Rates of Solvolysis of 2-Methyl-, 2-*tert*-Butyl-, 2-Phenyl-, and 2-Cyclopropyl-2-propyl *p*-Nitrobenzoates. Evidence That ^{13}C Chemical Shifts of Carbonium Ions Do Not Correlate with the Stabilities of Solvolytic Transition States and the Corresponding Cationic Intermediates

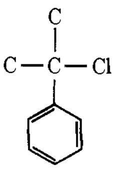
Sir:

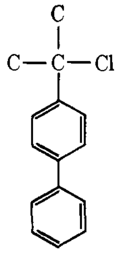
The rates of solvolysis in 80% aqueous acetone of the esters RMe_2COPNB exhibit major increases as the group R is varied from methyl (1.00) to phenyl (10^3) to cyclopropyl ($10^{5.5}$). Relief of B strain is not a significant factor in these derivatives. Yet these rates fail to correlate with the ^{13}C chemical shifts for the carbonium carbon of the respective cations of −135, −61, and −87 ppm.[1,2] Consequently, it does not appear possible at this time to base conclusions as to the rates of solvolysis, the electron-releasing properties of substituents, or the relative stabilities of carbonium ions on such ^{13}C shifts.

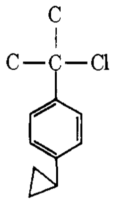
Ever since the pioneering work of Ingold on solvolysis,[3] rates of S_N1 reactions have been utilized by chemists to obtain information as to the factors influencing the stabilities of carbonium ions and the electronic distributions in such ions. Recently, it has been stated that there is a well-established relationship between ^{13}C chemical shifts and electron density in such ions.[1a,4] Obviously, it would be highly desirable to have available a relatively direct means of determining the electron density at various carbon atoms of a carbonium ion, rather than having to rely on deductions from solvolytic data.

For example, Olah and his coworkers have examined the ^{13}C chemical shifts for the carbonium carbon in the *tert*-butyl cation, the phenyldimethyl- and the cyclopropyldimethylcarbonium ions and have concluded from the observed values that the phenyl group must be more electron releasing than the cyclopropyl group.[1a]

This is contrary to the conclusion that is indicated by solvolytic results. Thus, the relative rates of solvolysis of para-substituted *tert*-cumyl chloride derivatives **1**, **2**, and **3** clearly indicate that the cyclopropyl group **3**[5a] must be more electron releasing than the phenyl group **2**.[5b] The same conclusion, that the electron-releasing properties of cyclopropyl are greater than those of phenyl, is also indicated by equilibrium and other studies.[6]



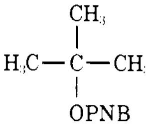




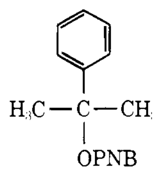
	1	2	3
rel rate	1.00	6.5	157

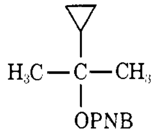
However, it might be argued that these data do not provide a fair test of the proposal. Perhaps structures should be examined which are directly related to the trimethyl-, phenyldimethyl-, and cyclopropyldimethylcarbonium ions utilized in the ^{13}C studies. Accordingly, we undertook to obtain kinetic data for the solvolysis of the three *p*-nitrobenzoates related to these three cationic intermediates under essentially identical conditions.

It was observed that the replacement of a methyl group in the *tert*-butyl system **4** by a phenyl group **5** increases the rate at 25° by a factor of 10^3. Replacement of the phenyl group by a cyclopropyl group **6** increases the rate at 25° by another comparable factor of $10^{2.5}$.



$$\begin{array}{c} CH_3 \\ | \\ H_3C-C-CH_3 \\ | \\ OPNB \end{array}$$

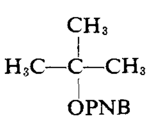




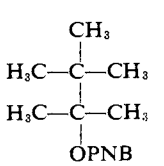
	4	5	6
log k_1 (sec^{-1})	−10.13	−7.14	−4.43
$\delta_{^{13}C^+}$	−135	−61	−87

In the solvolytic approach, it has been accepted that for systems in which differences in ground-state energies are not significant, relative rates provide information as to the relative stabilities of the respective transition states. According to the Hammond postulate, such transition states are close to the carbonium ion intermediates, so that the stabilities of the latter can be estimated from the rate data.[7] For systems not involving significant steric effects, the most important factor influencing stability of the cation is electron delocalization from the carbonium ion center.

Before we can proceed to interpret these results, it is necessary to establish that differences in B strain[8] are not a significant factor in the observed rates. A *tert*-butyl group must have larger steric requirements than a methyl, phenyl, or cyclopropyl group. Solvolysis of *tert*-butyldimethylcarbinyl *p*-nitrobenzoate (**7**) yields a rate 4.4 that of the *tert*-butyl derivative. Clearly, relief of B strain cannot represent a major contribution in the factors of 969 and 503,000 observed for the respective effects of a phenyl and cyclopropyl group in the corresponding derivatives.



$$\begin{array}{c} CH_3 \\ | \\ H_3C-C-CH_3 \\ | \\ OPNB \end{array}$$



$$\begin{array}{c} CH_3 \\ | \\ H_3C-C-CH_3 \\ | \\ H_3C-C-CH_3 \\ | \\ OPNB \end{array}$$

	1	7
rel rate	1.00	4.36

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[1] (a) G. A. Olah and A. M. White, *J. Amer. Chem. Soc.*, **91**, 5801 (1969); (b) G. A. Olah, C. L. Jewell, and A. M. White, *ibid.*, **91**, 3961 (1969); (c) G. A. Olah, C. L. Jewell, D. P. Kelley, and R. D. Porter, *ibid.*, **94**, 146 (1972).

[2] All ^{13}C chemical shifts are in parts per million from $^{13}CS_2$.

[3] See C. K. Ingold, "Structure and Mechanism in Organic Chemistry," 2nd ed, Cornell University Press, Ithaca, N. Y., 1970.

[4] (a) G. A. Olah and A. M. White, *J. Amer. Chem. Soc.*, 90, 1884 (1968). (b) G. A. Olah, *Science*, **168**, 1297 (1970). (c) It has been pointed out that ^{13}C chemical shifts depend upon several important factors in addition to electron density;[1a,4a] see also B. V. Cheney and D. M. Grant, *J. Amer. Chem. Soc.*, 89, 5319 (1967).

[5] (a) H. C. Brown and J. D. Cleveland, *ibid.*, 88, 2051 (1966); (b) H. C. Brown, Y. Okamoto, and T. Inukai, *ibid.*, 80, 4964 (1958); (c) H. C. Brown and T. Inukai, *ibid.*, 83, 4825 (1961). If we correct for the noncoplanarity of the *p*-phenyl substituent, the rate enhancement increases to 43.[5c] The rate enhancements then become: *p*-methyl, 26; *p*-phenyl (coplanar), 43; *p*-cyclopropyl, 157.

[6] N. C. Deno, H. G. Richey, Jr., J. S. Liu, D. N. Lincoln, and J. O. Turner, *ibid.*, 87, 4533 (1965). For an excellent review and discussion, see H. G. Richey, Jr., "Carbonium Ions," Vol. III, G. A. Olah and P. v. R. Schleyer, Ed., Wiley, New York, N. Y., 1972, Chapter 25, and references cited therein.

[7] G. S. Hammond, *J. Amer. Chem. Soc.*, 77, 334 (1955).

[8] H. C. Brown, "Boranes in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1972.

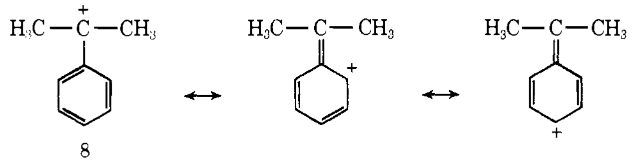
The rate constants and related data are summarized in Table I.

Table I. Rate Data for the Solvolysis of Tertiary 2-Propyl *p*-Nitrobenzoates, $R(CH_3)_2COPNB$, in 80% Acetone

R	$k_1^{25°} \times 10^6$, sec^{-1}	Rel rate, 25°	$\Delta H^{\ddagger}$, kcal mol^{-1}	$\Delta S^{\ddagger}$, eu
Methyl[a]	7.45×10^{-5} [e]	1.00	29.2	−7.1
tert-Butyl[b]	3.25×10^{-4} [e,f]	4.36	29.0	−4.8
Phenyl[c]	7.22×10^{-2} [e,g]	969	24.8	−8.2
Cyclopropyl[d]	37.5[d,h]	503,000	20.8	−9.0

[a] H. C. Brown and W. C. Dickason, *J. Amer. Chem. Soc.*, **91**, 1226 (1969). [b] Mp 139.8–140.2°. [c] L. F. King, *J. Amer. Chem. Soc.*, **61**, 2383 (1939). [d] M. Hanack and K. Goerber, *Chem. Ber.*, **96**, 2121 (1963). The product of solvolysis is unrearranged cyclopropyldimethylcarbinol: C. D. Poulter and S. Winstein, *J. Amer. Chem. Soc.*, **91**, 3650 (1969). [e] Calculated from data at other temperatures. [f] $k_1^{150°} = 814 \times 10^{-6}$ sec^{-1}; $k_1^{125°} = 89.6 \times 10^{-6}$ sec^{-1}. [g] $k_1^{75°} = 33.6 \times 10^{-6}$ sec^{-1}; $k_1^{100°} = 391 \times 10^{-6}$ sec^{-1}. [h] $k_1^{50°} = 614 \times 10^{-6}$ sec^{-1}.

Since differences in the ground-state energies are not significant in the *tert*-butyl and *tert*-cumyl derivatives, the factor of 10^3 in rates indicates that the transition state of the *tert*-cumyl derivative is stabilized by approximately 4 kcal/mol. The stabilization of the free ion is presumed to be modestly larger.[7] This stabilization is presumed to be due to charge delocalization from the carbonium center into the aromatic ring **8**.



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Indeed, the large rate enhancement effects of methyl[9a] (×26) and methoxy[9b] (×3360) substituents in the para position support this interpretation.

Similarly, the large rate enhancing effect of the cyclopropyl group ($10^{5.5}$) indicates that the transition state is stabilized by approximately 7.5 kcal/mol. This stabilization must also be the result of major charge delocalization from the carbonium center into the cyclopropane ring. Indeed, here also large rate enhancing effects, following σ^+, have been observed for methyl (×11) and ethoxy (×940) substituents in the cyclopropyl ring.[10]

The major increase in rate observed for the cyclopropyl derivative **6**, as compared to the phenyl derivative **5**, indicates that more charge must be delocalized from the carbonium carbon in **6**, as compared to **5**. If the ^{13}C shifts measure the electron densities on the individual carbon atoms, one would have anticipated a larger ^{13}C shift for the carbonium carbon in the ion from **6** as compared to that from **5**. The fact that the magnitude of the ^{13}C shift occurs in the opposite direction led Olah and his coworkers to conclude that phenyl is a better electron-releasing group than cyclopropyl, a conclusion directly opposite to that indicated by the present solvolytic study, as well as by other approaches.[6] Clearly it is desirable that we proceed with caution in basing conclusions as to electron densities on carbon atoms on ^{13}C shifts alone until this major discrepancy is resolved.[11]

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(9) (a) H. C. Brown, J. D. Brady, M. Grayson, and W. H. Bonner, *J. Amer. Chem. Soc.*, 79, 1897 (1957); (b) Y. Okamoto and H. C. Brown, *ibid.*, 79, 1909 (1957).

(10) P. von R. Schleyer and G. W. Van Dine, *ibid.*, 88, 2321 (1966). The data are for 100°, rather than the 25° values used otherwise.

(11) Other discrepancies are evident. For example, the rates of solvolysis of 1-methylcyclopentyl (1.00) and 2-methyl-*exo*-norbornyl *p*-nitrobenzoates (4.0) are comparable: H. C. Brown, F. J. Chloupek, and M.-H. Rei, *J. Amer. Chem. Soc.*, **86**, 1247 (1964). Yet the ^{13}C shifts for the corresponding cations, −142 and −76, are very different: G. A. Olah, A. M. White, J. R. DeMember, A. Commeyras, and C. Y. Lui, *ibid.*, **92**, 4627 (1970).

(12) Graduate research assistant on a grant (GP 31385) supported by the National Science Foundation.

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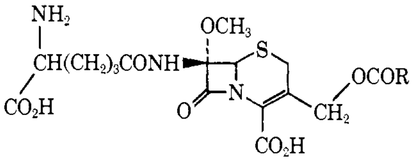
Direct 6-Methoxylation of Penicillin Derivatives. A Convenient Pathway to Substituted β-Lactam Antibiotics

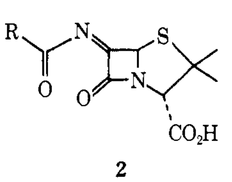
Sir:

The recent isolation and structure proof of the new β-lactam-containing antibiotics **1a–d** from *Streptomyces* have aroused considerable interest, since these materials contained a functionability heretofore unknown in the general group of penicillin and cephalosporin compounds, namely a 7-methoxyl group.[1] The enhanced activity against Gram-negative bacteria of these new antibiotics encouraged us to develop a method for the direct, one-step introduction of a methoxyl substituent at C-6 into the penicillin nucleus. Since a procedure for the conversion of penicillin to the cephalosporin system is now well established,[2] access would thereby be obtained to methoxyl-substituted penicillin and cephalosporin compounds. We report the first direct method for this transformation.[3]



1a, $R = CH_3$
b, $R = NH_2$
c, $R = -C(OCH_3){=}CHC_6H_4OH\text{-}p$
d, $R = -C(OCH_3){=}CHC_6H_4OSO_3\text{-}p$

Our approach has been the generation of a reactive



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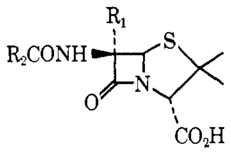

3, $R_1 = OCH_3$

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(1) (a) R. Nagarajan, L. D. Boeck, M. Gorman, R. L. Hamill, C. E. Higgens, M. M. Hoehn, W. M. Stark, and J. G. Whitney, *J. Amer. Chem. Soc.*, 93, 2308 (1971); (b) E. O. Stapley, D. Hendlin, S. Hernandez, M. Jackson, J. M. Mata, A. K. Miller, H. B. Woodruff, R. W. Miller, G. Albers-Schonberg, B. H. Arison, and J. L. Smith, Abstracts, XIth Interscience Conference on Antimicrobial Agents and Chemotherapy, Atlantic City, N. J., 1971, p 8.

(2) R. B. Morin, B. J. Jackson, R. A. Mueller, E. R. Lavagnino, W. B. Scanlon, and S. L. Andrews, *J. Amer. Chem. Soc.*, 91, 1401 (1969).

(3) A recent communication describes the partial synthesis of 6-α-methoxyl-substituted penicillins starting from 6-diazo compounds; *cf.* L. D. Cama, W. J. Leanza, T. R. Beattie, and B. G. Christensen, *J. Amer. Chem. Soc.*, 94, 1408 (1972).