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Structure–reactivity relationship for alcohol oxidations via hydride transfer to a carbocationic oxidizing agent

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Second-order rate constants were determined for the oxidation of 27 alcohols (R^1R^2CHOH) by a carbocationic oxidizing agent, 9-phenylxanthylium ion, in acetontrile at 60 °C. Alcohols include open-chain alkyl, cycloalkyl, and unsaturated alcohols. Kinetic isotope effects for the reaction of 1-phenylethanol were determined at three H/D positions of the alcohol ($KIE_{\alpha\text{-}D} = 3.9$, $KIE_{\beta\text{-}D3} = 1.03$, $KIE_{OD} = 1.10$). These KIE results are consistent with those we previously reported for the 2-propanol reaction, suggesting that these reactions follow a hydride-proton sequential transfer mechanism that involves a rate-limiting formation of the α-hydroxy carbocation intermediate. Structure–reactivity relationship for alcohol oxidations was deeply discussed on the basis of the observed structural effects on the formation of the carbocationic transition state ($C^{\delta+}$—OH). Efficiencies of alcohol oxidations are largely dependent upon the alcohol structures. Steric hindrance effect and ring strain relief effect win over the electronic effect in determining the rates of the oxidations of open-chain alkyl and cycloalkyl alcohols. Unhindered secondary alkyl alcohols would be selectively oxidized in the presence of primary and hindered secondary alkyl alcohols. Strained C_7—C_{11} cycloalkyl alcohols react faster than cyclohexyl alcohol, whereas the strained C_5 and C_{12} alcohols react slower. Aromatic alcohols would be efficiently and selectively oxidized in the presence of aliphatic alcohols of comparable steric requirements. This structure–reactivity relationship for alcohol oxidations via hydride-transfer mechanism is hoped to provide a useful guidance for the selective oxidation of certain alcohol functional groups in organic synthesis. Copyright © 2011 John Wiley & Sons, Ltd.

Supporting information may be found in the online version of this article.

Keywords: alcohol oxidations; alpha-hydroxy carbocation; hydride-transfer; structure–reactivity relationship

INTRODUCTION

Oxidation of alcohols to carbonyl compounds is a fundamental functional group transformation of great value to organic synthesis.[1–16] Regioselective oxidation of a hydroxyl group in a substrate containing multiple oxidizable hydroxyl groups of different reactivities and different local steric environments has historically challenged the development of the synthetic methodologies especially in the areas of carbohydrate and steroid synthesis.[11] Toward this goal, selective oxidation of secondary alcohols in the presence of primary alcohols has been achieved in the oxidation of some diols and polyhydroxylated compounds, but only by limited oxidizing agents.[11,17–23] In contrast, reports on oxidations discriminating between two or more secondary alcohols of different reactivities and different steric environments were considerably less.[11,24,25] To successfully achieve the regioselective oxidation of alcohols, information about the quantitative structure–reactivity relationship for alcohols toward certain oxidations is indispensible.

Kinetics of oxidation of alcohols by various oxidizing agents have been studied for the purpose of determination of the structure–reactivity relationship and the reaction mechanisms. Rocek and coworkers [26,27] has determined the kinetics for the Chromium (IV) oxidation of several primary as well as a few secondary aliphatic alcohols. The reactions were suggested to take place by an α-hydrogen atom transfer mechanism within a chromium (IV) ester complex intermediate. On the other hand, other workers have determined the kinetics of the oxidations of substituted benzyl alcohols by various oxidizing agents and observed a negative Hammett reaction constant that indicates an electron-deficient α-C in the alcohol moiety of the transition state (TS), thereby proposing a hydride-transfer mechanism.[28–30] These oxidizing agents include tripropylammonium fluorochromate,[28] [bistrifluoroacetoxy)iodo]benzene,[29] and pyridinium fluorochromate.[30] We found that the structure–reactivity relationship investigation has not been carried out for alcohol oxidations via hydride-transfer by the carbocationic oxidizing agents. Study of these latter reactions which clearly form an α-hydroxy carbocation intermediate product after hydride-transfer, are expected to result in a distinctive structure–reactivity

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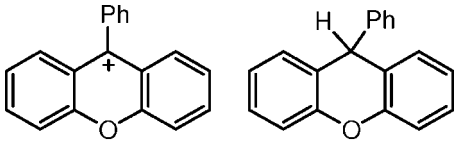
relationship, providing useful ways to attain the purpose of selective oxidation of alcohols in organic synthesis.

We report herein the rates of the oxidation of 27 alcohols (R^1R^2CHOH, **1**–**27**) by a carbocationic oxidizing agent, 9-phenylxanthylium ion ($PhXn^+$, counter ion; BF_4^-), to produce the corresponding ketones/aldehydes and 9-phenylxanthene



$PhXn^+$ $\quad$ PhXnH

(PhXnH), in acetontrile (AN) at 60 °C. Alcohols include open-chain alkyl, cycloalkyl, and unsaturated alcohols. All alcohols are secondary except for 1-propanol and three substituted benzyl alcohols. In order to confirm the hydride transfer mechanism for these types of reactions, KIE's for the reaction of 1-phenylethanol at its α-H/D, β-CH_3(CD_3), and OH(D) positions were determined. Structure–reactivity relationship for alcohol oxidations are then discussed on the basis of the structural effects on the formation of the carbocationic TS ($R^1R^2C^{\delta+}$—OH), concerning the electronic effect, the steric effect, the ring strain/size effect, the neighboring group participation effect, and the aromatic substitution effect. The potential application of the observed structure–reactivity relationship in regioselective oxidation of hydroxyl groups is discussed.

RESULTS AND DISCUSSION

We have recently reported the kinetic and mechanistic study of the oxidation of 2-propanol via hydride-transfer to carbocationic oxidants (R^+) in various solvent systems to form the corresponding ketone product, the hydride reduction products of carbocations (RH) and a proton (Eqn (1), $R^1 = R^2 = CH_3$).[31–33] R^+ used include $PhXn^+$ and 10-methylacridinium ion. Kinetic isotope effects (KIE) at the α-H(D) and OH(D) positions of the 2-propanol were observed to be primary and secondary, indicating a hydride-proton sequential transfer mechanism that involves a rate-limiting formation of the α-hydroxy carbocation (C^+—OH) followed by a rapid loss of proton to the basic species (most likely, excess alcohol) in the reaction solution.

$$R^1R^2C\underline{H}OH + R^+ \xrightarrow{k} R^1R^2C^+\text{-}OH + R\underline{H}$$
$$R^1R^2C^+\text{-}OH \xrightarrow{\text{rapid}} R^1R^2C{=}O + H^+ \qquad (1)$$

In this paper, kinetics of hydride-transfer reactions from alcohols to $PhXn^+$ in AN were determined spectroscopically (UV–Vis) by following the decay of the latter reactant at 373 nm with time. The detailed method to determine the pseudo-first-order rate constants (k^{obs}) of the reaction of 2-propanol in AN can be found in our previous work.[33] Kinetics of the reactions of all alcohols with $PhXn^+$ (1.0×10^{-3} M) were determined under pseudo-first-order conditions with alcohol concentrations being in large excess (0.015–0.5 M).

The kinetic scans for the reaction of 1-phenylethanol (**21**) were shown in Fig. 1. Only those for the first 1–2 half-life times were recorded. Product analysis for the reaction of 1-phenylethanol

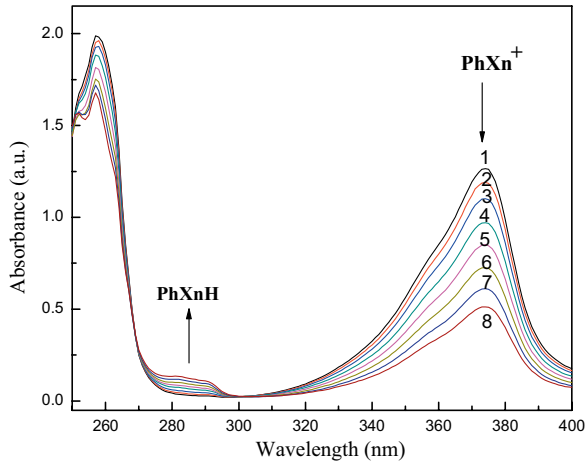


Figure 1. Kinetic scans determined by analysis of the reaction aliquots, taken from the reaction solution of $[PhXn^+]_0 = 0.001$ M and $[PhCH(OH)CH_3] = 0.10$ M in AN at 60 °C. The reaction aliquots were diluted by 25 times with AN/water (v/v = 3/1) containing 3 M $HClO_4$ (Experimental Section). Reaction times for spectra 1–8 are 5, 15, 35, 50, 75, 105, 140 and 179 min, respectively. The half-life time of the reaction is 121 min

was carried out; corresponding PhXnH and acetophenone products were isolated and their structures were characterized by ^{1}H NMR spectroscopy. Here, absorption decay at 373 nm was due to the $PhXn^+$ consumption and absorption rise at 285 nm due to the formation of PhXnH.[32,33] Representative kinetic scans for the reactions of other alcohols are shown in the Supplemental Information (Figs. S1–S3 for the reactions of 4-heptanol, cyclohexanol, and benzyl alcohol).

To understand the structure–reactivity relationship, the reaction mechanism must be clear. In order to further confirm the general hydride-proton sequential transfer mechanism for this kind of hydride-transfer reactions, KIEs at the α-H(D), β-CH_3(CD_3), and OH(D) positions of the 1-phenylethanol were determined by comparing the pseudo-first-order rate constants of the reactions of alcohols containing both isotopes under the same conditions. Values of primary $KIE_{\alpha\text{-}D}$, secondary $KIE_{\beta\text{-}D3}$, and secondary KIE_{OD} are listed in Table 1, consistent with the corresponding KIEs observed for the 2-propanol reaction in the same solvent (also listed in Table 1 for comparison)[33] and indicating a stepwise mechanism (1) (see the subsequent discussion). Additionally, this research group is currently working on the study of temperature dependence of α-D KIEs for some of the reactions studied in this paper, and has found that the $KIE_{\alpha\text{-}D}$ are all primary, further suggesting a rate-limiting hydride transfer mechanism for this class of reactions. Examples include the reactions of cyclohexanol ($KIE_{\alpha\text{-}D} = 3.1$), benzyl alcohol ($KIE_{\alpha\text{-}D} = 3.8$), and diphenylmethanol ($KIE_{\alpha\text{-}D} = 5.3$). Detailed discussions of these results will be reported in the future.

In these reactions, it is possible to form the ether adduct PhXnOR in a side-equilibrium complicating the determination of the kinetics of the hydride transfer process.[32] However, we have found that the formation of PhXnOR is insignificant in the 2-propanol reaction with relatively low alcohol concentrations (e.g. <0.6 M) in the AN solvent.[33] This has been demonstrated by the fact that the reaction was observed to be first-order each in the alcohol and in $PhXn^+$.[33] The reason is as follows, for the reaction that involves side-equilibrium formation of an ether

Table 1. KIE's of the hydride-transfer reaction from 1-phenylethanol (**21**) to $PhXn^+$ in AN at 60 °C[a]

Alcohol	$KIE_{\alpha\text{-}D}$	$KIE_{\beta\text{-}D3(6)}$[b]	KIE_{OD}
1-Phenylethanol[c]	3.9 ± 0.04 (4)	1.03 ± 0.04 (8)	1.10 ± 0.04 (6)
2-Propanol[d]	3.2 ± 0.01	1.05 ± 0.03	1.08 ± 0.01

[a] See texts for definition of the KIE's.
[b] There are three β-D's in 1-phenylethnol and six β-D's in 2-propanol.
[c] Numbers of repeat determinations are in parentheses.
[d] From our previous work.[33]

adduct (Eqn (2)),

$$PhXnOR + H^+ \overset{1/K}{\rightleftharpoons} PhXn^+ + ROH \xrightarrow{k^H} PhXnH + R{=}O + H^+ \qquad (2)$$

the rate law is as follows,

$$\begin{aligned} Rate &= d[PhXnH]/dt = -d[PhXn^+]_{total}/dt \\ &= k^H[PhXn^+][ROH][H^+]/\{[H^+] + K[ROH]\} \end{aligned} \qquad (3)$$

in which K is the equilibrium constant of the adduct formation and the subscript 'total' denotes the total concentration of $PhXn^+$ initially present in the reaction solution ($[PhXn^+]_{total} = [PhXn^+] + [PhXnOH]$).[33] Therefore, the reaction can only be first-order in ROH when K[ROH] is negligibly small in magnitude, i.e. the formation of the adduct is insignificant ($K \sim 0$). In this work, the effects of alcohol concentrations on the corresponding rates of the reactions of selected alcohols (R^1R^2CHOH) were determined (Table S1 in Supporting Information). Results show that the reactions studied are likewise first-order in R^1R^2CHOH within the alcohol concentration range used within experimental error. Additionally, the acid effect ($[HBF_4] = 4$ mM in AN, prepared using 50% HBF_4 aqueous solution) on the rates of many reactions was also tested, and no acid concentration effect was observed within experimental error, further suggesting a negligible side-equilibrium mechanism. Therefore, it is reasonable to conclude that the ether adduct formation is insignificant in the reactions studied in this work, regardless the reactions of primary or secondary alcohols, and the observed pseudo-first-order rate constants determined correspond with the rate of the hydride-transfer process, i.e. $k^{obs} = k^H$.

Second-order rate constants (k_1–k_{27}) of the reactions of 27 alcohols (R^1R^2CHOH) were derived from the determined pseudo-first-order rate constants (k^{obs}) and listed in Table 2 ($k = k^{obs}$/[ROH], Experimental Section). In order to find correlation between the kinetic results and the thermodynamic data of the reactions, the proton affinities $\Delta H_{H^+}(C{=}O)$) of the corresponding final aldehyde/ketone products[34] that demonstrate the stabilities of the direct hydride transfer products C^+—OH, are also placed in Table 2.

The TS structure of the hydride transfer oxidation of alcohols

KIE's on the hydride-transfer step at H/D positions of an alcohol (in this work, 1-phenylethanol) can provide information about the structure of the reaction TS. As expected, the KIE brought about by deuterium substitution at the α-C is observed to be primary (Table 1, $KIE_{\alpha\text{-}D} = 3.9$), indicating that the hydride-transfer step is rate-determining. The secondary KIEs, resulting from the three β-C—H/C—D bonds ($KIE_{\beta\text{-}D3} = 1.03$) and the O—H/O—D bonds ($KIE_{OD} = 1.10$) (Table 1), are consistent with a partially positively charged alcohol moiety in the TS.[32,33] The former is a result of the orbital overlap between the β-C—H σ orbital and the p orbital on the carbon of the $\alpha\text{-}C^{\delta+}$—OH in the TS, affecting the vibration of the β-C—H bonds. The latter results from the effect of the developing positive charge on the vibration of the O—H bond in the $\alpha\text{-}C{=}OH^{\delta+}$ moiety of the TS. Since the β-C—H and the O—H bonds are more easily weakened, and therefore more readily allow dispersion of the positive charge on the CH_3—$C^{\delta+}$—OH moiety as compared to the corresponding C—D/O—D bonds, normal secondary KIE's resulted.

$KIE_{\alpha\text{-}D}$ for the reaction of 1-phenylethanol (3.9) is larger than that observed in the 2-propanol reaction (3.2). The difference may be an indication that the transferring hydride ion is more equally bound to the reactive C sites of both reactants in the former than in the latter. Similar magnitudes of β-D KIE's and OD KIE's in two systems suggest that the electron density of the α-C of the alcohol moiety of the TS's in both reactions are similar.

According to the KIE results, the general structure of the TS for the reactions studied in this work may be described to be penta-coordinated as shown in Scheme 1. The structure–reactivity relationship for alcohols to release a hydride ion thus reflects the structural effects on the conversion from a sp^3—CH—OH to a sp^2—$C^{\delta+}$—OH in the TS, and hence to a sp^2—C^+—OH in the product. Therefore, any groups in the alcohol (R^1 and R^2) which are able to stabilize the positively charged α-C in the TS or facilitate the geometry shift from a tetrahedral sp^3—CH—OH to a trigonal sp^2—C^+—OH would promote the hydride departure process. The following discussion of the structure–reactivity results in Table 2 will thus concern the electronic effect, the steric effect and the effect caused by the change in geometry shape at the alcohol α-carbon.

Kinetics–thermodynamics correlation analysis and substituent effects on non-cyclic alcohol oxidations

Correlation between the kinetics of the reactions and the proton affinities of the corresponding carbonyl products is plotted in Fig. 2. Only reactions with products whose proton affinities are known are shown, and those of particular interest in the discussions are labeled. Poor correlation was found. Since the proton affinity values largely reflect the electronic effects on the stability of the direct hydride-transfer products C^+—OH's, results suggest that steric hinderance effect plays an important role in the alcohol oxidations. The steric effect arises most likely because the 9-phenyl substituent in the oxidizing agent of $PhXn^+$ is rotated with respect to the xanthyl cation so that its ortho H's

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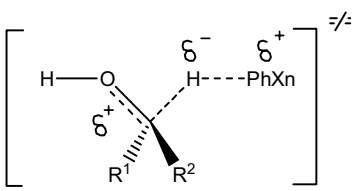
Table 2. Second-order rate constants (per M/min) of the hydride-transfer reactions from various alcohols to $PhXn^+$ in AN at 60 °C and hydride affinities (kJ/mol) of the corresponding aldehyde/ketone products

R^1R^2CHOH	R^1	R^2	$k \times 10^3$	$-\Delta H_{H^+}(C=O)$[a]
Primary alkyl alcohol				
1	H	CH_2CH_3	0.655	786.0
Open-chain secondary alkyl alcohols				
2	CH_3	CH_3	16.5[b]	812.0
3	CH_3	CH_2CH_3	11.8	827.3
4	CH_3	$CH_2CH_2CH_3$	15.8	827.7
5	CH_3	$CH(CH_3)_2$	2.58	
6	CH_3	$C(CH_3)_3$	0.0783	840.1
7	CH_2CH_3	CH_2CH_3	3.78	836.8
8	$CH_2CH_2CH_3$	$CH_2CH_2CH_3$	4.79	845.0
9	$CH(CH_3)_2$	$CH(CH_3)_2$	Very slow	850.3
10	CH_3	CH_2OCH_3	0.717	
11	CH_3	$CH_2OC(CH_3)_3$	5.58	
Unsaturated alcohols				
12	CH_3	$CH{=}CH_2$	50.5	834.7
13	CH_3	$C{\equiv}CH$	1.65	
14	CH_3	Ph	56.1	861.1
15	CH_3	*p*-ClPh	19.3	
16	Ph	Ph	0.317	882.3
17	H	Ph	63.2	834.0
18	H	*p*-CH_3Ph	224	
19	H	*p*-ClPh	19.4	
Cycloalkyl alcohols ($R_1R_2CHOH{=}(CH_2)_{n-1}CHOH$)				
20	$n=5$		9.01	823.7
21	$n=6$		21.7	841.0
22	$n=7$		152	845.6
23	$n=8$		159	849.4
24	$n=9$		144	852.6
25	$n=10$		82.4	
26	$n=11$		49.5	
27	$n=12$		17.2	

[a] From Ref.[34]
[b] From Ref.[33]

restrict access of the alcohols to the center of charge at C-9. This can be particularly supported by examination of the reaction kinetics of the two alcohols of most steric requirements, 3,3-dimethyl-2-butanol (**6**) and diphenylmethanol (**16**). Both of these reactions are distinctively slower than that of 2-propanol (**2**), even if the extra methyl groups and two phenyl groups in the respective alcohols can favorably stabilize the positive charge developed in the alcohol moiety of the TS through inductive and resonance effects, respectively. On the other hand, the observed reaction of 1-propanol (**1**) being 25 times slower than that of



Scheme 1. Suggested structure for the alcohol oxidation hydride-transfer TS

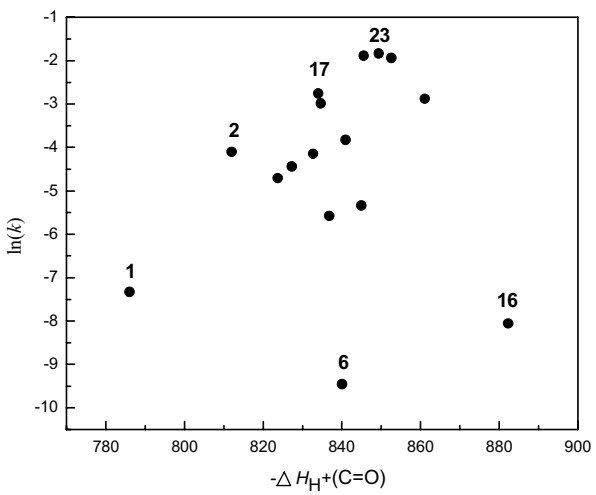


Figure 2. Correlation analysis between kinetics and proton affinities of the carbonyl products for the alcohol oxidations by $PhXn^+$

2-propanol (Table 2) implicates that primary alcohols possess significantly low reactivities as compared to the corresponding secondary ones. Our results thus suggest that using $PhXn^+$ as an oxidizing agent, unhindered secondary alcohol groups can be selectively oxidized in the presence of primary and sterically hindered secondary alcohol groups.

Oxidation of sugar molecules into their keto forms is of interest in chemical synthesis[11] and important in the corresponding biological metabolism process.[35] Study of the effect of alkoxylation at the β-C of the alcohols on their oxidation kinetics can help understand the corresponding processes. We found that such substitution lowers the hydride-donating abilities of the resulting alcohols. The rates of the reactions of alcohols with CH_3O (**10**) and $(CH_3)_3CO$ (**11**) substitutions in 2-propanol were observed to be 0.043 and 0.34 times that of 2-propanol. This can be explained in terms of the electron-withdrawing inductive effect of the alkoxyl groups that destabilize the $C^{\delta+}$—OH moiety in the TS. Since the $(CH_3)_3C$ group is a stronger electron-donating group than the CH_3 group, the latter reaction is faster than the former. But there is no apparent reason for the observation of such a large rate difference between the two reactions. Nevertheless, our results implicate that the alcohol functional group in sugar molecules is difficult to be oxidized, and the hydride-transfer oxidation of alcohols can discriminate between alcohols with and without electronegative atoms such as oxygen near the reaction center.

Oxidation of unsaturated alcohols occupies an important position in the synthesis of the carbonyl compounds. Unsaturated functional groups connected to the α-C of the alcohol are expected to enhance the hydride donation ability of the alcohols through resonance stabilization on the $C^{\delta+}$—OH in the TS. Our results support the inference. For example, 3-buten-2-ol (**12**) and 1-phenylethanol (**14**) react 4.3 and 21.7 times faster than 2-butanol (**3**) and 3-methyl-2-butanol (**5**), respectively. The two alcohol pairs (**12** vs. **3** and **14** vs. **5**) are of similar steric requirements and thus are comparable. Results are consistent with the thermodynamic stability order of the C^+—OH products (compare the corresponding proton affinity values in Table 2). These results indicate that unsaturated alcohols especially aromatic alcohols would be efficiently and selectively oxidized by $PhXn^+$ in the presence of aliphatic alcohols of comparable steric requirements.

Effects of representative substitution on the phenyl group of aromatic alcohols upon the corresponding reaction rates are observed. The electron-withdrawing group Cl at the *para* position in both benzyl alcohol and 1-phenylethanol decreases the rates of the corresponding reactions (**15** vs. **14** and **19** vs. **15**), while the electron-donating *p*ara-CH_3 group increases the rate (**18** vs. **17**). This is indicative of positively charged benzylic $C^{\delta+}$—OH moiety in the reaction TS. Kinetic determinations for the reactions of other substituted benzyl alcohols are under way in order to carry out a complete Hammett correlation study. Furthermore, the observation that the oxidation of 3-butyn-2-ol (**13**) is slower than that of 2-propanol (**2**) is also consistent with a positively charged TS mechanism. The highly electronegative sp—C in the alkynyl group (as compared to the sp^3—C in the methyl group) destabilizes the $C^{\delta+}$—OH TS, decreasing the reaction rate.

Ring size/ring strain effects on cycloalkyl alcohol oxidations

Ring compounds sometimes exhibit a remarkable change in chemical reactivity with ring size. Generally, the change correlates with the change in internal strain (I-strain) of the ring compounds that accompany the formation and cleavage of a chemical bond to the ring atom in the rate-determining step.[36,37] The I-strain of the ring compounds consists of angle strain, eclipsing (torsional) strain, and transannular (spatial) crowding strain. It is thus predictable that the oxidation of the strained cycloalkyl alcohols that accompanies a geometry change from a sp^3 CH—OH to a sp^2 C^+—OH at the reactive site would benefit from the partial loss of the internal ring strain. To the best knowledge of the authors, however, efforts on the discrimination of the oxidation of cycloalkyl alcohols with different ring size have not been made in organic synthesis.

Kinetic comparison of the hydride transfer oxidations of cycloalkyl alcohols containing 5–12 carbons indeed shows such ring-strain relief effects (Table 2). The medium-sized C_7—C_{11} cycloalkyl alcohols showed enhanced reactivity over the corresponding strain-free cyclohexyl (C_6) derivative, whereas the C_5 and C_{12} substances showed lower reactivity. In organic synthesis, our results implicate a possibility in selective oxidation of C_7 and C_8 cycloalkyl alcohols in the presence of cyclopentyl alcohol (about 17 times rate difference!).

In order to discuss the structure–reactivity relationship in detail, it would be meaningful to compare our reactions with the reported S_N1 solvolysis reactions of the cyclic substrates that form the normal cycloalkyl carbocations. We found that our results are interestingly largely similar to the observed kinetic behaviors in solvolysis reactions. For example, the solvolysis of the C_7—C_{12} 1-chloro-1-methylcycloalkanes in 80% aqueous ethanol solutions also showed enhanced reactivity over the strain-free cyclohexyl (C_6) derivative (Fig. 3 for the direct comparison of the two systems).[38,39] In literature, in addition to the suggested ring strain relief effect, the rate enhancement was also proposed to partly come from the additional 1,5- or 1,6-transannular hydrogen participation effect in the reaction of C_8—C_{11} substrates.[40–43] Such neighboring hydrogen participation results in the 1,5- or 1,6-hydrido-bridged forms of the corresponding cycloalkyl carbocations (Scheme 2).[43,44] But as discussed below, the latter factor may less likely contribute to the structure–reactivity relationship observed in our reactions.

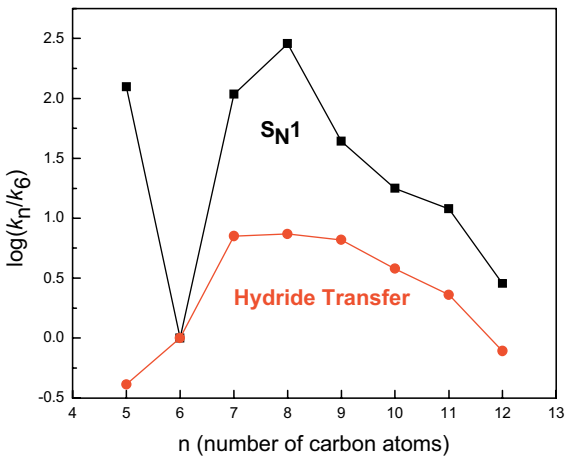


Figure 3. Comparison of the ring-size (*n*) effect on the formation of both normal cycloalkyl C^+ (S_N1 data from solvolysis of 1-chloro-1-methylcycloalkanes at 25 °C[39], black solid square) and cycloalkyl C^+—OH (hydride-transfer data for oxidation of cycloalkyl alcohols, red solid circle, color visible online). Rates of the reactions are normalized to that of the reaction of the cyclohexyl derivative in both systems

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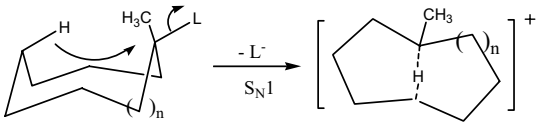
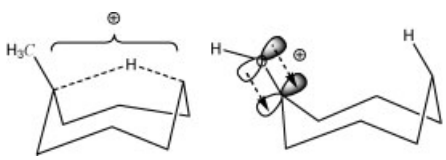


Scheme 2. Proposed formation of the C_8—C_{12} 1-methylcycloalkyl carbocations assisted by the 1,5(6)-transannular hydrogen participation ($n = 1$–4) in S_N1 reactions

Further careful examination of the two apparent differences in kinetic behaviors of the two systems in Fig. 3 would uncover the root reason for the observed structure–reactivity relationship in our reactions. First, the oxidation of cyclopentanol (**20**) was observed to be 2.4 times slower than that of strain-free cyclohexanol (**21**), which reverses the reactivity order of 125:1 observed in the S_N1 ionization of the corresponding C_5 and C_6 1-chloro-1-methylcycloalkanes.[39] The latter rate order has also been discussed in the two currently popular *Advanced Organic Chemistry* textbooks as an example for the torsional strain relief effect on the enhancement of the reactivity of ring compounds.[36,37] This implicates that, another effect in the reaction of C_5 substrate, gain of angle strain due to a change from a sp^3 (109.5°) to a sp^2 (120°) hybridization, which could make the reaction slower than that of the C_6 derivative, was masked. Our results, however, suggest that the latter angle strain gaining effect wins over the torsional strain relief effects during the hydride-transfer oxidation of cyclopentanol, resulting in the rate order of $k(C_6) > k(C_5)$.

Second, the extent of rate increase observed in the oxidation of medium-sized C_7—C_{11} alcohols relative to the C_6 alcohol, is much smaller than that observed in the corresponding S_N1 reactions ($(k_n/k_6)_{SN1} >> (k_n/k_6)_{hydride} = k_{22} \sim k_{27}/k_{21}$, Fig. 3). For example, the oxidation of cyclooctanol (**23**) is only 7.4 times faster than that of cyclohexanol (**21**), whereas a 286-fold rate increase was observed in the analogous S_N1 reactions of the methylcyclooctyl substrate over the methylcyclohexyl one.[39] Note that there would be little change in angle strain in the conversion from cyclooctanol to cyclooctanone. Our results thus suggest a relatively weak torsional and transannular crowding strain relief effects being involved in the oxidation of cycloalkyl alcohols. Possibly, removal of a small hydride leaving group during the alcohol oxidations could account for such a weak strain relief effect as compared to the S_N1 reactions with a large leaving group. But this alone may not explain such a large difference in the extent of rate increase.

The large difference in extent of rate increase may also come from the difference in the extent of transannular 1,5- or 1,6-hydrogen participation stabilization effects in the two reaction systems. For alcohols to release a hydride ion, the delocalization of the developing positive charge onto the hydroxyl group in the TS would greatly reduce the neighboring hydrogen group participation effect (Scheme 3). This can be



Scheme 3. 1,5-hydrogen participation stabilization effect is significantly stronger on the 1-methylcyclooctyl cation than on the corresponding C^+—OH cation

supported by the observed small but nearly constant increase in proton affinities of C_6–C_8 cycloketones (by ~4.0 kJ/mol, Table 2).[45] Also, the increase in proton affinities is similar to that for the corresponding open-chain alkyl ketones, further suggesting that the transannular hydrogen stabilization effect has little effect on the thermodynamic stability of the medium-sized cycloalkyl C^+—OH's, and hence on the $C^{\delta+}$—OH —OH moiety in the TS's.

Furthermore, as the cycloalkyl alcohol ring expands, the steric interaction between the alcohol and $PhXn^+$ would gradually increase. This would also reduce the difference in rates of the large cycloalkyl alcohol reactions from the cyclohexyl one. Example to support the latter may be that the reaction of cyclododecanol (**27**) is even slower than that of cyclohexanol ($k_{27}/k_{21} = 0.78$, Table 2), in spite of the expected C_{12}-ring strain relief effect and carbocation stabilization effect by additional CH_2 groups (though small) from the former alcohol during the reaction.

Therefore, the observed relatively small rate ratio $k(C_{7-11})/k(C_6)$ in alcohol oxidations would come from the weaker ring strain relief effect due to the departure of a small-sized hydride ion, the weaker 1,5(6)-hydrogen participation effect due to the lower positive charge density developed at the reactive ring-C during the reaction, as well as the increasing steric effect as the ring expands.

CONCLUSIONS

The oxidation of alcohols by a sterically hindered carbocationic oxidizing agent of $PhXn^+$ in AN uses hydride-proton sequential transfer mechanism that involves a rate-limiting formation of the α-hydroxy carbocation intermediate and PhXnH. Efficiencies of the alcohol oxidations are largely dependent upon the alcohol structures. Steric hindrance effect and ring strain relief effect win over the electronic effect of alkyl groups in determining the rates of the oxidations of open-chain alkyl and cycloalkyl alcohols. The delocalization of the positive charge to the hydroxyl group of the alcohol in the TS reduces the need for additional stabilization of the carbocation intermediate from two other groups (R^1 and R^2) of the alcohol. Unhindered secondary alkyl alcohols would be selectively oxidized in the presence of primary and sterically hindered secondary alkyl alcohols. Seven- and eight-membered cycloalkyl alcohols react about 17 times faster than cyclopentyl alcohol. Aromatic alcohols would be efficiently and selectively oxidized in the presence of aliphatic alcohols of comparable steric requirements.

The steric hindrance effect may partly account for our previously observed unexpected relatively small rate ratio for the hydride transfer reactions from isopropanol to $PhXn^+$ and to a much less sterically hindered but much more stable cation of 10-methylacridinium ion (MA^+) ($k_{PhXn+}/k_{MA+} \sim 1.8 \times 10^3$ in isopropanol/AN (v/v = 1) at 69 °C).[32] The former hydride acceptor is more reactive than the latter by about 53 kJ mol^{-1} according to the pK_R+ values of the two carbocations.[46,47]

EXPERIMENTAL

General procedures

9-Phenylxanthylium tetrafluoroborate ($PhXn^+BF_4^-$) was synthesized by dehydration of 9-phenylxanthanol with 50% HBF_4 aqueous solution according to the published procedure.[48] Diphenyl methanol, 1-(*p*-chlorophenyl)ethanol, cyclononanol,

cyclodecanol, and cycloundecanol were synthesized by reduction of the corresponding ketones with $NaBH_4$ in methanol, and were identified by NMR spectroscopy (Supplemental Information). 1-Phenylethanol-α-d and 1-phenylethanol-β,β,β-d_3 were synthesized by reduction of the acetophenone and acetophenone-β,β,β-d_3 by $NaBD_4$ and $NaBH_4$, respectively. 1-Phenylethanol-O-d was prepared by OH/OD exchange reaction of the corresponding normal alcohol in D_2O/THF catalyzed by DCl according to the literature procedure.[49] The D-content of the deuterated 1-phenylethanols was examined by NMR spectroscopy and was found to be higher than 98.5%. Other alcohols were purchased and purified by conventional methods before use. Acetonitrile was distilled twice (first time over the P_2O_5 drying agent) under nitrogen atmosphere.

Kinetic procedures

Stock solution (80 μl of 0.1 M) of $PhXn^+$ in AN was added to an 8 ml AN solution containing a typical alcohol of a certain concentration in a well sealed 10 ml reaction vial, which was pre-thermostated in a water bath with temperature maintained at 60 °C. About 0.3 ml of the reaction aliquots were periodically taken into sample vials pre-cooled in ice. The samples were then immediately placed in a freezer (∼ −20 °C) until 6–8 reaction aliquots within 1–2 half-lives of the reaction had been collected (the half-life time of the reactions was usually longer than 90 min). The reaction aliquots were analyzed by diluting 80 μl of them in 1.92 ml AN/H_2O (v/v = 3/1) containing 3 M $HClO_4$,[33] and the corresponding UV spectra at different reaction times, i.e. the kinetic scans, were obtained. Absorbance (*Abs*) decreasing with time (*t*) at 373 nm due to the consumption of $PhXn^+$ was recorded. The obtained *Abs-t* data were fit to the first-order integrated rate equation, $-\ln(Abs) = k \cdot t +$ constant, and the slope of the linear plot of -ln(*Abs*) versus *t*, was taken as the pseudo-first-order rate constant (k^{pfo}) of the reaction. The linear plots usually had regression coefficients (R^2) >0.996. Each kinetic run was repeated at least two times and the determination error was usually within 7%. The second-order rate constant was calculated by dividing the k^{pfo} by the alcohol concentration, and was taken as an averaged value if the rate constants were determined using multiple alcohol concentrations.

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