$$\log \frac{1}{K_{\mathrm{ER,I}}} = 0.81(\pm 0.34) \log P - 0.77(\pm 0.20)\sigma^* + 3.53(\pm 0.33) \quad \begin{array}{ccc} n & r & s \\ 15 & 0.929 & 0.302 \end{array} \qquad (9)$$

with eq 6 or 7, the slopes for the hydrophobic and electronic terms are in reasonable agreement.

A most interesting aspect of eq 7 is the negative coefficient of the E_s-4 term. Bearing in mind that the more negative the E_s value of a substituent, the larger it is, this coefficient means that the bulkier groups in the para position *increase* binding. While this could be interpreted as a kind of correction term for π-4 (note that the value of the coefficient with π-4 drops in going from eq 6 to eq 7), it could also mean that the substituents help in producing an induced fit of the type postulated by Koshland.[10]

It is most interesting that eq 1, using $\Sigma\pi$, does not give as good a correlation as eq 4, using π-4, even though the former parameter contains more information. Also, in eq 8 the π-3 term has a negative coefficient. In the 1023 equations there is no evidence that 3 substituents aid complex formation *via* a hydrophobic interaction. In most of the equations where a π-3 term occurs, its coefficient has a negative sign. In a number of the equations the coefficient is positive, but esentially zero (*i.e.*, <0.1). In most of the few examples where the coefficient is positive and greater than 0.1, the 95% confidence intervals are quite large and, in fact, overlap zero. At best, 3 substituents have no hydrophobic or steric effect; at worst, there may be an inhibitory effect by such substituents on complex formation.

The lack of importance of π-3 in the above analysis indicates the directional nature of the hydrophobic effect in enzyme–substrate interaction. A similar effect has been uncovered in the interaction of phenyl glucosides with emulsin[11] and in the interacton of phenethanolamines with *N*-methyl transferase.[12] No doubt many other such examples will be discovered.

In deriving eq 1–8, one data point (3-CH_3) was not used. This derivative was invariably poorly fit. The reason for this is not clear. One might speculate that since there is no hydrophobic interaction by 3 substituents, the region in which these functions find themselves is polar. It may be that polar 3 functions such as Cl, NO_2, OH, etc. fit into this region better because of their dipole moments and that CH_3, lacking a strong dipole moment, fits poorly.

In summary it can be said that the present analysis of $K_{\mathrm{ER,I}}$ values for aromatic amides agrees well with the previous analysis of aliphatic amides.[2] The important difference is that the more rigid aromatic molecules show a directional hydrophobic bonding effect which it is not easy to see with the more flexible aliphatic compounds. The two studies show that it should be possible to obtain more precise information about the inhibitor complex *via* a study of well-designed derivatives using regression analysis.

Acknowledgment. This work was supported by Grants CA-11110 and CA-12462 from the National Institutes of Health and GB-28015 and GP-28061 from the National Science Foundation.

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[10] D. E. Koshland, Jr., in "The Enzymes," Vol. 1, P. D. Boyer, H. A. Lardy, and K. Myrbäck, Ed., Academic Press, New York, N. Y., 1960, p 305.

[11] C. Hansch, E. W. Deutsch, and R. N. Smith, *J. Amer. Chem. Soc.*, **87**, 2738 (1965).

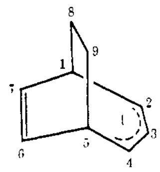
[12] C. Hansch and W. R. Glave, *J. Med. Chem.*, **15**, 112 (1972).

Communications to the Editor

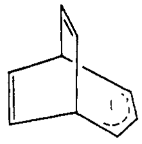
The Bicyclo[3.2.2]nona-2,6-dienyl Carbanion. Preparation, Basicity, and Laticyclic Stabilization[1]

Sir:

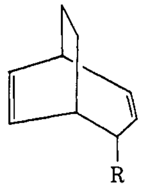
The elegant theoretical analysis of bicycloaromatic stabilization in π-bridged ions by Goldstein and Hoffmann[2] prompted us to seek experimental verification of these concepts. In our previous work,[3] it was concluded that longicyclic stabilization was negligible. We now wish to report a test of laticyclic stabilization using the bicyclo[3.2.2]nona-2,6-dienyl carbanion I. The preparation, nmr spectrum, and relative basicity of this ion are reported.



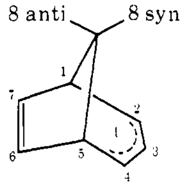
I



II



III a, R = H
b, R = O
c, R = OCH_3



IV

The carbanion I was generated from the methoxy ether precursor IIIc by previously reported procedures.[3] The ether IIIc was prepared by standard procedures[3,4] from the ketone IIIb.[5] Quenching of the

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[1] Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

[2] M. J. Goldstein and R. Hoffmann, *J. Amer. Chem. Soc.*, **93**, 6193 (1971).

[3] J. B. Grutzner and S. Winstein, *J. Amer. Chem. Soc.*, **94**, 2200 (1972).

[4] All new compounds gave satisfactory elemental analyses and structures were verified by spectral techniques.

[5] T. Uyehara and Y. Kitahara, *Chem. Ind. (London)*, 354 (1971).

anion solution with methanol gave a 68% yield of hydrocarbon IIIa (mp 35–36°). No other volatile products could be detected by gas chromatography.

The chemical shifts for I are given in Table I together with the data for the related ions II and IV and the corresponding hydrocarbons. The chemical shifts of the allylic and ethylenic hydrogens of I are comparable to those previously reported for II and IV and show that I is a delocalized homoaromatic[6] anion. The apparent indifference of the saturated bridge protons (H-8, -9) in I to the presence of the anion is notable, particularly when it is contrasted with the marked upfield shift of the saturated bridge protons H-8 in IV. This observation provides strong support for the interpretation that the upfield shift observed in IV is due to a substantial ring current effect.[7] It should be noted that the bridge protons in IV lie directly over the center of the ring in a greatly shielded region whereas the bridge protons in I lie over the periphery of the ring close to the zero shielding region of the induced ring current. This lack of anion influence on the saturated bridge protons of I rules out any substantial through-space electric field induced shift that might have provided an alternative explanation of the shifts in IV.

Table I. Chemical Shifts of Anions and Hydrocarbons

Proton	I	I-H	II	II-H	IV	IV-H
1	2.5	2.5	2.29	3.1	2.45	2.57
2	3.25	5.92	3.05	5.87	2.84	5.92
3	5.75	5.32	5.24	4.89	5.39	5.15
4	3.25	2.25	3.05	2.10	2.84	2.17, 1.79
5	2.5	2.5	2.29	3.1	2.45	2.57
6	5.04	6.05	4.98	6.07	3.67	5.65
7	5.04	6.43	4.98	6.47	3.67	6.18
8,9 syn	1.71	1.83	4.98		0.42	1.66
8,9 anti	1.71	1.83	4.98		0.84	1.90

In order to examine the importance of laticyclic stabilization in II we chose to determine the relative basicities of I and II. The basicity of II should be lower than that of I due to the inductive effect of the additional double bond and any additional stabilization due to laticyclic interaction. One such determination has been reported by Staley[8] for the 3-methyl-substituted compounds, using an isotopic exchange procedure (KOBu–Me_2SO) where the substituted trienyl anion was found to be more stable by a factor of 750. We have chosen an alternative method which should prove of general utility for estimation of relative kinetic carbanion stabilities. The method involves measurement of the rate of the pseudo-first-order deprotonation of the ether solvent by the carbanion[9,10] (reaction 1). This

$$R^-M^+ + H\text{-}S \xrightarrow{k_1} R\text{-}H + S^-M^+ \qquad (1)$$

method has the advantage that the carbanions themselves are the reactants, and so the kinetic basicities are independent of the relative ground-state energies of the parent hydrocarbons. In addition, the reactant carbanions are present as ion pairs and higher aggregates which correspond to the conditions commonly employed for synthetic purposes. Thus, the kinetic basicity should provide a more direct correlation with chemical reactivity than the more common isotopic exchange techniques. Of course, for the present study, such ion pairing effects tend to obscure the inherent stability difference between I and II. However, we believe that the errors introduced here are no worse than any other available kinetic method for basicity comparison. We are currently extending the scope of these studies to test their generality and to provide a comprehensive basicity scale.

The results for anions I and II and their reaction with tetrahydrofuran (THF) and 1,2-dimethoxyethane (DME) are shown in Table II. In each case, the reaction was monitored by following the disappearance of anion and the appearance of hydrocarbon by nmr spectroscopy.

Table II. Kinetic Parameters for Solvent Deprotonation by I and II

Anion	Solvent	Temp, °C	10^6k, sec^{-1}[a]	$t_{1/2}$, days	$\Delta\Delta G^{\neq}$,[b] kcal/mol
I	THF	21	0.21	41	
		50	3.8	2.0	
		90	170	0.05	
	DME	21	6.3	1.3	
		50	97	0.08	
II	THF	90	5.8	1.4	2.4
	DME	21	(0.092)	(87)	(2.5)
		50	8.8	0.9	1.6

[a] Rates are accurate and reproducible to ±10% except for II in DME at 21° where the error may be as large as ±50% (single run). [b] Calculated from $RT \ln k_I/k_{II} = \Delta\Delta G^{\neq}$.

Within the limits of nmr intensity measurements, good first-order kinetics were observed at each temperature throughout the reaction. A threefold concentration change did not affect the observed rate. The results clearly show that, in these ether solvents, the additional double bond only leads to 2.5 kcal/mol additional stabilization of II compared with the homoaromatic anion I.[11] Thus, laticyclic stabilization is a minor contributor to the overall stability of the trienyl anion by comparison with allylic and homoaromatic stabilization. Similar conclusions about laticyclic stabilization may be drawn from the well-known 7-norbornyl, 7-norbornenyl, and 7-norbornadienyl cation series. Again homoaromatic stabilization is dominant and the additional double bond provides relatively minor additional stabilization attributable to laticyclic interaction. That this is a general conclusion was noted in passing by Goldstein and Hoffmann[2] and is reemphasized here. Any molecule which has the potential for laticyclic stabilization must contain compo-

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(6) S. Winstein, *Quart. Rev., Chem. Soc.*, 23, 141 (1969).

(7) S. Winstein, M. Ogliaruso, M. Sakai, and J. M. Nicholson, *J. Amer. Chem. Soc.*, 89, 3656 (1967).

(8) S. W. Staley and D. W. Reichard, *J. Amer. Chem. Soc.*, 91, 3998 (1969).

(9) The deprotonation of ethers by carbanions have been reported by many authors. For some pertinent references see (a) H. Gilman, A. M. Haubein, and H. Hartzfeld, *J. Org. Chem.*, 19, 1034 (1954); (b) J. G. Smith and I. Ho, *J. Org. Chem.*, 37, 4260 (1972); (c) G. D. Sargent, *Tetrahedron Lett.*, 3279 (1971); (d) A. Maercker and W. Theysohn, *Justus Liebigs Ann. Chem.*, 747, 70 (1971); (e) R. B. Bates, L. M. Kroposki, and D. E. Potter, *J. Org. Chem.*, 37, 560 (1972).

(10) The decomposition products were detected by nmr spectroscopy as the reaction proceeded—ethylene from THF and vinyl methyl ether from DME. The vinyl methyl ether was confirmed by isolation of the 2,4-dinitrophenylhydrazone of acetaldehyde on work-up.

(11) We have also attempted to obtain the thermodynamic basicity difference between I and II by equilibrating I, I-H, II, and II-H. Within the present limits of sensitivity, an equilibrium constant of ⩾20 has been measured in favor of the trienyl anion.

nents for homoaromatic stabilization. In every case the homoaromatic interaction provides the major stabilizing influence and the laticyclic interaction is a second-order effect. This point is emphasized by the results of simple Hückel calculations given in Table III.

Table III. Hückel Stabilization Energies for I and II[a]

	z			
y	0	0.2	0.4	0.6
0	0	0	0	0
0.2	114	4	12	36
0.4	348	7	36	86
0.6	710	12	52	122

[a] In units of $10^{-3}\beta$. Assuming $\beta_{23} = \beta_{34} = \beta_{67} = \beta$; $\beta_{27} = \beta_{46} = y\beta$; $\beta_{69} = \beta_{78} = z\beta$. All other interactions were neglected. The values for $z = 0$ correspond to the homoaromatic stabilization of I and the other columns give the *additional* stabilization provided by the 8–9 double bond in II.

It should be noted that we are not ruling out extensive delocalization between the three π bridges, but simply point out that such interaction will not lead to significant net stabilization energy, in contrast to homoaromatic interaction between two π bridges. Similar conclusions have been reached by other workers[12] about the relationship between delocalization and stabilization in bridged π systems. As a result of the work reported here and previous studies, it is our belief that while laticyclic and longicyclic interactions may be of considerable theoretical interest, they have little to contribute to the milieu of ionic stabilization mechanisms by comparison with homoaromatic and other stabilization mechanisms.

(12) (a) P. Bischoff, J. A. Hashmall, E. Heilbronner, and V. Hornung, *Helv. Chim. Acta*, **52**, 1745 (1969); (b) H. E. Zimmerman, *Accounts Chem. Res.*, **4**, 272 (1971), and references cited therein.

(13) David Ross Fellow, 1970–1972; Phillips Petroleum Fellow, 1972–1973.

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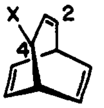
Stabilization and Destabilization of Unsaturated Bicyclo[3.2.2]nonyl Anions

Sir:

Some time ago, one of us predicted that π-electron stabilization of anion **1a** would exceed that of the bishomoaromatic **2a**, albeit by less than a factor of two.[1] The otherwise unstabilized allylic anion **3a** serves as conventional reference for both.



1

2

3

a, X = :⊖
b, X = H

More recent photoelectron data[2a] have now disqualified one of many theoretical approximations used to achieve such conclusions—explicit neglect of "through-bond" interaction.[2b] Still others remain to be tested.[1b,3] Nor is the peripheral experimental evidence entirely unambiguous in its interpretation.[1b,4]

We are therefore particularly pleased to be able to report quantitative confirmation of the original predictions. As measured by KO-*t*-Bu–Me$_2$SO-catalyzed detritiation of **1b**-*t*, **2b**-*t*, and **3b**-*t*, stabilization of the trienyl anion **1a** exceeds that of the dienyl **2a** by 4.0 ± 0.3 kcal/mol.[5] The latter, in turn, is stabilized by more than 5.6 kcal/mol. The first value recalls the solvolytically measured 3.7 kcal/mol advantage of the 7-norbornadienyl cation over the 7-norbornenyl.[6] The second may be compared with the solvolytically measured 12.4 kcal/mol stabilization of the 7-norbornenyl cation.[7]

1b was prepared by Na-K reduction of 4-methoxybicyclo[3.2.2]nona-2,6,8-triene;[4b,8,9a] **2b** was similarly obtained from **1b**.[9b] Tritiated dimethyl sulfoxide served to label both under conditions similar to those of subsequent detritiation kinetics. That the label was almost exclusively at C-2 or C-4 (>99% for **1b**, >93% for **2b**) was demonstrated both by pmr analysis of the products of parallel deuterium incorporation experiments and by nonlinear least-squares analysis of detritiation data.[10]

The detritiation k_{obsd} of both hydrocarbons increased with primitive concentration[12] of base to reach a broad maximum between 0.08 and 1.0 *M*.[13] Within this common range of related kinetic investigation,[4c,11,13] k_{obsd} varied by less than 15% and never exceeded 1.2 times its value at 0.057 *M* (Table I).[14]

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(1) (a) M. J. Goldstein, *J. Amer. Chem. Soc.*, **89**, 6357 (1967); (b) M. J. Goldstein and R. Hoffmann, *J. Amer. Chem. Soc.*, **93**, 6193 (1971); (c) footnote 9 in ref 1a.

(2) (a) M. J. Goldstein, S. Natowsky, E. Heilbronner, and V. Hornung, *Helv. Chim. Acta*, **56**, 294 (1973); (b) R. Hoffmann, *Accounts Chem. Res.*, **4**, 1 (1971).

(3) M. J. S. Dewar and W. W. Schoeller, *Tetrahedron*, **27**, 4401 (1971); S. Yoneda, S. Winstein, and Z. Yoshida, *Bull. Chem. Soc. Jap.*, **45**, 2510 (1972); *Tetrahedron*, **28**, 2395 (1972).

(4) (a) J. C. Barborak, J. Daub, D. M. Follweiler, and P. v. R. Schleyer, *J. Amer. Chem. Soc.*, **91**, 7760 (1969); J. C. Barborak and P. v. R. Schleyer, *J. Amer. Chem. Soc.*, **92**, 3184 (1970); (b) J. B. Grutzner and S. Winstein, *J. Amer. Chem. Soc.*, **94**, 2200 (1972); (c) S. W. Staley and D. W. Reichard, *J. Amer. Chem. Soc.*, **91**, 3998 (1969); (d) P. Ahlberg, D. L. Harris, and S. Winstein, *J. Amer. Chem. Soc.*, **92**, 4454 (1970); P. Ahlberg, *Chem. Scr.*, **2**, 231 (1972); (e) M. V. Moncur and J. B. Grutzner, *J. Amer. Chem. Soc.*, **95**, 6449 (1973).

(5) Earlier work[4c] had permitted a 3.9 kcal/mol estimate with the added assumptions of identical $\Delta S^{\ddagger}$ for exchange of **1b** and **2b**, obedience to a common basicity function, and indifference to 3-methyl substitution.

(6) S. Winstein and C. Ordronneau, *J. Amer. Chem. Soc.*, **82**, 2084 (1960). $\Delta S^{\ddagger}$ is assumed constant.

(7) S. Winstein, M. Shatavsky, C. Norton, and R. B. Woodward, *J. Amer. Chem. Soc.*, 77, 4183 (1955).

(8) M. J. Goldstein and B. G. Odell, *J. Amer. Chem. Soc.*, **89**, 6356 (1967).

(9) (a) Mp 43°. Other data agree with those reported.[4b,9c] (b) Mp 53° (lit. mp 35–36°)[4e]; *m/e* 120; nmr τ (CCl$_4$) 3.62 (t, 1.03), 4.11 (m, 1.96), 4.73 (d of t, 1.01), and 7.21–8.63 (m, 8.01) ppm. *Anal.* Found: C, 89.82; H, 10.05. (c) M. Jones, Jr., and D. S. Reich, *J. Amer. Chem. Soc.*, **89**, 3935 (1967).

(10) As in the bicyclo[3.2.1]octadienyl series,[11] dimethyl sulfoxide adequately prevents the rearrangements observed in other media.[4b,c]

(11) J. M. Brown and J. L. Occolowitz, *J. Chem. Soc. B*, 411 (1968).

(12) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill, New York, N. Y., 1970, p 85.

(13) (a) A. Schriesheim and C. A. Rowe, Jr., *J. Amer. Chem. Soc.*, **84**, 3160 (1962); (b) J. E. Hoffmann, R. J. Muller, and A. Schriesheim, *J. Amer. Chem. Soc.* **85**, 3000 (1963); (c) S. B. Tjan, H. Steinberg, and Th. J. de Boer, *Recl. Trav. Chim. Pays-Bas*, **88**, 680 (1969); (d) P. K. Freeman and T. A. Hardy, *Tetrahedron Lett.*, 3939 (1971); (e) M. J. Maskornick, *Tetrahedron Lett.*, 1797 (1972).

(14) A more extensive base dependence study, to be reported subsequently, permits extrapolation to infinite dilution.