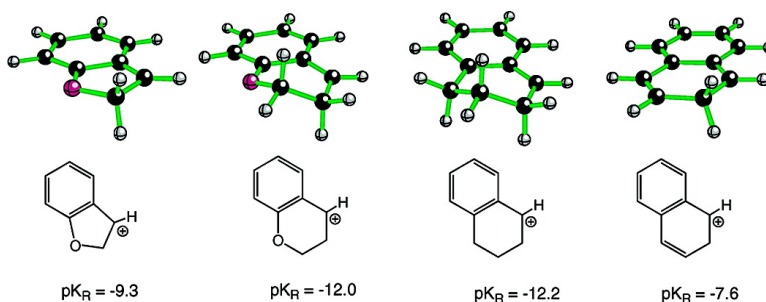## Article

Unexpectedly Small Ortho-Oxygen Substituent Effects on Stabilities of Benzylic Carbocations

M. Fujio, J. R. Keeffe, R. A. More O'Ferrall, and A. C. O'Donoghue

pKR = -9.3   pKR = -12.0   pKR = -12.2   pKR = -7.6

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Unexpectedly Small Ortho-Oxygen Substituent Effects on Stabilities of Benzylic Carbocations

M. Fujio,[†] J. R. Keeffe,[‡] R. A. More O'Ferrall,*,[§] and A. C. O'Donoghue[§]
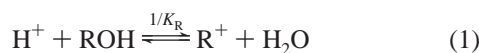
Contribution from the Department of Chemistry and Centre for Synthesis and Chemical Biology, University College Dublin, Belfield, Dublin 4, Ireland, Department of Chemistry and Biochemistry, San Francisco State University, 1600 Holloway Avenue, San Francisco, California 94132, and Institute for Materials Chemistry and Engineering, Kyushu University, Hakozaki, Higashi-ku, Fukuoka 82, Japan

Received July 23, 2003; Revised Manuscript Received May 7, 2004; E-mail: rmof@ucd.ie

Abstract: Equilibrium constants are reported for the ionization of benzylic alcohols to carbocations stabilized by cyclic or acyclic *o*-alkyl or *o*-oxygen substituents. The measurements were stimulated by the observation of small or inverse effects of replacement of an *o*-CH$_2$ group by O or S in the cyclopentyl ring of indanol (k_O/k_{CH_2} = 1.2) or in the cyclohexyl ring of tetralol (k_O/k_{CH_2} = 0.6, k_S/k_{CH_2} = 0.3) on *rates* of carbocation formation. Values of pK_R (K_R = [ROH][H$^+$]/[R$^+$]) have been obtained by combining rate constants, k_H, for the acid-catalyzed ionization of the alcohols with k_{H_2O} for attack of water on the carbocation measured by the azide clock method. For carbocations derived from the following alcohols, values of pK_R are as indicated: 1-indanol, -11.7; 2,3-dihydro-3-hydroxybenzofuran (benzofuran hydrate), -9.3; 1-tetralol, -12.2; 4-chromanol, -12.0; 4-thiochromanol, -12.3; *o*-methyl-1-phenylethanol, -13.8; *o*-methoxy-1-phenylethanol, -11.7. The measurements show that, in contrast to its small kinetic effect, the equilibrium effect of replacing the *o*-CH$_2$ group by O in the cyclopentyl ring of indanol is 250-fold, whereas the effect of the same replacement in the cyclohexyl ring of tetralol is only 1.6. It is concluded (a) that the efficiency of conjugation of annular *o*-oxygen substituents to a benzylic carbocation center is sensitive to conformational restrictions arising from ring strain and (b) that, in the case of indanol, the kinetic effect of the same oxygen atom is subject to an imbalance of favorable resonance and unfavorable inductive effects at the transition state.

Introduction

In the past 15 years, the combination of laser flash photolysis[1] and trapping experiments based on the "azide clock" method [2] has provided a wide range of quantitative measurements of stabilities of carbocations in aqueous media.[3-6] These stabilities may be expressed as equilibrium constants, pK_R, for ionization of the alcohols (or, strictly, the reverse reaction of water with the carbocations), as shown in eqs 1 and 2. The ionization reaction is illustrated by the conversion of 3-hydroxy-2,3-

$$H^+ + ROH \underset{}{\overset{1/K_R}{\rightleftharpoons}} R^+ + H_2O \qquad (1)$$

$$K_R = \frac{[H^+][ROH]}{[R^+]} \qquad (2)$$

dihydrobenzofuran (benzofuran hydrate, **1**) to the 2,3-dihydrobenzofuranyl carbocation (**2**), which is an intermediate in the acid-catalyzed dehydration of **1** to form benzofuran (**3**), as shown in Scheme 1.

The purpose of this paper is to use the azide clock method to examine the effects of oxygen substituents at an ortho position relative to a benzylic carbocationic charge center, as in the dihydrobenzofuranyl carbocation (**2**). A normal perception would be that substituents directly conjugated with the carbocation center as in **2** should be strongly stabilizing and should strongly accelerate reactions leading to carbocation formation.

Surprisingly, despite the apparently favorable planar geometry constrained by the benzofuranyl ring, the accelerating effect of the oxygen atom in **1**, as judged by comparison with the corresponding structure lacking the oxygen, 1-indanol **4** (Scheme 2), is only 1.2-fold.[7] This indeed is not an isolated observation. Similarly small effects are observed for six-membered as well as five-membered rings and for rings containing sulfur substituents as well as for those containing oxygen.[7]
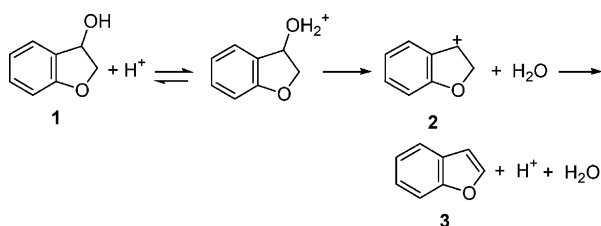
[†] Kyushu Unversity.
[‡] San Francisco State University.
[§] University College Dublin.
(1) McClelland, R. A.; Kanagasabapathy, V. M.; Banait, N. S.; Steenken, S. *J. Am. Chem. Soc.* **1989**, *111*, 3966−3972 and references therein.
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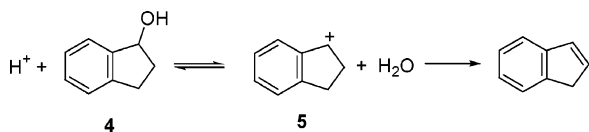(5) Pirinccioglu, N.; Thibblin, A. *J. Am. Chem. Soc.* **1998**, *120*, 6512−6517.

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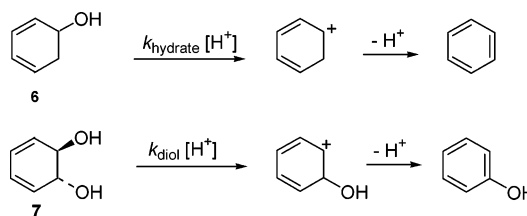
Scheme 1

Scheme 2

Scheme 3

Chart 1

dehydration of the alcohol or hydrate to solvolysis of the corresponding carboxylate esters. We also examine *ab initio* calculations of the stabilities of the carbocations to shed further light on the relative importance of resonance and inductive interactions.

Results

Values of pK_R of interest in this paper are derived from measurements of equilibrium constants for reactions of carbocations to form the alcohols shown in Chart 1. For 1-phenylethanol and its *p*-methyl and *p*-methoxy derivatives (**11**–**13**), values are available or could be extrapolated from measurements in the literature,[2a,11–14] and, as indicated above, the same is true of benzofuran hydrate (**1**).[6] For 1-indanol and 1-tetralol (**4** and **14**), rate constants (although not equilibrium constants) for acid-catalyzed ionization to the carbocation have been measured, based on measurements of rates of racemization of the chiral alcohols.[7] For naphthalene hydrate (**19**), a rate constant for carbocation formation has also been reported,[8] and an unpublished estimate of the equilibrium constant is available.[9]

In this work therefore, the following series of measurements were undertaken: (a) rate constants for racemization of chiral chromanol and thiochromanol **15** and **16** and (b) ratios of azide to alcohol products formed from solvolyses of trifluoroacetates of 1-indanol, 1-tetralol, 4-chromanol, 4-thiochromanol, and the *o*-methyl and *o*-methoxy derivatives of 1-phenylethanol (i.e., the alcohols **4** and **14**–**18**) in aqueous solution or aqueous– trifluoroethanol (TFE) solvent mixtures in the presence of varying concentrations of azide ions. Rate constants for these solvolysis reactions, and for solvolyses of chloroacetates of indanol, tetralol, and bezofuran hydrate, were also measured
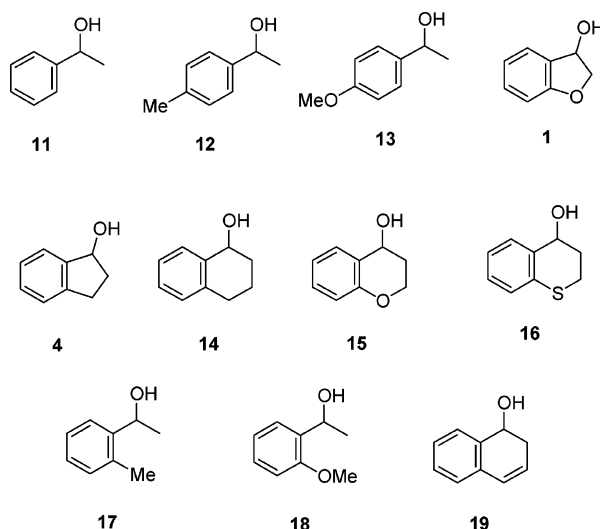
What is the origin of these strikingly small effects? Independent measurements of rate constants[8] for acid-catalyzed carbocation formation from benzene hydrate **6** and benzene *trans*-dihydrodiol **7** (Scheme 3)[9] offer a reminder that, in the absence of conjugation, a β-hydroxyl substituent can be strongly decelerating. The ratio of rate constants $k_{diol}/k_{hydrate}$ shows that the second hydroxyl group slows the reaction by 10^7-fold.
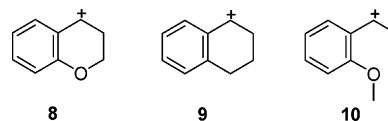
Where conjugation does occur, inductive and resonance effects work against each other. For *p*-oxygen substituents, there is ample evidence that a favorable resonance effect overrides any adverse inductive effect. However, less attention has been given to ortho substituents, and it seems possible that the small effect for benzofuran hydrate derives from the large magnitude of an *o*-oxygen inductive effect. An alternative, or additional, possibility is that the small effect is kinetic in origin and arises from an imbalance in the expression of resonance and inductive effects at the transition state relative to the reaction product.[10] An objective of the present paper is to distinguish these and other possibilities by comparing kinetic examples of exo- and endocylic *o*-oxygen substituent effects with corresponding equilibrium measurements, which reflect inductive and resonance effects on the stabilities of the fully formed carbocations.

The equilibrium constant, pK_R, for reaction of the 2-dihydrobenzofuranyl carbocation **2** to form benzofuran hydrate has been reported in an earlier paper.[6] In this paper, measurements of carbocation stabilities are extended to the corresponding six-membered chroman and thiochroman rings. For five- and six-membered rings, the carbocations formed (e.g., **8**) are compared with the corresponding carbocyclic cations lacking an oxygen or sulfur atom (e.g., **9**). In addition, the effects of endocyclic oxygen substituents are compared with those of acyclic *o*- and *p*-alkoxy substituents (e.g., **10**). To assess the influence of the leaving group, the kinetic measurements are extended from

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for mixtures of water with ethanol, acetone, and trifluoroethanol and, if possible, for pure water.

Racemization. Rate constants for acid-catalyzed loss of optical activity from partially resolved *o*-methyl-1-phenylethanol, *o*-methoxy-1-phenylethanol, chromanol, and thiochromanol were measured polarimetrically at 25 °C. For *o*-methoxy-1-phenylethanol, the measurements refer to aqueous solutions containing 0.05−0.25 M HClO$_4$. However, for the other alcohols, low solubility combined with a low specific rotation precluded measurements in water, and measurements were confined to trifluoroethanol−water mixtures. Second-order rate constants (k_H) in water were extrapolated, therefore, from measurements at a series of water−alcohol compositions on the basis of a linear solvent free energy relationship. Values of log k_H for various solvent compositions, X, were plotted against log k^X for the dehydration of the 2,3-hydrate of benzothiophene (**20**), which was taken as the reference reaction for the relationship.

20
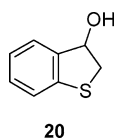
The dehydration of the benzothiophene hydrate was chosen as the reference because rate constants could conveniently be measured spectrophotometrically, and mechanistically these rate constants correspond to rate-determining formation of a carbocation,[7] the same process as measured by the acid-catalyzed racemizations. First-order rate constants were determined at different acid concentrations and solvent compositions and are shown in Table S1; second-order rate constants, k^X, and values of k^X/k^{H_2O} (where k^{H_2O} is the rate constant for reaction in water) are shown in Table S2. The values of k^X pass through a shallow minimum and then increase as the fraction of TFE in the solvent increases. This is apparent from values of $\log(k^X/k^{H_2O})$ for different volume fractions of TFE, which are negative in the range 0−35% TFE, i.e.: 0, 0%; −0.03, 10%; −0.04, 20%; −0.20, 30%; 0.07, 40%; 0.23, 50%; 0.42, 60%; 0.66, 70%.

First-order rate constants for the racemization reactions of **15**−**18** in water and TFE−H$_2$O mixtures are shown in Table S3. Corresponding data for **1**, **4**, and **14** are contained in ref 7. Plots of logs of second-order rate constants (log k_H) against log-(k^X/k^{H_2O}) for the benzothiophene hydrate give satisfactory linear correlations (shown in Figure S1) with slopes close to unity. These allowed values of k_H in water to be extrapolated to give the values shown in Table 1. Where the data are limited, extrapolation was assisted by assuming that the correlation lines have the same slope. The ratio of k_H in 50:50 TFE−H$_2$O to that in water was nearly constant and equal to 1.4 ± 0.1. This value was used to adjust measurements of k_H reported by Richard, Rothenburg, and Jencks in TFE−H$_2$O mixtures for 1-phenylethanol and its *p*-methyl and *p*-methoxy derivatives to values in pure water.[2a]

Azide Ion-Trapping Experiments. Trifluoroacetate esters of *o*-methyl- and *o*-methoxy-1-phenylethanol, indanol, tetralol, chromanol, and thiochromanol were prepared and solvolyzed in water or water−trifluoroethanol mixtures in the presence of varying concentrations of azide ions. The products of the solvolyses were analyzed by HPLC after 10 half-lives of reaction
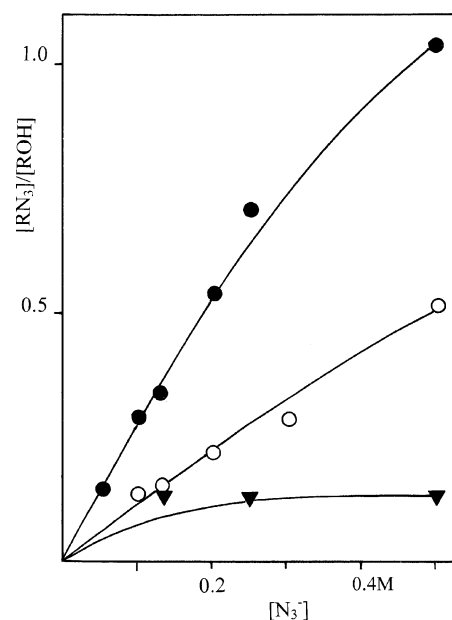
Figure 1. Plots of ratios of concentrations of azide to alcohol formed as products of solvolysis of the following trifluroacetate esters in the presence of sodium azide: 1-(*o*-methoxyphenyl)ethyl in water (●), tetralyl in water (○), and 1-(*o*-methylphenyl)-ethanol in 50% (v:v) aqueous trifluoro-ethanol (▼).

to obtain ratios of peak areas for aralkyl azides, alcohols, and trifluoroethyl ethers.[2a] Percentage peak areas at different azide concentrations in water are shown for the trifluoroacetates in Table S4. From values of the ratios for azide and alcohol, the corresponding concentration ratios, [RN$_3$]/[ROH], were evaluated at azide concentrations in the range 0−0.5 M (with ionic strength 0.5 M maintained with sodium perchlorate). It was assumed, as has been demonstrated for related substrates,[2a,11,15] that extinction coefficients are unchanged between aralkyl substrates bearing azido, hydroxy, and trifluoroethyl substituents. Ratios of rate constants for attack of azide ion and water on the carbocation k_{az}/k_{H_2O} (M^{-1}) were then obtained from the limiting slopes of plots of [RN$_3$]/[ROH] ($=k_{az}[N_3^-]/k_{H_2O}$) against the concentration of azide ion at low azide ion concentrations. Good linearity was found up to 0.25 M for all substrates except *o*-methyl-1-phenylethyl trifluoroacetate. This is illustrated for tetralyl trifluoroacetate and *o*-methoxymethyl trifluoroacetate in Figure 1. The lines drawn through the points were calculated on the assumption that the curvature at high concentrations of azide ion derives from competing hydrolysis of the trifluoroacetate esters to form alcohol catalyzed by azide ion. (Strictly speaking this "hydrolysis" is also a solvolysis reaction, albeit proceeding by an associative rather than a dissociative mechanism.) The two reactions are shown in Scheme 4. The catalysis of the hydrolysis by azide ion is probably nucleophilic but may be basic. For the two substrates shown, the ratio of rate constants for hydrolysis and solvolysis were 0.25 and 0.35 M^{-1} respectively. Assuming that the hydrolysis rate constants are first order in trifluoroacetate ester and first order in azide ion implies that at a concentration of 0.2 M azide ion less than 10% of the ester undergoes hydrolysis. More extensive hydrolysis was observed only for the *o*-methylbenzyl trifluoroacetate, which is consistent with the expectation, based on rate constants for acid-catalyzed

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Table 1. Rate and Equilibrium Constants for the Reactions of Carbocations To Form Alcohols in Water and 50:50 (v:v) Trifluoroethanol−Water Mixtures at 25 °C[a]

	Water			50:50 TFE-H$_2$O[b]		
	$10^3 k_H$ M^{-1}s^{-1}	$10^{-9} k_{H_2O}$ s^{-1}	pK_R	$10^3 k_H$ M^{-1}s^{-1}	$10^{-9} k_{H_2O}$ s^{-1}	pK_R
o-methyl-1-phenylethanol	0.20	(6.0)[c]	(−13.5)[c]	0.30	(4.5)[c]	(−13.2)[c]
o-methoxy-1-phenylethanol	3.2	1.6	−11.7	-	2.2	-
1-indanol	6.0[d]	2.3	−11.6	10.5	1.9	−11.3
2,3-dihydrobenzofuran-3-ol	7.4[d]	.0155	−9.3	-	-	-
1-tetralol	2.8[d]	3.8	−12.1	-	-	-
4-chromanol	1.7	1.6	−12.0	2.63	3.2	−12.1
thiochromanol	0.74	1.4	−12.3	1.20	2.8	−12.4

[a] The best estimates of errors are ±0.25 unit for pK_R, ±15% for k_H, and ±50% for k_{H_2O} (see Experimental Section). [b] Values refer to 0.2 M N$_3^-$ concentrations, whereas values for pure water are extrapolated to zero concentrations of azide ion. [c] Brackets indicate greater uncertainty in these values because of inefficiency of the azide trapping, yielding values of k_{H_2O}; indeed, k_{H_2O} in water is taken as 1.4 times the value in 50:50 (v:v) TFE−H$_2$O. [d] Differs from the previously reported value because of re-extrapolation of measurements of the rate constants for acid-catalyzed racemization in ref 7 by the means described in this paper.

Scheme 4
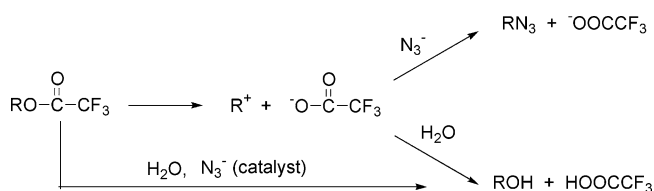
racemization of the alcohols, that its rate of solvolysis is an order of magnitude slower than that of the other substrates studied.

The measurements of rate constant ratios, k_{az}/k_{H_2O}, allowed values of k_{H_2O}, the rate constant for reaction of the carbocation with water, to be derived. The assumption is made that the reaction with azide ion is diffusion controlled, with $k_{az} \cong 5.0 \times 10^9$ M^{-1} s^{-1}. The value of k_{H_2O} is obtained by combining this value with k_{az}/k_{H_2O}. Rate constants, k_{H_2O}, are listed in Table 1. The rate constant for the *o*-methyl-1-phenylethyl carbocation was extrapolated from measurements in TFE−H$_2$O mixtures as described below.
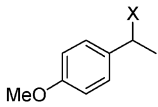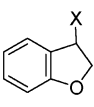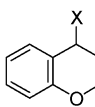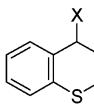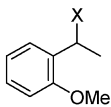
For measurements in TFE−H$_2$O mixtures, values of k_{az}/k_{H_2O} and k_{H_2O} were derived in the same way as for pure water. It should be noted that, for TFE−H$_2$O mixtures, HPLC peak areas

are recorded for the aralkyl trifluoroethyl ether as product as well as the alcohol and azide. Table S5 shows measurements of these peak areas from solvolysis of 1-indanyl, *o*-methoxy-1-phenylethyl, tetralyl, and 4-chromanyl trifluoroacetates in 70% trifluoroethanol−water solvent mixtures (v:v). Table S6 shows corresponding peak areas from solvolysis of *o*-methyl-1-phenylethyl trifluoroacetate in 50% trifluorethanol−water.

The small extent of azide trapping in the solvolysis of *o*-methyl-1-phenylethyl trifluoroacetate apparent from Table S6 is consistent with the slowness of this reaction noted above. In the presence of azide ions, the reaction product comprises mainly the alcohol formed from the competing ester hydrolysis reaction. In Table S6, it is also apparent that the ratio of alcohol to trifluoroethyl ether increases as the concentration of azide ion increases. This is understandable in terms of Scheme 4 if we recognize that the ether is formed only in the solvolysis reaction and not in the hydrolysis and that the extent of (azide-catalyzed) hydrolysis, which yields only alcohol, increases with increasing concentration of azide ion.

In Figure 1, it is shown that a plot of values of [RN$_3$]/[ROH] against azide ion concentration of the *o*-methylphenylethyl trifluoroacetate can be fitted quantitatively in terms of Scheme 4. However, because of the extensive hydrolysis, k_{H_2O} is less

Table 2. Oxygen Substituent Effects on Rateand Equilibrium Constants for Carbocation Formation[a]

	MeO–(phenethyl)	benzofuran	chromanyl (O)	thiochromanyl (S)	o-OMe phenethyl
$K_R^O/K_R^{CH_2}$ [b]	10,000	250	1.6	0.5	160
$k_H^O/k_H^{CH_2}$ [c] ($X = OH_2^+$) [d]	132	1.2	0.6	0.25	12
$k_{solv}^O/k_{solv}^{CH_2}$ (X = Cl or OOCR)	1320 [e]	37 [f]	6 [g]	3 [g]	(>110) [h]

[a] k^O/k^{CH_2} for bicyclic compounds, k_{MeO}/k_{Me} for substituted phenethyl substrates. [b] Ratios of equilibrium constants, $1/K_R$, for acid-dependent carbocation formation from alcohols. [c] Acid-catalyzed carbocation formation from alcohols. [d] $X = OH_2^+$ is generated by a pre-equilibrium protonation so that in the reactant X = OH. [e] Solvolysis of aralkyl chlorides, ref 22. [f] Solvolyses of chloroacetate esters. [g] Solvolyses of trifluoroacetate esters in 60 and 70% aqueous acetone; in pure ethanol, the value is reduced by ca. 40%. [h] Solvolysis of o-MeO and o-Me cumyl chlorides, ref 23; steric effects are expected to be greater here than for α-phenylethyl chlorides; the brackets indicate that the value is subject to uncertainty.

accurately determined than for other substrates. In pure water, an adequate fit could not be achieved, and k_{H_2O} was derived from the value in 50:50 TFE–H$_2$O and the average ratio of k_{H_2O} values in the two solvent compositions for other substrates mentioned above (1.4).

The influence of solvent composition on the azide:alcohol product ratios for different trifluoroacetate esters was investigated by HPLC analysis of solvolysis products in aqueous solvent mixtures containing 0–70% trifluoroethanol and 0.2 M NaN$_3$. Except for the o-methylphenylethyl trifluoroacetate, the extent of competing hydrolysis at this azide concentration is less than 10%. Table S7 shows the dependence of alcohol, azide, and trifluoroethyl ether peak areas on solvent composition for o-methyl- and o-methoxy-1-phenylethyl, indanyl, 4-chromanyl, and 4-thiochromanyl trifluoroacetates.

Values of k_{H_2O} evaluated from the data of Table S7 are recorded as a function of solvent composition for indanyl, 4-chromanyl, and 4-thiochromanyl carbocations in Table S8. These substrates were selected because measurements of the solvent dependence in 0–70% TFE were also made (or for indanol could be extrapolated) for rate constants for acid-catalyzed racemization of the alcohol (Table S3). Interpolated values of these rate constants are also included in Table S8. Assuming that the rate constants may be identified with values for formation of the carbocation, k_H, the equilibrium constant, K_R, for hydrolysis of the carbocation (eqs 1 and 2) may be obtained as $K_R = k_{H_2O}/k_H$.

Values of pK_R are also included in Table S8. The solvent dependence of pK_R is of interest because measurements based on azide ion trapping are commonly reported in 50% aqueous trifluoroethanol. The results show that at low concentrations of trifluoroethanol pK_R decreases slightly, but that as the fraction of trifluoroethanol is increased, it increases. Plots of pK_R against $\log(k^X/k^{H_2O})$ for the dehydration of benzothiophene hydrate are linear, with slopes of −1.4. In 50% (v:v) aqueous trifluoroethanol, values of pK_R are 0.3 unit less than in water, and in 70% trifluoroethanol, they are 1 unit less than in water. Previous measurements for the 9-fluorenylmethyl[11] and anthracenyl[17] cations have shown rather larger differences of 0.8–1.0 unit between water and 50% trifluoroethanol. It is not clear why the benzylic cations studied here display a smaller difference.

Values of pK_R for water and 50% aqueous trifluoroethanol are summarized in Table 1, together with k_H and k_{H_2O}.

Solvolysis Rate Constants. Solvolytic rate constants for the chloroacetates of the alcohols benzofuran hydrate, indanol, and tetralol (**1**, **4**, and **14**) were measured in aqueous solution. The objective of these measurements was to allow a comparison of oxygen substituent effects on acid-catalyzed carbocation formation from the alcohols with those for the solvolysis reactions. For the alcohols **1** and **4**, the measurements were extended to trifluoroacetate esters, and trifluoroacetate esters of chromanol (**15**) and thiochromanol (**16**) were also prepared. For these esters, the solvolyses were too fast for direct measurement in water, and rate constants were evaluated in aqueous mixtures with ethanol, acetone, and trifluoroethanol.

The solvolytic rate constants for the trifluoroacetate esters were monitored conductimetrically[18] at 25 or 0 °C and are listed as functions of solvent composition in Table S9. Grunwald–Winstein plots[19,20] of log k against the solvent parameter Y_{OTs} (cf. eq 3) gave slopes, m, in the range 0.6–0.8, but showed too much scatter for accurate extrapolation of rate constants in water.

$$\log(k/k_{H_2O}) = mY_{OTs} \qquad (3)$$

Rate constants for the chloroacetate esters are shown in Table S10. Oxygen substituent effects were derived from measurements of solvolytic rate constants for the chloroacetate esters of 1-indanol (2.9×10^{-4} s^{-1}) and 3-hydroxy-2,3-dihydrobenzofuran (1.06×10^{-4} s^{-1}) in water at 25 °C and for the trifluoroacetate esters of 1-tetralol (9.8×10^{-5} s^{-1}), 4-chromanol (5.8×10^{-4} s^{-1}), and 4-thiochromanol (1.8×10^{-4} s^{-1}) in 70% acetone–water (v:v) at 25 °C. These substituent effects are shown in Table 2.

Calculation of Stabilities of Carbocations and Protonated Alcohols. Gas-phase electronic energies, uncorrected for zero

(16) Cox, R. A. *Adv. Phys. Org. Chem.* **2000**, *35*, 1–66.
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(19) Schadt, F. G.; Bentley, T. W.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1976**, *98*, 7667–7675.
(20) Bentley, T. W.; Llewellyn, G. *Prog. Phys. Org. Chem.* **1990**, *17*, 121–158.

Chart 2

k_O/k_{CH_2} 1.2

k_O/k_{CH_2} 0.5

k_{MeO}/k_H 3700
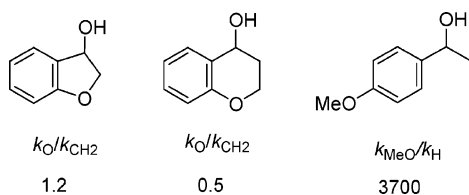
point or thermal vibrational energies, were calculated for the alcohols **1**, **4**, **14**, **15**, and **19** and corresponding carbocations, with geometries optimized at the HF/6-31G* level. Frequency calculations at this level showed that all species occupy minima on their potential energy surfaces. The energy calculations were carried out at the MP2/6-31G* level. Calculations were also carried out for the *O*-protonated conjugate acids of indanol **4** and 3-hydroxy-2,3-dihydrobenzofuran **1**. For the protonated alcohols, no minimum energy could be found, and it was necessary to constrain the $C-OH_2$ bond lengths so that heterolysis to the carbocation−water complex did not occur. This presumably was a reflection of lack of solvation in the gas phase. The constrained distances were set at 0.005−0.010 Å greater than the C−O distances in the parent alcohols. By varying the distances over this range, it was established that there was no significant effect on the computed *difference* between the basicities of the indanol and 3-hydroxy-2,3-dihydrobenzofuran. The electronic energies obtained by these methods are listed in Table S11 of the Supporting Information.

Discussion

The purpose of this paper is to examine and elucidate equilibrium constants for the formation of benzylic carbocations containing *o*-oxygen substituents. As already indicated, a stimulus for the study was provided by the measurement of surprisingly small kinetic effects of *o*-oxygen substituents within five- and six-membered rings.[7] These are illustrated in Chart 2 by ratios of rate constants $k_O/k_{CH_2} = 1.2$ and 0.5 for acid-catalyzed formation of carbocations from benzo-fused five- and six-membered heterocyclic and carbocyclic alcohols, respectively. By comparison, a *p*-methoxy substituent increases the rate of carbocation formation from 1-phenylethanol by 3700-fold. The question is posed, do the small effects of cyclic oxygen substituents imply a suppressed resonance effect, an enhanced inductive effect, or indeed a combination of these?

Before attempting an answer to this question, two further questions need to be addressed. First, how do the cyclic oxygen substituents compare with an (acyclic) *o*-methoxy substituent? And, second, how important is it that the cyclic oxygen substituents in Chart 2 are compared with (cyclic) *alkyl* groups, whereas the *p*-methoxy substituent is compared with a *hydrogen* atom?

The effects of *o*- and *p*-methoxy and methyl substituents on acid-catalyzed ionization of 1-phenylethanols are summarized in Chart 3. It can be seen that, for an *o*-methoxy substituent, $k_{MeO}/k_H = 160$ is smaller than for a *p*-methoxy substituent, $k_{MeO}/k_H = 3700$. This difference is understandable in terms of steric hindrance to resonance interaction between the *o*-oxygen substituent and carbocation center. Nevertheless, the effect of the *o*-MeO group remains much larger than that of an endocyclic oxygen substituent.

The effect of an oxygen substituent is reduced if the reference substituent is an alkyl group rather than a hydrogen atom. Thus,
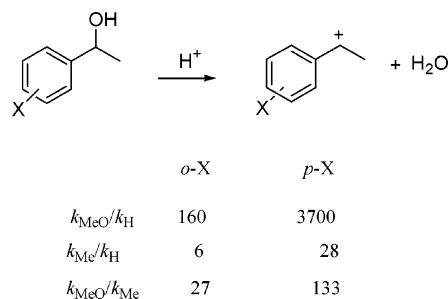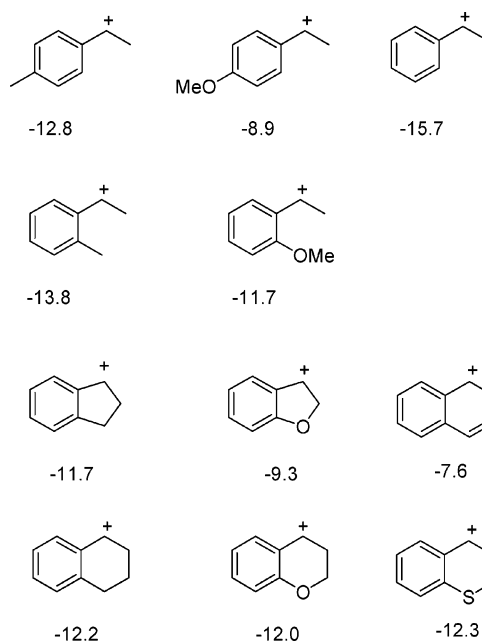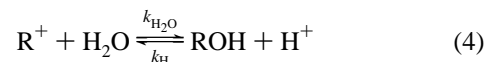
Chart 3

	o-X	*p*-X
k_{MeO}/k_H	160	3700
k_{Me}/k_H	6	28
k_{MeO}/k_{Me}	27	133

Chart 4

−12.8 −8.9 −15.7

−13.8 −11.7

−11.7 −9.3 −7.6

−12.2 −12.0 −12.3

$k_{MeO}/k_{Me} = 133$ for a para substituent and 27 for an ortho substituent. This implies that the small effect of the cyclic oxygen derives at least in part from its comparison with a cycloalkyl reference. Nevertheless, the effect of the *o*-methoxy group remains respectively 10 and 25 times larger than that of oxygen in the five- and six-membered rings.

Carbocation Stabilities. Insight into the small effects of oxygen substituents is provided by a comparison of kinetic with equilibrium measurements. The relevant equilibrium is the acid-catalyzed conversion of an alcohol to a carbocation, shown in eq 1. The equilibrium constant K_R (or $pK_R = -\log K_R$) may be derived by combining rate constants k_H for the acid-catalyzed ionization of an alcohol and k_{H_2O} for reaction of the carbocation with water, measured by the azide clock method (eqs 4 and 5).

$$R^+ + H_2O \underset{k_H}{\overset{k_{H_2O}}{\rightleftharpoons}} ROH + H^+ \qquad (4)$$

$$K_R = \frac{k_{H_2O}}{k_H} \qquad (5)$$

The values of pK_R of interest are shown under the relevant structures in Chart 4. For 1-phenylethanol and its *p*-methyl and *p*-methoxy derivatives, values are taken from the literature.[2a] These refer to 50:50 trifluoroethanol−water mixtures and have been modified in Chart 4 by −0.3 unit to account for the difference from those in pure water. The remaining values

are from this work or (in the case of the naphthalenonium ion) unpublished results.[9]

In the first column of Chart 4, pK_R's are shown for carbocation reference structures. These consist of the methyl-substituted phenylethyl cations and benzoannulated cyclopentenyl or cyclohexenyl cations. In the second column are pK_R's for the corresponding oxygen-substituted cations, with a methyl substituent replaced by methoxy or, in the cyclic cations, a methylene group by oxygen. The first and second *rows* of the chart show para- and ortho-substituted phenylethyl cations, as well as the parent unsubstituted cation. The third and fourth rows show the benzocyclopentenyl and benzocyclohexenyl cations and their oxygen, sulfur, or π-bonded analogues.

The pattern of oxygen substituent effects on equilibrium stabilities of carbocations in most respects matches their kinetic effects. The principal discrepancy arises for the five-membered rings. Thus, for the carbocations derived from indanol and benzofuran hydrate, there is a 250-fold difference in thermodynamic stabilities. This compares with the kinetic effect of only 1.2-fold. It is noteworthy that the indanyl cation, with which the 2,3-dihydrobenzofuranyl cation is compared, is more than 100-fold more stable relative to its alcohol than the *o*-methylphenethyl cation ($pK_R = -11.7$ compared with -13.8). This may be attributed to a lack of steric effects and to favorable inductive and conformational effects on the stability of the cyclic carbocation. That the oxygen substituent effect in the 2,3-dihydrobenzofuranyl cation is hardly more effective than in the open-chain and sterically hindered *o*-methoxy cation (250-fold compared with 100-fold differences in K_R) may imply that the rigidity of the five-membered ring is unfavorable to resonance between the oxygen atom and the carbocation center. *A fortiori*, this seems the most likely explanation of the much smaller effect of oxygen (less than 2-fold) in the six-membered ring of the chromanyl cation. The smallness of this effect is corroborated by the even smaller stabilizing effect of S; indeed an *o*-S atom actually reduces the stability of the carbocation by 2-fold.

The equilibrium results thus tend to suggest that conformational effects hinder full expression of the resonance effect of oxygen. Remarkably, the suppression of resonance effects of O and S substituents contrasts strikingly with the behavior of a double bond in a six-membered ring. Comparison of $pK_R = -7.6$ for the naphthalenonium ion (third row of Chart 5) with $pK_R = -12.2$ for the tetralyl cation (**9**) shows that the double bond increases the stability of the carbocation by more than 10^4-fold. This implies that there is no conformational restriction of resonance for a double bond in a (benzo-fused) six-membered ring with a carbocation center and, indeed, that the resonance is probably enhanced.

Calculations of Carbocation Stabilities. The effects of endocyclic oxygen atoms and π-bonds on carbocation stabilities are confirmed by calculations at the MP2/6-31G*//HF/6-31G* level. The results of the calculations are best summarized by a comparison of experimental differences in pK_R (ΔpK_R) between the oxygen- (or π-) substituted carbocations and their carbocyclic analogues and the corresponding calculated differences in energy ($\Delta\Delta E$) in the gas phase. The values of ΔpK_R and $\Delta\Delta E$ correspond to isodesmic reactions, combining oxygen-substituted and unsubstituted reactants and carbocations, as illustrated for the benzofuranyl and indenyl hydrates and carbocations in
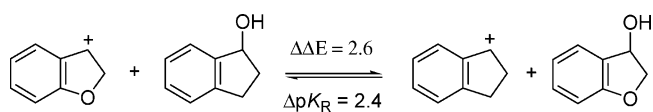
Scheme 5

$$\Delta\Delta E = 2.6$$
$$\Delta pK_R = 2.4$$

Chart 5

ΔpK_R		2.4	0.2	4.6
$\Delta\Delta G$ (kcal mol^{-1})		3.1	0.3	6.3
$\Delta\Delta E$(calc)		2.6	-0.4	5.4

Scheme 5. Inclusion of zero point energies has no appreciable effect on the $\Delta\Delta E$ values.

Values of $\Delta\Delta E$ and ΔpK_R are summarized beneath the structures of the relevant oxygen- or π-substituted carbocations in Chart 5. Also shown are values of $\Delta\Delta G = 1.36\Delta pK_R$ (at 25 °C), which provide a more direct comparison with $\Delta\Delta E$. For the dihydrobenzofuranyl cation, ΔpK_R and $\Delta\Delta E$ are the same as in Scheme 5. For the chromanyl cation and naphthalenonium ion, the isodesmic comparison is provided by the tetralyl cation (and the appropriate alcohols).

It can be seen that the trend in ΔpK_R values in Chart 5 is closely mirrored in the values of $\Delta\Delta E$. This provides a satisfying confirmation that the measurements in solution are not complicated by solvation effects but reflect factors implicit in the gas-phase values and, indeed, in the calculations. While the interpretation of relative pK_R values in terms of efficiency of resonance interaction between the oxygen or π-bond and carbocation center is not unambiguously corroborated, inspection of the calculated structures (**21−23**) of the three carbocations
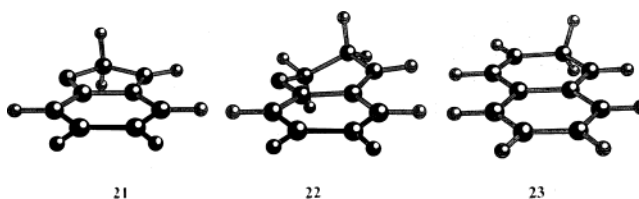
studied indicates that the benzofuranyl cation and naphthalenonium ion are substantially planar, whereas the heterocyclic ring of the chromanyl cation is strongly puckered. Thus, the dihedral angle calculated between atoms 2, 1, 8, and 9 in both the chromanyl carbocation (**22**) and chromanol is close to 16°. It is not possible to judge the extent of impairment of resonance implied by the nonplanarity of the chromanyl cation. Qualitatively, however, the structure is consistent with the explanation already offered for the minimal effect of oxygen in the six-membered ring and with the contrasting behavior of an oxygen atom and a π-bond in the six-membered ring observed experimentally.

Thus, the calculations confirm that conformational effects influence the efficiency of resonance interactions between a carbocation center and a cyclic *o*-oxygen or π-substituent within a six-membered ring. There is less support for a similar restriction of resonance for oxygen in a five-membered ring since the 2,3-dihydrobenzofuranyl cation (**20**), like the naphthalenonium cation (**22**), is planar. However, the experimental

Scheme 6

$\Delta\Delta E$ (kcal mol^{-1})   +3.5   -2.6

Scheme 7
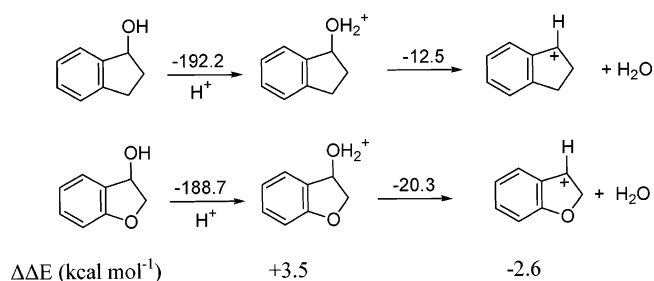
comparisons between pK_R values described above suggest that the stability of the dihydrobenzofuranyl carbocation may also be impaired, and if so, the presence of ring strain within the planar structure seems the most likely explanation.

How Important Are Oxygen Inductive Effects? If we now turn to the comparison of kinetic and equilibrium effects, we can revisit the contrast between the relatively "normal" effect of oxygen in a five-membered ring on the thermodynamic stability of a carbocation, $K_R^O/K_R^{CH_2} = 250$, and the much smaller kinetic effect of the same oxygen substitution, $k_R^O/k_R^{CH_2} = 1.2$. This disparity suggests an additional impairment of resonance or (and) an enhanced inductive effect of oxygen in the transition state for carbocation formation compared with the fully formed carbocation.

Imbalance of resonance and inductive effects has generally been discussed in terms of a lag in or enhancement of resonance at the transition state in comparison with the reactants and products involved in the equilibrium.[10,21] However, there may also be a contribution from an enhanced inductive effect arising from structural features of the transition state not present in either reactants or products. Thus, in the dehydration of alcohols, carbocation formation occurs in two steps and involves formation of an *O*-protonated conjugate acid of the alcohol reactant as a reactive intermediate. As a consequence, part of the positive charge in the transition state is located on an H$_2$O leaving group. This introduces an unfavorable inductive interaction, which is present in neither reactant nor carbocation and, therefore, has no influence on the equilibrium. In the limit that the transition state is close in structure to the protonated alcohol, the effect may override a favorable resonance interaction of oxygen with the developing carbocation charge center.

This influence of *O*-protonation is confirmed by calculations of the energies of protonation of the alcoholic oxygen atoms. Although energy minima were not found for the protonated alcohols (or saddle points for the transition states for their ionization), calculations could be compared for fixed carbon–oxygen (C–OH$_2^+$) distances. In practice, the C–OH$_2^+$ bond length was chosen to be a little longer than the C–O distance in the alcohol, but small variations in this distance did not lead to qualitative changes in the results. The calculated geometries of alcohol and carbocation structures were optimized at an HF/6-31G* level.

The reaction sequences in Scheme 6 show energies for conversion of the alcohol reactant to (i) the protonated alcohol and (ii) the free carbocation, for both indanol and benzofuran hydrate. Below the benzofuranyl structures are shown the values of $\Delta\Delta E$, indicating the differences in energies for conversion of the two alcohols to the appropriate cationic species.
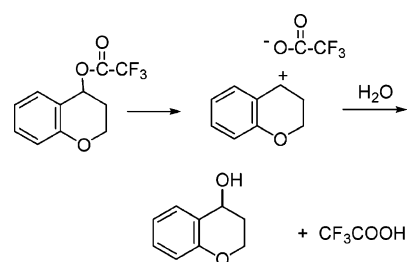
The value of $\Delta\Delta E = -2.6$ kcal mol^{-1} for the free carbocation has already been discussed. Attention is drawn here to the difference between the sign of this value and $\Delta\Delta E = +3.5$ kcal mol^{-1} for conversion of alcohol molecules to protonated alcohols. The positive sign of $\Delta\Delta E$ makes it clear that the effect of the endocyclic oxygen on the stability of the protonated alcohol is dominated by its adverse inductive effect, which is the reverse of its stabilizing effect on the carbocation.

Solvolysis Reactions. The influence of inductive effects arising from the interaction of oxygen substituents with the leaving group can be further assessed from solvolysis reactions in which the leaving group bears a negative rather than a positive charge in the transition state. Rate constants for solvolysis of a number of trifluoroacetate and chloroacetate ester derivatives of the alcohols related to the carbocations in Chart 4 have been measured, including solvolysis of the chromyl trifluoroacetate shown in Scheme 7.

Rate constant ratios representing the effects of oxygen substitution in five- and six-membered rings in the solvolysis reactions are shown in Table 2. These are compared with corresponding ratios of rate and equilibrium constants for formation of the same carbocation from alcohols and hydrates. The table also shows rate and equilibrium constant ratios for *o*- and *p*-methoxy- and *o*- and *p*-methyl-substituted 1-phenylethyl alcohols or chlorides.

From Table 2, it can be seen that substituent effects (k_O/k_{CH_2}) in the solvolysis reactions are substantially larger than those in the acid-catalyzed ionizations of the alcohols, i.e., 37 compared with 1.2 for the five-membered ring and 6 compared with 0.6 for the six-membered ring. This is consistent with transition states in which the leaving groups bear a negative charge, leading to a less unfavorable inductive effect from an oxygen substituent and allowing a more dominant role for the resonance effect of oxygen.

Effects of *o*- and *p*-methoxy substituents on the ionization of 1-phenylethyl alcohols are also enhanced when the leaving group bears a negative rather than a positive charge. Despite the fact that the inductive effect is expected to be less important from the para position than from the ortho position, the accelerating effect of the oxygen is still much greater in the solvolysis than in the ionization reaction; thus, *p*-MeO/*p*-Me = 1320 for Cl as a leaving group,[22] compared with 133 for OH$_2^+$. A similar increase is seen for the *o*-MeO group (110 compared with 12); although the comparison here is for cumyl chlorides,[23] these should provide a lower limit for the 1-phenylethyl chlorides for which resonance stabilization of the carbocation is subject to less steric constraint.

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(22) Tsuno, Y.; Kusuyama, Y.; Sawada, M.; Fujii, T.; Yukawa, Y. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 3337–3346.

(23) Okamoto, Y.; Brown, H. C. *J. Am Chem. Soc.* **1957**, *79*, 1909–1912.
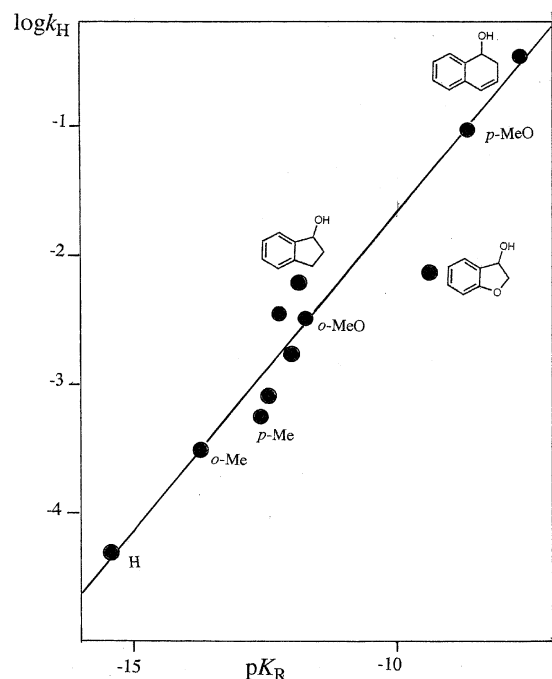
Figure 2. Plot of log k_H for the acid-catalyzed conversion of benzylic alcohols to the corresponding carbocations against pK_R for the carbocation in aqueous solution at 25 °C.

Comparison of Kinetic and Equilibrium Effects. If we compare rate and equilibrium constants for the full range of carbocation reactions studied by plotting log k_H against pK_R as in Figure 2, it can be seen that most of the reactions are well correlated by a straight line, log $k_H = 0.49pK_R + 3.2$. This implies that the inductive effect associated with a leaving group bearing a positive charge in the transition state systematically affects all substrates. There are minor deviations, suggesting that the rate constants of the cycloalkanols, tetralol, and indanol are enhanced and that the reverse is true of chromanol and thiochromanol. However, the single major deviation is the slow reaction of benzofuran hydrate.

The factor responsible for the negative deviation of benzo-furan hydrate can sensibly be identified as impairment of resonance stabilization. This presumably arises from confor-mational restrictions upon conjugation of the oxygen with the carbocationic charge center, reflecting strain within the five-membered ring. By analogy with other studies of imbal-ance,[10,21,24] it is reasonable to suppose that this impairment is greater in the transition state than in the carbocation. Interest-ingly, a similar imbalance is *not* observed for substituent effects of oxygen and sulfur in a six-membered ring, even though it seems clear from experiment and calculations that the strain in the fully formed chromanyl and thiochromanyl cations is greater than that in the dihydrobenzofuranyl cation. Nor is imbalance observed in the reactions of the sterically restricted *o*-methoxy phenethyl cation.

Conclusion

We can conclude, therefore, that the small kinetic and equilibrium effects of oxygen or sulfur substituents for car-bocation-forming reactions of chromanol or benzofuran hydrate and their thio analogues stem from stereochemical restrictions

to conjugation of the endocyclic oxygen or sulfur atom with the carbocation charge center. The kinetic effects of O- and S-substituents are further diminished by unfavorable inductive effects when H_2O is the leaving group and bears a positive charge in the transition state which is not present in the reactants or (carbocation) intermediates. The stereochemical constraints on the conjugation of an *o*-oxygen substituent are accentuated for transition states when the oxygen is contained in a five-membered ring and (probably) relaxed when in a six-membered ring.

Experimental Section

Material and Methods. Most of the alcohols used in this paper were commercially available (Aldrich) or, in the case of benzofuran and benzothiophene hydrates, their synthesis had been described earlier.[7] However, *o*-methoxy-1-phenylethanol and thiochromanol were prepared from the corresponding ketones by reduction with sodium borohydride. The procedure is described for the former compound only.

o-Methoxyacetophenone (5.0 g, 33 mmol) and sodium borohydride (2.14 g, 60 mmol) were heated under reflux in ethanol (60 mL) for 1.5 h. Acetone (60 mL) was added, and the solvent was evaporated. The resulting white solid was treated with water (30 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The combined extracts were washed with HCl and H_2O, dried over sodium sulfate, and evaporated to yield *o*-methoxy-1-phenylethanol as a clear oil which solidified overnight to form a white solid (mp 32−34 °C, lit. bp 76−78 °C, 0.02 mm).[25] ^1H NMR (CDCl$_3$) δ 1.50 (d, 3H, J = 6.6 Hz, 1-CH$_3$), 2.72 (s, 1H, OH), 3.86 (s, 3H, OCH$_3$), 5.08 (m, 1H, CH), 6.86−7.36 (m, 4H, aromatic). ^{13}C NMR (CDCl$_3$) δ 22.9 (CH$_3$), 55.1 (OCH$_3$), 66.1 (CH), 110.3, 120.7, 125.9, 128.1 (aromatic CHs), 133.5, 156.3 (aromatic C's).

Thiochromanol was obtained as a yellow solid.[26] ^1H NMR (CDCl$_3$) δ 1.78−1.90 (m, 1H, CH) 2.01−2.1 (m, 1H, CH), 2.63−2.71 (m, 1H, CH), 2.87 (s, 1H, OH), 3.07−3.17 (m, 1H, CH), 4.52 (m, 1H, CH), 6.89−7.15 (m, 4H, aromatic).

The racemic alcohols *o*-methyl- and *o*-methoxy-1-phenylethanol, chromanol, and thiochromanol were converted to optically active forms by preparation of a mixture of diastereomeric camphanyl esters by reaction with (−)-(1S)-camphanic chloride in dry pyridine, following a procedure used earlier.[7,27] The esters were separated by fractional crystallization, and the less soluble isomer was isolated in at least 5:1 excess. This diastereomer was hydrolyzed to the optically active alcohol with potassium hydroxide in aqueous THF.

The alcohols indanol and tetralol were converted to their chloro-acetoxy esters by reaction with chloracetyl chloride, following the procedure for the preparation of 3-chloroacetoxy-2,3-dihydrobenzo-furan.[7] The esters were isolated as clear oils which were too unstable for chromatograpy. They gave the following NMR spectra, which contained no indication of appreciable impurity. 1-Chloroacetoxy-1,2,3,4-tetrahydronaphthalene, ^1H NMR δ 1.80−202 (m, 4H CH$_2$'s), 2.72−2.81 (m, 2H, CH$_2$'s) 3.99 (s, 2H, COCH$_2$Cl), 6.04 (t, 1H, CH), 7.08−7.27 (m, 4H aromatic). 1-Chloroacetoxyindane, ^1H NMR δ 2.16 (m, 1H, CH), 3.13 (m, 1H, CH), 4.04 (s, 2H, COCH$_2$Cl), 6.28 (dd, 1H, CH) 7.21−7.44 (m, 4H, aromatic).

The alcohols tetralol, indanol, chromanol, thiochromanol, 1-(2′-methoxyphenyl)ethyl alcohol, and 1-(2′-methylphenyl)ethyl alcohol were converted to trifluoroacetate esters by the procedure described below for tetralol. Like the chloroacetate esters, the trifluoroacetate esters were too unstable for chromatography and had to be stored in a freezer. However, they gave satisfactory analyses and NMR spectra with no indication of impurities.

Trifluoroacetic anhydride (2.1 g, 10 mmol) was added dropwise with stirring to tetralol (0.74 g, 5 mmol) and pyridine (0.79 g, 10 mmol) in

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ethyl ether (8 mL), which was cooled to −10 °C in an ice−salt bath. The reaction mixture was stirred for 1 h, after which pentane (75 mL) was added and the mixture filtered to remove pyridinium trifluoroacetate. The product was washed, dried, and solvent evaporated to give 1-trifluoroacetoxy-1,2,3,4-tetrahydronaphthalene as a pale yellow oil (0.95 g, 78%). ^{1}H NMR (CDCl$_3$) δ 1.87−2.15 (m, 4H, CH$_2$'s), 2.78−2.92 (m, 2H, CH$_2$), 2.78−2.92 (m, 2H, CH$_2$), 6.17 (t, 1H, CH), 7.16−7.30 (m, 4H, aromatic). Anal. Calcd for C$_{12}$H$_{11}$O$_2$F$_2$: C, 59.02; H, 4.54; F, 23.34. Found: C, 59.17; H, 4.69; F, 22.86.

4-Trifluoroacetoxy-3,4-dihydrochromene was obtained as a clear oil (yield 0.10 g, 10%). ^{1}H NMR (CDCl$_3$) δ 2.18−2.35 (m, 2H, CH$_2$), 4.23−4.38 (m, 2H, CH$_2$), 6.12 (t, 1H, CH), 7.16−7.31 (m, 4H, aromatic).

4-Trifluoroacetoxy-3,4-dihydrothiochromene was obtained as a clear oil (yield 0.66 g, 57%). ^{1}H NMR (CDCl$_3$) δ 2.16−2.49 (m, 2H, CH$_2$), 2.85−3.28 (m, 2H, CH$_2$), 6.17 (t, 1H, CH), 7.03−7.38 (m, 4H, aromatic). Anal. Calcd For C$_{11}$H$_9$O$_2$F$_3$S: C, 50.38; H, 3.46; F, 21.73; S, 12.23. Found: C, 50.16 H, 3.55; F, 22.10; S, 12.24.

1-Trifluoroacetoxyindane was obtained as a clear oil (0.66 g, 57%). ^{1}H NMR δ 2.26 (m, 1H, CH), 2.56 (m, 1H, CH), 2.94 (m, 1H, CH), 3.19 (m, 1H, CH), 6.37 (t, 1H, CH), 7.25−7.46 (m, 4H, aromatic). Anal. Calcd for C$_{11}$H$_9$O$_2$F$_3$: C, 57.40; H, 3.94; F, 24.96. Found: C, 57.02; H, 4.08; F, 25.01.

1-(2′-Methoxyphenyl)ethyl trifluoroacetate was isolated as a clear oil. ^{1}H NMR δ 1.61 (d, 3H, J = 6.0 Hz, CH$_3$), 6.85−7.69 (m, 4H, aromatic). Anal. Calcd for C$_{11}$H$_{11}$O$_3$F$_3$: C, 53.23; F, 22.96. Found: C, 53.23; H, 4.60; F, 22.68.

1-(2′-Methylphenyl)ethyl trifluoroacetate was isolated as a clear oil. ^{1}H NMR δ 1.63 (d, 3H, J = 6.6 Hz, CH$_3$), 2.39 (s, 3H, 2′-CH$_3$), 6.23 (dd, 1H, CHCH$_3$), 7.14−7.40 (m, 4H aromatic). Anal. Calcd for C$_{11}$H$_{11}$O$_2$F$_3$: C, 56.90; H, 4.77; F, 24.55. Found: C, 56.95; H, 4.76; F, 25.0.

NMR spectra were recorded on a JEOL JNMGX270 instrument operating at 270 MHz for proton NMR and 68 MHz for ^{13}C NMR or a Varian Unity 500 MHz instrument.

Rate constants for dehydration of 3-hydroxy-2,3-dihydrobenzothiophene (**20**) were measured spectrophotometrically as previously described for other alcohols.[7] Instruments used were a Perkin-Elmer PE 124 double-beam spectrophotometer and a Spectronic Genesys 2PC single-beam spectrometer equipped with an automatic cell changer. Rate constants for racemization were measured using a Perkin-Elmer 241 polarimeter equipped with a Philips 8251 chart recorder. A 2 mL polarimetric cell was maintained at 25 ± 0.1 °C with a water-circulating bath. The instrument was calibrated with a solution of D-glucose containing 1% aqueous ammonia. Approximately 0.02 M solutions of chiral alcohols in trifluoroethanol were added by pipet to perchloric acid solutions to give a final concentration in the range 4−12 mM. These solutions were transferred to the polarimetric cell with a Pasteur pipet, ensuring that no air bubbles were trapped in the process. Loss of optical activity was monitored over 3−6 half-lives of reaction; changes in optical rotation were typically 0.05°. Further details of the procedure have been reported previously.[7]

Conductance measurements were carried out using a procedure developed by Fujio et al.[19] The conductance cells were equipped with platinum electrodes; they contained 25 or 50 mL of 10^{-3}–10^{-4} M solutions of substrate. Conductivity readings were recorded automatically using CM-50AT and CM-60S conductivity meters connected to a printer (Toa Electronics Ltd). Usually, the measurements were made in mixtures of more- and less-ionizing solvents, in which case a solution of the substrate was prepared in the less-ionizing component. However, where both components were ionizing, as for TFE−H$_2$O mixtures, the substrate was dissolved in a few drops of acetone and introduced by Pasteur pipet.

Product Analyses. Product analyses from solvolysis of aralkyl trifluoroacetates in the presence of sodium azide were carried out by HPLC. The solvolyses were allowed to proceed to 10 half-lives based

on conductimeric or HPLC monitoring of the reactions. The reactions were conducted at room temperature (20 ± 2 °C) and were initiated by injection of a few microliters of a freshly prepared solution of the substrate in acetonitrile into water or a trifluoroethanol−water mixture containing sodium azide to give a final concentration of ∼2.5 mM (or as low as 0.5 mM in purely aqueous solutions). When the solvolysis was judged to be complete 25 μL aliquots of the reaction mixture were injected onto the chromatography column (a Waters Associates reverse phase 10 μm octadecylsilane column in a radial compression unit). Separation of product components was achieved by isocratic elution with water−methanol mixtures containing 50−65% methanol at a flow rate of 1 mL/min. The mixtures were deaerated before use by filtration under reduced pressure. The experiments were performed using a Waters 600E HPLC system with a Waters 486 tunable UV detector. The analytical wavelength was maintained at 600 nm for the first 3−4 min of a measurement to eliminate the appearance of a large peak due to elution of unreacted azide ion. The wavelength was then changed to 220 nm.

The products of solvolysis of each ester comprised a mixture of aralkyl alcohol, trifluoroethyl ether, and azide. The alcohol peak was identified by comparison of its retention time with that of a pure sample. The azide and trifluoroethyl ether peaks were assigned from the dependence of their product areas on the concentration of azide ion and trifluoroethanol content of the solvent. The order of elution was alcohol > azide > trifluoroethyl ether. The peak areas were obtained by electronic integration, using a Millennium 200 software package. It was assumed that the extinction coefficients for the three elements were the same. This has been checked for similar structures of substrates.[2a,11,15]

Ratios of rate constants for attack of water (k_{H_2O}) and azide ion (k_{az}) were obtained from limiting slopes of plots of ratios of areas of alcohol and azide product peaks measured by HPLC against the concentrations of azide ion. As shown in Figure 1, the plots show departures from linearity at high concentrations of azide ion. As discussed above, this was interpreted in terms of azide-catalyzed hydrolysis of the trifluoroacetate esters competing with the carbocation-forming solvolysis, as in Scheme 4. A comparable competition between azide ion acting as a nucleophile and as a base has been described by Richard.[28] Based on Scheme 4, the following relationship is obtained for the dependence of the product ratio of alcohol to azide, [RN$_3$]/[ROH], on the concentration of azide ion.

$$\frac{[\text{RN}_3]}{[\text{ROH}]} = \frac{(k_{az}/k_{H_2O})[\text{N}_3^-]}{1 + a[\text{N}_3^-] + a(k_{az}/k_{H_2O})[\text{N}_3^-]^2} \tag{6}$$

In this equation, $a = k_h/k_s$, the ratio of rate constants for the azide-catalyzed hydrolysis (k_h) and uncatalyzed solvolysis (k_s) reactions. It can be seen that if a is zero, eq 6 reduces to the equation of a straight line with slope k_{az}/k_{H_2O}. In the limit of low concentrations of azide ion, the slope of the line also approaches k_{az}/k_{H_2O}. Values of a providing best fits to the data in aqueous solution were 0.3, 0.3, 0.4, 0.5, and 0.6 for tetralyl, indanyl, *o*-methoxyphenylethyl, chromanyl, and thiochromanyl trifluoroacetates, respectively. The largest value, 0.6, implies that, at 0.2 M sodium azide, 11% of the reaction is proceeding by hydroloysis rather than solvolysis. In 70% trifluoroethanol−water mixtures (v:v), values of a for indanyl and *o*-methoxyphenylethyl trifluoroacetates were reduced to 0.1, consistent with the lower water content of the solvent. A larger value of a = 0.5 for tetralyl trifluoroacetate may represent an error in the data point for 0.5 M sodium azide. The chromanyl trifluoroacetate also showed a drop in fraction of azide product at 0.5 M sodium azide despite good linearity of the plot of [RN$_3$]/[ROH] against the concentration of azide ion up to 0.25 M. Extensive ester hydrolysis was observed only for the slowly

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solvolyzing *o*-methylphenylethyl trifluoroacetate, for which $a = 4.0$ in 50% TFE−H$_2$O and could not be determined in water. The value of $k_{H_2O}/k_{az} = 0.8$ for this substrate is of lower precision than for others, therefore.

With respect to errors, the racemization rate constants (k_H) are probably somewhat less precise than commonly determined spectrophotometric rate constants. Especially after extrapolation to water from measurements in mixed solvent (Figure S1), they are likely to be subject to an error of ±15%. Values of k_{H_2O} may be subject to an error of 50% because of variations in the rate constant for nucleophilic trapping by azide ion, k_{az}.[2b] Combining these errors suggests that the pK_R values should be subject to an uncertainty of ±0.25 log unit.

Computational Methods. Calculated structures of alcohols, protonated alcohols, and carbocations were built and optimized at the ab initio HF/3-21G or HF/6-31G* levels of theory using Spartan or MacSpartan software packages.[29] Geometry optimizations and frequency calculations were then completed at the HF/6-31G* level, followed by single-point calculations at the MP2/6-31G* level using the GAUSSIAN 94 or GAUSSIAN 98 quantum mechanical packages.[29−31]

Supporting Information Available: Tables S1−S10 listing kinetic and equilibrium data for the ionization of alcohols **4**

and **14**−**18** and for solvolysis and/or azide trapping of trifluoroacetate or chloroacetate esters of alcohols **1**, **4**, and **14**−**18**; Table S11 showing calculated electronic energies of protonated alcohols **1**, **4**, **14**, **15**, and **19** and/or the corresponding carbocations; measurements of k_H in TFE−H$_2$O mixtures recorded in Table 1 are plotted in Figure S1. This material is available free of charge via the Internet at http://pubs.acs.org.

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