9) H. C. Brown and M.-H. Rei, *J. Org. Chem.*, **31**, 1090 (1966).

(10) Confidence in the validity of this procedure is provided by the following comparison. The rate constant for *p*-methoxy-*t*-cumyl chloride in 90% acetone⁸ can be estimated to be $309,000 \times 10^{-6} \text{ sec}^{-1}$ in ethanol from an extrapolation of the linear plot for the rate constants in the two solvents (Y. Okamoto, T. Inukai, and H. C. Brown, *J. Am. Chem. Soc.*, **80**, 4972 (1958)). This compares with the value $294,000 \times 10^{-6} \text{ sec}^{-1}$ obtained by use of the present extrapolation from 10% ethanol-90% ethyl ether.

(11) In the three solvents, 10% ethanol-90% ether, 20% ethanol-80% ether, 100% ethanol, the observed relative rates for 1-phenylcyclopentyl chloride/*t*-cumyl chloride (62, 65, and 51, respectively) and for 2-phenyl-2-norbornyl chloride/1-phenylcyclopentyl chloride (10.3, 10.2, and 10.9, respectively) remained quite constant.

(12) P. von R. Schleyer and D. C. Kleinfelter, quoted by J. A. Berson in "Molecular Rearrangements," Part I, P. de Mayo, Ed., Interscience Publishers, Inc., New York, N. Y., 1963, p 130.

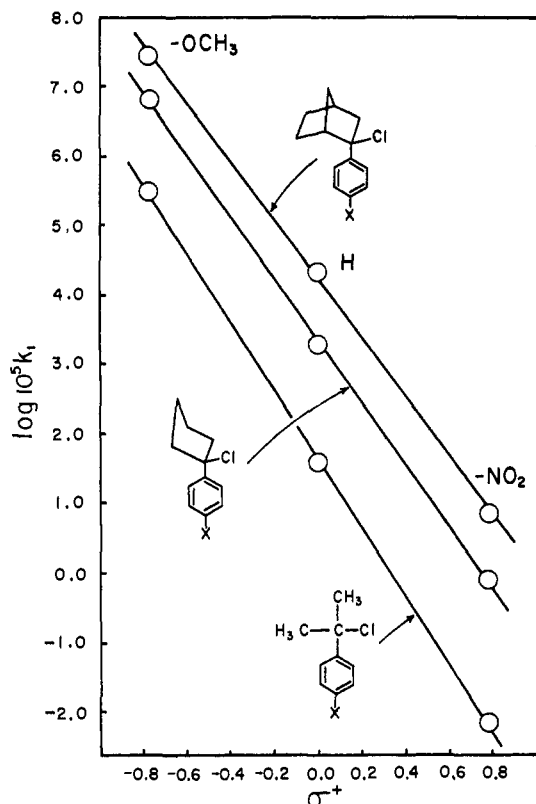


Figure 1. Plot of $\log k$ vs. σ^+ for the ethanolysis of substituted aryl dimethylcarbinyl, 1-arylcyclopentyl, and 2-aryl-*exo*-norbornyl chlorides.

enormous range of electron demand—from the highly stabilized 2-anisyl norbornyl derivative to the much more electron-demanding 2-*p*-nitrophenyl norbornyl derivative.

The existence of π participation in the norbornyl system is clearly indicated by Wiley's results with 3',6'-dimethoxy-*exo*-benznorbornyl tosylate¹³ and by Tanida's elegant studies with substituted 7-benznorbornyl tosylates.¹⁴ However, all of our attempts to confirm the frequently postulated σ participation in saturated norbornyl derivatives not undergoing rearrangement to more stable structures have uniformly yielded negative answers. At the present time we know of no experiment which provides independent confirmation for the proposal that the high *exo/endo* rate ratios in saturated norbornyl derivatives are due to σ participation. Accordingly, we are abandoning further efforts along this line¹⁵ and are turning our attention to exploration of steric hindrance to ionization as a possible explanation for the behavior of norbornyl derivatives.

(13) G. A. Wiley, reported in A. Streitwieser, Jr., "Molecular Orbital Theory for Organic Chemists," John Wiley and Sons, Inc., New York, N. Y., 1961, pp 390–391.

(14) H. Tanida, T. Tsuji, and H. Ishitobi, *J. Am. Chem. Soc.*, **86**, 4904 (1964).

(15) Schleyer has informed us that he is examining norbornyl derivatives containing methyl and methoxy substituents in the 6 position in a further effort to obtain evidence for the postulated 2,6 bridging in the transition state for solvolysis of such derivatives.

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The Kinetics of the Pepsin-Catalyzed Hydrolysis of N-Acetyl-L-phenylalanyl-L-tyrosine Methyl Ester¹

Sir:

Previous work has established that pepsin catalyses the hydrolysis of N-acyl L-dipeptides^{2–4} and N-acyl L-tripeptide esters.⁵ The N-acyl dipeptides contain a free C-terminal carboxyl group which ionizes in the low pH region of pepsin activity and the N-acyl tripeptide esters all contained a positively charged histidine moiety. Baker⁶ showed that N-acetyl-L-phenylalanyl-L-tyrosine was hydrolyzed by pepsin to give N-acetyl-L-phenylalanine and tyrosine. Therefore, we have studied the pH dependence of the pepsin-catalyzed hydrolysis of a neutral substrate, N-acetyl-L-phenylalanyl-L-tyrosine methyl ester. This eliminates correcting the pH-rate profile (Figure 1) for the ionization of the substrate. The observed pK_a values of the catalytically important groups as obtained from such a pH-rate profile are a direct measure of those functioning on the enzyme.

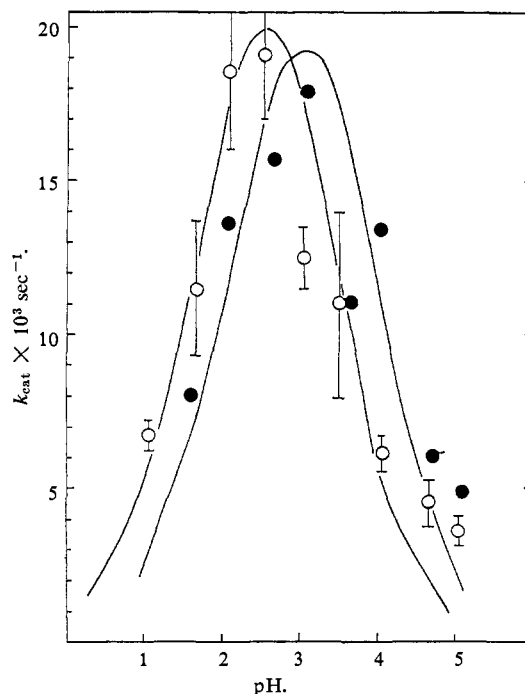


Figure 1. The pepsin-catalyzed hydrolysis of N-acetyl-L-phenylalanyl-L-tyrosine methyl ester in water (O) and in deuterium oxide (●) at 25.0° in 3.16% dioxane.

Figure 1 shows the bell-shaped pH-rate profiles for the pepsin-catalyzed hydrolysis of N-acetyl-L-phenylalanyl-L-tyrosine methyl ester in water and deuterium oxide containing 3.16% dioxane.^{7,8} The pK_a 's

(1) This research was supported by Grant GM12022 from the National Institutes of Health.

(2) M. S. Silver, J. L. Denburg, and J. J. Steffens, *J. Am. Chem. Soc.*, **87**, 886 (1965).

(3) W. T. Jackson, M. Schlamowitz, and A. Shaw, *Biochemistry*, **4**, 1537 (1965).

(4) E. Zeffren and E. T. Kaiser, *J. Am. Chem. Soc.*, **88**, 3129 (1966).

(5) K. Inouye, I. M. Voynick, G. R. Delpierre, and J. S. Fruton, *Biochemistry*, **5**, 2473 (1966).

(6) L. E. Baker, *J. Biol. Chem.*, **193**, 809 (1951); L. E. Baker, *ibid.*, **211**, 701 (1954).

(7) Kinetic runs were obtained by using the spectrophotometric method of Silver² by measuring initial rates at 237 m μ and plotting the data according to the procedure of H. Lineweaver and D. Burk, *J. Am. Chem. Soc.*, **56**, 658 (1934). ($E_0 = 1.5 \times 10^{-5} M$; $S_0 = 0.26 - 1.10$ mM.) Pepsin, Worthington Lot PM703 two times crystallized, was