The Selectivity of Charged Phenyl Radicals in Hydrogen Atom Abstraction Reactions with Isopropanol

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Received: March 14, 2008; Revised Manuscript Received: June 12, 2008

The vertical electron affinity is demonstrated to be a key factor in controlling the selectivity of charged phenyl radicals in hydrogen atom abstraction from isopropanol in the gas phase. The measurement of the total reaction efficiencies (hydrogen and/or deuterium atom abstraction) for unlabeled and partially deuterium-labeled isopropanol, and the branching ratios of hydrogen and deuterium atom abstraction, by using a Fourier transform ion cyclotron resonance (FT-ICR) mass spectrometer, allowed the determination of the selectivity for each site in the unlabeled isopropanol. Examination of hydrogen atom abstraction from isopropanol by eight structurally different radicals revealed that the preferred site is the CH group. The selectivity of the charged phenyl radicals correlates with the radical's vertical electron affinity and the reaction efficiency. The smaller the vertical electron affinity of a radical, the lower its reactivity, and the greater the preference for the thermodynamically favored CH group over the CH_3 group or the OH group. As the vertical electron affinity increases from 4.87 to 6.28 eV, the primary kinetic isotope effects decrease from 2.9 to 1.3 for the CD group, and the mixture of primary and α-secondary kinetic isotopes decreases from 6.0 to 2.4 for the CD_3 group.

Introduction

One of the mechanisms by which drugs cause DNA strand cleavages is thought to be initiated by hydrogen atom abstraction from the sugar moiety of DNA by aromatic carbon-centered σ-radical (phenyl radicals and derivatives) or biradical intermediates formed from drugs in biological systems.[1–4] The reactivity of phenyl radicals and the parameters that influence the efficiency of hydrogen atom abstraction by phenyl radicals have been examined in both gas phase and solution, and polar effects have been determined to play a major reactivity controlling role.[5–15] However, the selectivity of these intermediates is still not well understood, although knowledge concerning the factors that control their selectivity would facilitate the design of more selective antitumor drugs.

Regioselectivity in the hydrogen atom abstraction reactions of simple radicals (e.g., Cl• and HO•) with substrates such as ethanol and isopropanol have been studied in the gas phase and in solution.[16–20] However, to the best of our knowledge, only a few studies have focused on the regioselectivity of phenyl radicals toward hydrogen atom donors. The relative susceptibility of different types of C−H bonds for phenyl radical attack in solution has been evaluated by Bridger and Russell in a comprehensive paper published in 1963.[21] Chlorine atom abstraction from carbon tetrachloride by the phenyl radical was used as the standard reaction, and the relative rates of hydrogen and chlorine atom abstraction was determined on the basis of the ratio of the products, benzene and chlorobenzene. However, this approach yields only indirect information on the relative reactivities of the different types of C−H bonds. König, Musso and Záhorzky studied the reactivity of the phenyl radical toward methanol and labeled isotopologues in solution. They concluded that the reactivity of the phenyl radical toward the C−H bond is three times greater than for the O−H bond. However, the isotope effects used to obtain the results were based on the decomposition of nitrosoacetanilide and phenyldiazonium tetrafluoroborate which does not yield very accurate results.[22] In 1989, Kopinke and co-workers determined by using T-labeled compounds the relative reactivities of primary, secondary, and tertiary C−H bonds in saturated hydrocarbons toward phenyl radical attack in the liquid phase at 373 K and in the gas phase at 900 K.[23]

The studies discussed above have provided useful knowledge on the selectivity of phenyl radicals toward different hydrogen atoms in a substrate. However, none of these studies included structurally different phenyl radicals.

Phenyl radicals are highly reactive and therefore difficult to study in solution. However, the gas-phase environment of a mass spectrometer is well suited for the examination of these species. If the radicals studied by mass spectrometry have a charged site, their manipulation and detection is easy. Charged phenyl radicals with chemically inert charged sites (a subgroup of distonic ions[24,25]) have been demonstrated to possess gas-phase reactivity that is similar to that of the corresponding neutral phenyl radicals in solution.[10,13,23,26–31] An examination of the reactivity of some of these charged phenyl radicals toward unlabeled and selectively deuterium-labeled ethanol was recently reported.[32] A kinetic isotope effect was found to introduce a bias in the relative abundances of the product ions formed upon hydrogen or deuterium atom abstraction from partially labeled ethanols compared to the unlabeled analogue.[32] A procedure was developed for the quantitative determination of the selectivity of the phenyl radicals toward the different hydrogen atoms in the unlabeled ethanol.[32] We report here the application of this method to examine the selectivity of eight phenyl radicals (Scheme 1) toward unlabeled isopropanol by using the deuterium-labeled and unlabeled isotopologues shown in Figure 1.

Experimental Section

All experiments were carried out by using a dual-cell Finnigan model FTMS2001 Fourier transform ion cyclotron resonance mass spectrometer (FT-ICR) with an Odyssey data station. This

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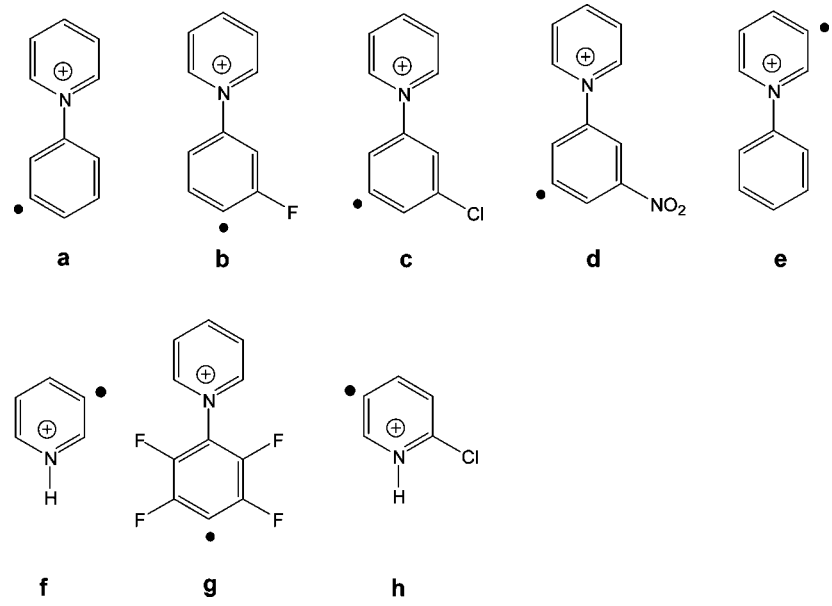
10.1021/jp802257m CCC: $40.75
Published on Web 09/06/2008

SCHEME 1



instrument contains a dual cell consisting of two identical 2 in. cells. The dual cell is collinearly aligned with the magnetic field produced by a 3 T superconducting magnet. The two cells are separated by a common wall called the conductance limit, which contains a 2 mm hole in the center for transfer of ions between the two cells. This plate and the other trapping plates were maintained at +2 V unless specified otherwise. The dual cell is differentially pumped by two Edwards diffusion pumps (800 L/s), each backed by an Alcatel 2012 mechanical pump. A nominal base pressure of less than 1×10^{-9} torr was measured by an ionization gauge on each side of the dual cell.

Two partially labeled forms of isopropanol, $(CD_3)_2CHOH$ (isotopic purity: 99.58 atom% D; chemical purity: 99.5%) and $(CH_3)_2CDOH$ (isotopic purity: 99.18 atom% D; chemical purity: 99.8%), were purchased from Isotec, Inc., Sigma-Aldrich, and used as received. Unlabeled isopropanol (99.5%) was purchased from Sigma-Aldrich. Their purities were verified by mass spectrometry. Except for bromobenzene (Fisher Scientific Company), 3-iodopyridine (KARL Industries Inc.) and pyridine (Mallinckrodt), all other commercially available radicals' precursors were purchased from Aldrich Chemical Co., Inc., including: 1,3-diiodobenzene, 1-bromo-3-fluoro-4-iodobenzene, 1,3-dichloro-5-iodobenzene, 1,2,4,5-tetrafluoro-3,6-diiodobenzene, 1-iodo-3,5-dinitrobenzene and 2-chloro-5-nitropyridine. These reagents were used as received.

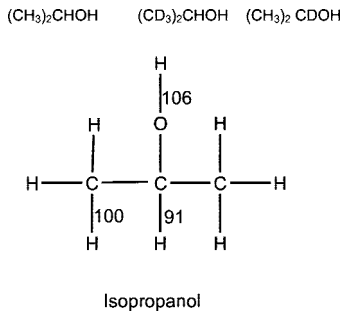
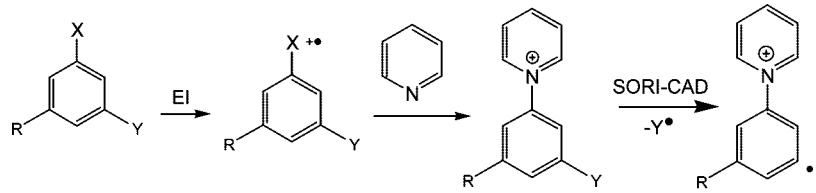


Figure 1. Isotopologues of isopropanol examined in this study, and the calculated (B3LYP/6-311++G(d,p)) homolytic bond dissociation energies (BDEs) in kcal/mol.[34] The validity of the calculations was confirmed by a comparison of the available experimental BDE value for the CH group (91 ± 1 kcal/mol[35]) and the calculated value (91 kcal/mol). The experimental BDE values for the CH_3 group and OH group are not available.

Isopropanol isotopologues were introduced into one cell (called analyzer cell) of the FT-ICR via a batch inlet system equipped with a variable leak valve. Pyridine and bromobenzene were introduced into the other cell (called source cell) via another batch inlet. 3-Iodopyridine, 2-chloro-5-nitropyridine, 1,3-diiodobenzene, 1-bromo-3-fluoro-4-iodobenzene, 1,3-dichloro-5-iodobenzene, and 1,2,4,5-tetrafluoro-3,6-diiodobenzene were introduced into the source side by using a Varian leak valve. 1-Iodo-3,5-dinitrobenzene was introduced into the source cell by using a solids probe which was heated to 65 °C. The radicals were formed by using a multistep procedure developed in our laboratories.[27] Briefly, the precursor ions for the charged phenyl radicals (**a**, **b**, **c**, **d**, **g**) were generated by the reaction of pyridine with radical cations formed by electron ionization (EI, typically 11−30 eV electron energy, 5−6 μA filament current, and 30−100 ms ionization time) of the compounds listed in the beginning of this paragraph. The precursor ions for 3-dehydropyridinium (**f**) and 2-chloro-5-dehydropyridinium (**h**) were generated by protonation of 3-iodopyridine and 2-chloro-5-nitropyridine, respectively, via a self-chemical ionization process. The precursor ion for *N*-phenyldehydropyridinium (**e**) was produced by reaction of iodopyridine and bromobenzene radical cation formed by EI.

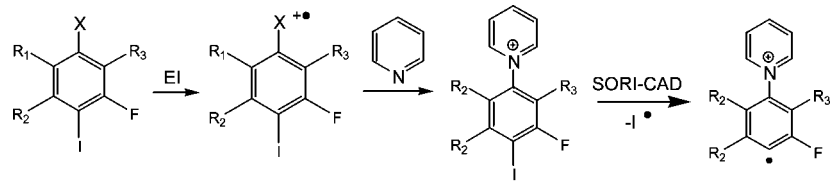
The other cell was cleaned by ejecting any ions formed upon EI via the application of a potential of −2 V to the remote trapping plate of that cell for 12 ms. The precursor ions were transferred through a 2 mm hole in the common trapping plate into the other cell by grounding the conductance limit plate for 123−210 μs, and were cooled for 1.0−1.5 s by allowing radiative emission and collisions with the neutral molecules present at a constant pressure of 10^{-8} or 10^{-7} Torr in this cell. The cooled ions were subjected to homolytic carbon−iodine or carbon−nitrogen bond cleavage to form the desired charged phenyl radicals (**a**−**h**) by using sustained off-resonance irradiated collision-activated dissociation (SORI-CAD).[33] This was accomplished by activating the ions by an rf pulse with a frequency 1 kHz higher than the cyclotron frequency of the ions and subjecting them to collisional activation with an argon target (pulsed into the cell at a nominal peak pressure of $\sim 1 \times 10^{-5}$

SCHEME 2



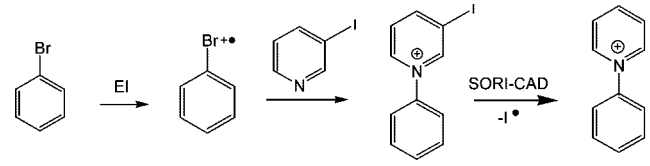
a: R = H, X = I, Y = I
c: R = Cl, X = Cl, Y = I
d: R = NO_2, X = I, Y = NO_2

SCHEME 3



b: R_1-R_3 = H, X = Br
g: R_1-R_3 = F, X = I

SCHEME 4



Torr) for 0.3−0.6 s. The produced charged phenyl radicals were cooled for about 0.3−1.0 s by radiative emission and collisions with argon that was pulsed into the cell at high pressure during the SORI-CAD procedure. The cooled charged radicals were isolated by ejecting all of the other ions from the cell through the application of a stored-waveform inverse Fourier transform[34] (SWIFT) excitation pulse to the excitation plates of the cell. The isolated charged radicals were allowed to react with each hydrogen atom donor for a variable period of time (typically 2−250 s) until ≥90% of the radical population had reacted away. Detection was carried out by using "chirp" excitation at 2.6 MHz bandwidth, 124 $V_{p\text{-}p}$ amplitude, and 3.2 kHz/μs sweep rate. All spectra were recorded as 64k data points and subjected to one zero fill prior to Fourier transformation.

The elemental compositions of the primary products were identified on the basis of their exact mass-to-charge ratios (m/z). There were no secondary products. The product branching ratios were determined by dividing the abundance of each product ion by the sum of the abundances of all of the product ions for each reaction time. The averages of the product branching ratios at all reaction times studied are given as the product branching ratios.

Since the concentration of the neutral compounds was much higher than that of the charged radicals, the reactions between the radicals and the neutral compounds follow pseudo-first-order kinetics. The pseudo-first-order reaction rate constant (k') was determined from the slope of a semilogarithmic plot of the relative abundance of the reacting ion versus reaction time (square of the linear correlation coefficient ≥0.99). The second-order reaction rate constant (k_{exp}) was obtained by dividing k' by the concentration of the neutral hydrogen atom donor determined from its pressure. The difference between the absolute pressure and the pressure measured by the ion gauges was corrected by using an ion gauge correction factor, which was estimated each day by measuring rates of proton transfer from protonated methanol to the isopropanol isotopologues. Those reactions can be assumed to occur at collision rate (highly exothermic, barrierless reactions). The collision rate constants (k_{coll}) were calculated by a parametrized trajectory theory.[35] The reaction efficiencies are given as k_{exp}/k_{coll}.

The determination of the reaction efficiencies for two labeled isopropanol isotopologues and unlabeled isopropanol allows setting up three equations. The hydrogen/deuterium atom abstraction products' branching ratios for two labeled isopropanols were used to set up two additional equations. The hydrogen atom abstraction group efficiencies for the CH_3, CH_2, OH, CD_3, and OD groups are the five unknowns. The Maple software was used to obtain the five unknowns from the five equations.

Computational Methods

The Gaussian 98 A.7 suite of programs[36] was used to perform calculations. For calculation of vertical electron affinities (EA), the equilibrium geometries were optimized by using the hybrid density functional B3LYP (Becke's three parameter nonlocal exchange functional[37–39] with the nonlocal correlation functional of Lee, Yang, and Parr[40]) with 6-31+G(d) basis set. The frequencies were calculated in order to verify that the stationary points obtained correspond to minima (no imaginary frequencies). The geometries of the ground-state species were directly used in single-point calculations of the excited states formed by addition of an electron to the radical σ-orbital. The vertical EAs were derived by taking the difference between the calculated electronic energies for the excited state and the ground state. Hydrogen atom affinities of the eight phenyl radicals were calculated by using isodesmic reactions with benzene at the B3LYP/6-311++G(d,p) level of theory. Vibrational frequency calculations were used to obtain zero-point energy (ZPE) corrections which were scaled with a factor of 0.989.

Results and Discussions

Summary of the Experimental Results. Eight phenyl radicals (Scheme 1) were synthesized in FT-ICR according to previously published multistep procedures (Schemes 2–5).[9,10,14,27] The isolated charged phenyl radicals were allowed to react with hydrogen and/or deuterium atom donors (isopropanol isotopo-

SCHEME 5

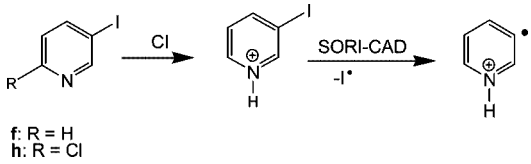


TABLE 1: Total Efficiencies[a,b] (EFF) and Product Branching Ratios[c] (BR) of Reactions of Phenyl Radicals a−h with Unlabeled and Partially Labeled Isopropanol isotopologues

Radical EA[d]	$(CH_3)_2CHOH$ EFF. (%) BR. (H/D)	$(CD_3)_2CHOH$ EFF. (%) BR. (H/D)	$(CH_3)_2CDOH$ EFF. (%) BR. (H/D)
a EA = 4.87eV	0.15±0.03 100% / 0%	0.14±0.02 98.6±0.3%/1.4±0.3%	0.063±0.011 23±1%/77±1%
b EA = 5.08eV	0.96±0.07 100% / 0%	0.87±0.07 97.5±0.3%/2.5±0.3%	0.55±0.08 17.6±0.2%/82.4±0.2%
c EA = 5.11eV	0.36±0.05 100% / 0%	0.33±0.05 97.4±1.7%/2.6±1.7	0.18±0.02 22.5±0.7%/77.5±0.7%
d EA = 5.40eV	1.4±0.2 100% / 0%	1.2±0.04 94.0±0.5%/6.0±0.5%	0.72±0.13 28±2%/72±2%
e EA = 5.78eV	11±0.3 100% / 0%	8.9±1.3 90.9±0.6%/9.1±0.6%	7.7±0.8 39.8±0.4%/60.2±0.4%
f EA = 6.11 eV	20±2 100% / 0%	14±2 83.1±0.2%/16.9±0.2%	17±0.4 51.5±0.2%/48.5±0.2%
g EA = 6.18eV	13±2 100% / 0%	9.9±0.6 77%±1/23±1%	10±1 51.8±0.5%/48.2±0.5%
h EA = 6.28	28±1 100% / 0%	21±3 76±2%/24±2%	25±2 51.3±0.2%/48.7±0.2%

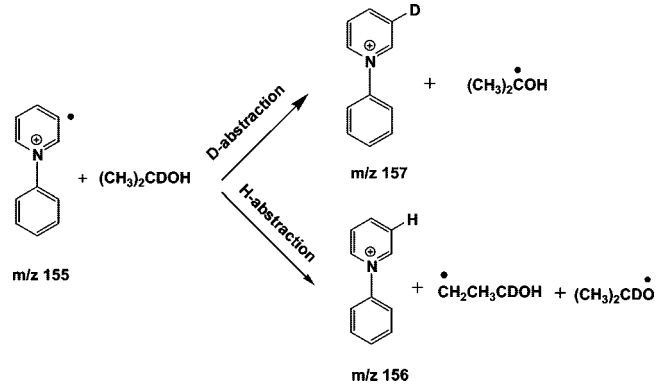
[a] EFF: the percentage of collisions that leads to product (k_{exp}/k_{coll}). [b] The stated uncertainties are ±1 standard deviation. [c] Branching ratio is equal to the percentage of products arising from hydrogen/deuterium atom abstraction. [d] Radical's vertical EA is calculated at the BLYP/6-31+g(d) level of theory.

logues) for varying time periods. The measured reaction efficiencies (k_{exp}/k_{coll}) and product branching ratios are summarized in Table 1. A survey of the data shows that hydrogen and/or deuterium atom abstraction is the exclusive reaction observed (Scheme 6). An examination of the reactivity of each isopropanol isotopologue toward each radical shows that the total efficiency of hydrogen and deuterium atom abstraction increases as the calculated vertical electron affinity (at the B3LYP/6-31+G(d) level of theory) of the radical increases. This result is consistent with our previous studies on the correlation between reaction efficiencies and vertical electron affinities of charged phenyl radicals.[9,14,32,41]

Each radical reacts with the three different isopropanol isotopologues at different reaction efficiencies and yields different product branching ratios (Table 1). For example, the total efficiencies of hydrogen and deuterium abstraction by radical **e** from $(CH_3)_2CHOH$, $(CD_3)_2CHOH$, and $(CH_3)_2CDOH$ are 11%, 8.9%, and 7.7%, respectively. The hydrogen/deuterium abstraction product branching ratio for $(CD_3)_2CHOH$ is 90.9%/9.1%, while it is 39.8%/60.2% for $(CH_3)_2CDOH$. Similar differences were observed in a previous study for partially deuterium-labeled and unlabeled ethanol.[32] These observations imply the presence of a kinetic isotope effect (KIE) that causes the selectivity toward a partially labeled hydrogen atom donor and an unlabeled one to be different.

Selectivity of Hydrogen Atom Abstraction from Each Reactive Site in Unlabeled Isopropanol. We have previously developed a procedure for the quantitative determination of the

SCHEME 6



selectivity of the phenyl radicals toward the different hydrogens in the unlabeled ethanol.[32] KIE includes a primary isotope effect (associated with C−D vs C−H bond being broken) and two kinds of secondary isotope effects, α-secondary isotope effect due to the difference in the residual isotopic composition at the carbon atom undergoing C−H/C−D bond cleavage, and β-secondary isotope effect arising from isotopic substitution in an adjacent group. If the β-secondary isotope effect is assumed to be negligible, the total reaction efficiency equals the sum of the reaction efficiencies for each group, i.e.,

$$EFF_{(CH_3)_2CHOH} = EFF_{(CH_3)_2} + EFF_{CH} + EFF_{OH} \quad (1)$$

$$EFF_{(CD_3)_2CHOH} = EFF_{(CD_3)_2} + EFF_{CH} + EFF_{OH} \quad (2)$$

$$EFF_{(CH_3)_2CDOH} = EFF_{(CH_3)_2} + EFF_{CD} + EFF_{OH} \quad (3)$$

where $EFF_{(CH_3)_2CHOH}$, $EFF_{(CD_3)_2CHOH}$, and $EFF_{(CH_3)_2CDOH}$ are the measured total reaction efficiencies for both hydrogen and deuterium atom abstraction from $(CH_3)_2CHOH$, $(CD_3)_2CHOH$ and $(CH_3)_2CDOH$, respectively. $EFF_{(CH_3)_2}$, EFF_{CH}, EFF_{OH}, $EFF_{(CD_3)_2}$ and EFF_{CD} are unknown group efficiencies (without statistical correction for the number of hydrogen atoms) for hydrogen or deuterium atom abstraction. The measured branching ratios for hydrogen atom abstraction products vs deuterium atom abstraction products can be expressed by the following two equations:

$$(EFF_{CH} + EFF_{OH})/EFF_{(CD_3)_2} = \text{H/D branching ratio for } (CD_3)_2CHOH \quad (4)$$

$$EFF_{CD}/(EFF_{(CH_3)_2} + EFF_{OH}) = \text{D/H branching ratio for } (CH_3)_2CDOH \quad (5)$$

The five unknowns ($EFF_{(CH_3)_2}$, EFF_{CH}, EFF_{OH}, $EFF_{(CD_3)_2}$, and EFF_{CD}) in the above five equations were mathematically solved. The calculated $(CH_3)_2$, CH, and OH group efficiencies for the eight charged phenyl radicals are reported in Table 2. Note that the OH group efficiencies are very small and hence expected to be accompanied by large errors, and some of them are undetectable (for radical **b**, **d** and **g**). As described in our previous paper,[32] $(CH_3)_2$, CH and OH group efficiencies are divided by their sum to obtain contribution ratios which allow the evaluation of the percentage that each group contributes to the total hydrogen atom abstraction efficiency in unlabeled isopropanol (listed in parentheses in Table 2). The contribution ratios from CH group are 91%, 89%, 89%, 82%, 72%, 56%, 59%, and 54% for radicals **a**, **b**, **c**, **d**, **e**, **f**, **g**, and **h**, respectively. Obviously, hydrogen atom abstraction from the CH group dominates. There are six hydrogen atoms in the $(CH_3)_2$ groups

TABLE 2: Group Efficiencies (EFF), Contribution Ratios (in Parentheses), and Site Selectivities (Bold) for Hydrogen Atom Abstraction from Isopropanol by Eight Charged Phenyl Radicals

radical	EFF_{CH} (contribution ratio) **selectivity**	$EFF_{(CH3)2}$ (contribution ratio) **selectivity**	EFF_{OH} (contribution ratio) **selectivity**
a - EA = 4.87 eV	0.14% (91%) **91%**	0.012% (7.8%) **1.3%**	0.0025% (1.6%) **1.6%**
b - EA = 5.08 eV	0.86% (89%) **89%**	0.11% (11%) **1.8%**	not available
c - EA = 5.11 eV	0.32% (89%) **89%**	0.039% (11%) **1.8%**	0.0019% (0.5%) **0.5%**
d - EA = 5.40 eV	1.2% (82%) **82%**	0.27% (18%) **3.0%**	not available
e - EA = 5.78 eV	7.9% (72%) **72%**	2.9% (26%) **4.3%**	0.15% (1.4%) **1.4%**
f - EA = 6.11 eV	11% (56%) **56%**	8.4% (42%) **7.0%**	0.39% (2.0%) **2.0%**
g - EA = 6.18 eV	7.8% (59%) **59%**	5.4% (41%) **6.8%**	not available
h - EA = 6.28 eV	15% (54%) **54%**	12% (43%) **7.3%**	0.79% (2.7%) 2.7%

but only one in the CH group and OH group. To compare the relative reactivities of these groups, the selectivities for the CH_3, CH and OH groups were obtained by dividing the contribution ratio by the number of hydrogen atoms in that particular group, i.e.,

Selectivity for the CH_3 groups =

$$1/6 \times EFF_{(CH_3)_2}/(EFF_{(CH_3)_2} + EFF_{CH} + EFF_{OH}) \quad (6)$$

Selectivity for the CH group =

$$EFF_{CH}/(EFF_{(CH_3)_2} + EFF_{CH} + EFF_{OH}) \quad (7)$$

Selectivity for the OH group =

$$EFF_{OH}/(EFF_{(CH_3)_2} + EFF_{CH} + EFF_{OH}) \quad (8)$$

For example, the calculated selectivities for hydrogen atom abstraction by the charged phenyl radical **a** from CH, CH_3 and OH groups in isopropanol are 91% (91%/1), 1.3% (7.8%/6) and 1.6% (1.6%/1), respectively. Therefore, the charged phenyl radical **a** is about 70 times more reactive toward the CH group in isopropanol than toward the CH_3 groups. For the radicals **b**−**h**, this value varies between 49 and 7. For comparison, the selectivities reported for Cl• upon hydrogen atom abstraction from the CH and CH_3 groups in isopropanol are 85% (85%/1) and 2.5% (15%/6) (Cl• is about 34 times more reactive toward the CH group than toward the CH_3 groups).[16,17]

All of the eight charged phenyl radicals show preference for the CH group (Table 2). This finding is explained by the lower bond dissociation energy of the C−H bond in the CH group (91 kcal/mol) than in the CH_3 group (100 kcal/mol) and of the O−H bond in the OH group (106 kcal/mol).[42] However, hydrogen atom abstraction by all eight radicals from all of the three hydrogen atom donor sites in isopropanol is exothermic (the hydrogen atom affinities calculated for each radical at the B3LPY/6-311++G(d,p) level of theory are: **a**: 113 kcal/mol, **b**: 116 kcal/mol, **c**: 113 kcal/mol, **d**: 114 kcal/mol, **e**: 116 kcal/mol, **f**: 117 kcal/mol, **g**: 119 kcal/mol, **h**: 118 kcal/mol). The strong preference for the thermodynamically favored CH group is consistent with the relative reactivities of tertiary > secondary > primary C−H bonds of saturated hydrocarbons in hydrogen atom abstraction by the phenyl radical studied by Kopinke and co-workers,[23] and our previous study on charged phenyl radicals' reaction with ethanol.[32]

As pointed out above, the extent of the preference for the CH group is not the same for all phenyl radicals. Generally, the slower the overall hydrogen atom abstraction reaction, the more the CH group is favored over the CH_3 groups. For example, the selectivity of radical **a** toward the CH group in isopropanol (91%) is much greater than for radical **h** (54%), and the total hydrogen atom abstraction efficiency of radical **a** is much lower (0.15%) than for radical **h** (28%). Figure 2 shows a plot of the selectivity of hydrogen atom abstraction from each reactive site of isopropanol by the eight phenyl radicals vs the total hydrogen atom abstraction efficiency. The fundamental tradeoff between reactivity and selectivity, i.e., highly reactive species are usually not very selective and vice versa, applies to these hydrogen atom abstraction reactions in the gas phase. A plot of the relationship between the ratios of the charged phenyl radicals' selectivity toward the CH/CH_3 group vs the total hydrogen atom abstraction efficiency is shown in Figure 3. For

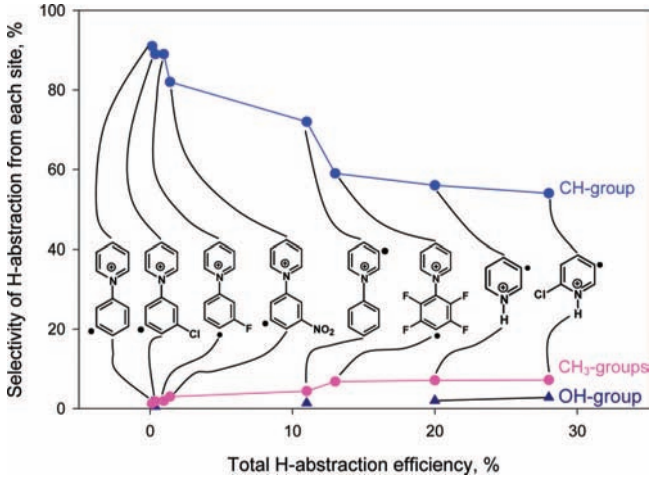


Figure 2. Regioselectivity (number of hydrogen atom is statistically corrected) of hydrogen abstraction from unlabeled isopropanol vs the total hydrogen abstraction efficiency for each charged phenyl radical.

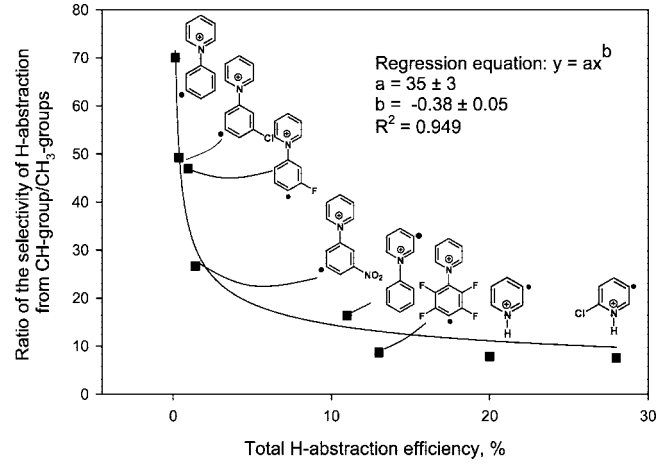


Figure 3. Ratio of the selectivity of hydrogen atom abstraction from the CH group/CH_3 groups (y in the equation) vs total hydrogen atom abstraction efficiency (x in the equation) for each charged phenyl radical. The solid line is a power trend line ($R^2 = 0.949$) obtained by using the regression model $y = ax^b$ in SigmaPlot software. The estimated values of the coefficients a and b are shown.

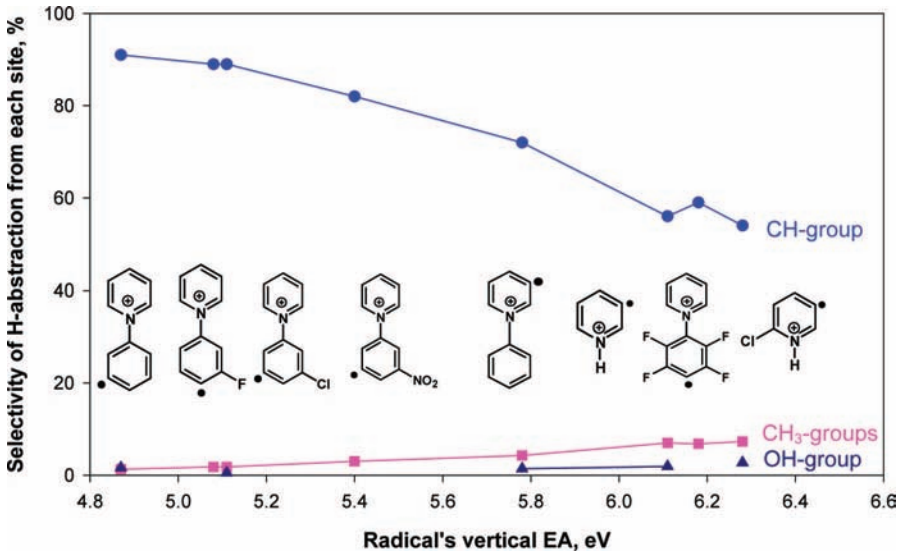


Figure 4. Regioselectivity (statistically corrected for the number of hydrogen atoms) of hydrogen atom abstraction from unlabeled isopropanol vs the vertical EA of each charged phenyl radical.

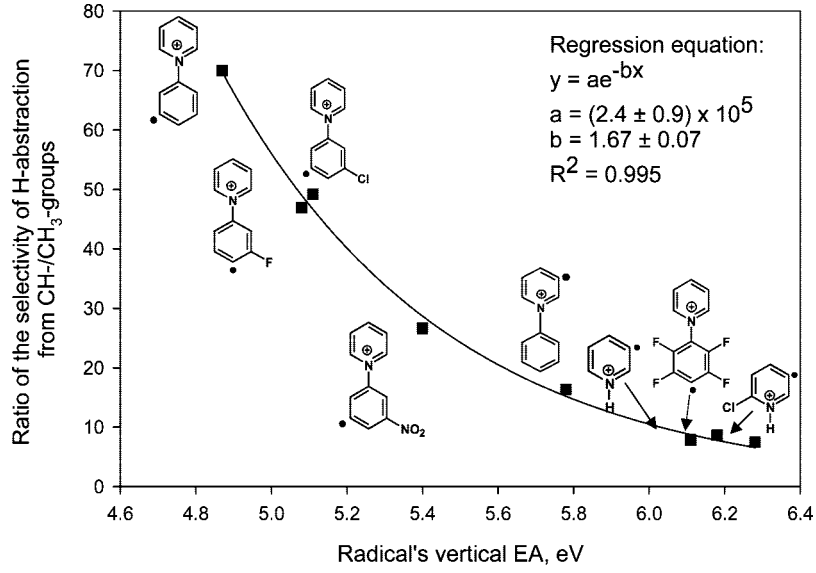


Figure 5. Ratio of the selectivity of hydrogen atom abstraction from the CH/CH_3 groups (y in the equation) vs vertical EA (x in the equation) of each charged phenyl radical. The solid line is the exponential trend line ($R^2 = 0.995$) obtained by applying the regression equation $y = ae^{-bx}$ in SigmaPlot software.

the eight phenyl radicals studied here, the ratio of selectivity for the CH/CH_3 groups decreases as a power function as the total hydrogen atom abstraction efficiency from isopropanol increases. This result may prove to be useful in predicting the extent of selectivity of hydrogen atom abstraction based on the total hydrogen atom abstraction efficiency of a radical. However, many more radicals have to be studied in order to validate this empirical equation.

The lower the radical's vertical electron affinity, the more the radical favors the CH group over the CH_3 group. Figure 4 shows a plot of the selectivity of phenyl radicals in hydrogen atom abstraction toward each site vs the radical's vertical electron affinity. Generally, as the vertical electron affinity of a radical decreases, the selectivity toward the CH group shows an increasing trend while the selectivity toward the CH_3 group shows a decreasing trend. The ratio of the selectivity of the charged phenyl radicals toward the CH/CH_3 groups against the radicals' vertical electron affinity is plotted in Figure 5. An exponential correlation is observed. On the basis of this

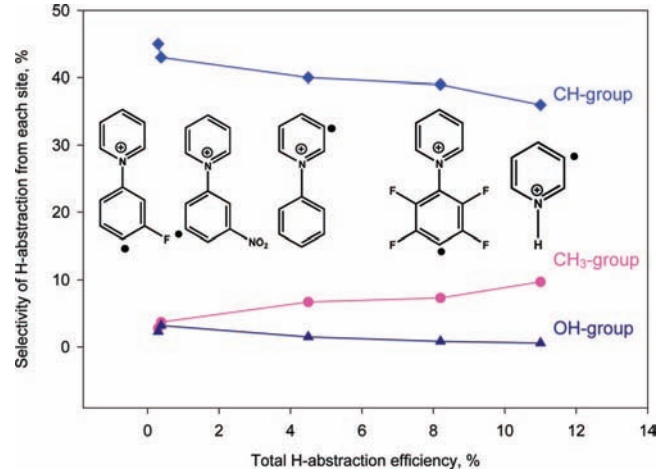


Figure 6. Regioselectivity (statistically corrected number of hydrogen atoms) of hydrogen atom abstraction from unlabeled ethanol vs the hydrogen atom abstraction efficiency of each charged phenyl radical. The data in the graph have been published previously.[32]

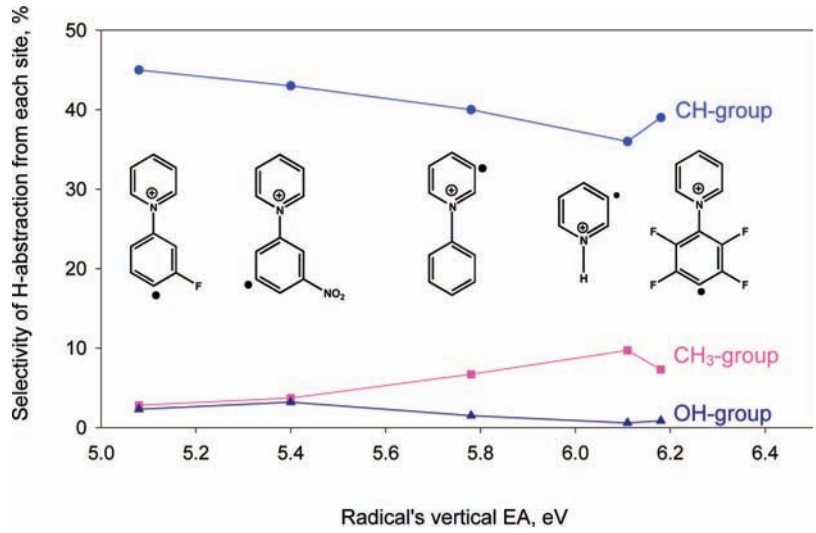


Figure 7. Regioselectivity (statistically corrected for the number of hydrogen atoms) of hydrogen abstraction from unlabeled ethanol vs the vertical EA of each charged phenyl radical. The data in the graph have been published previously.[32]

TABLE 3: Calculated Primary Kinetic Isotope Effects for Hydrogen/Deuterium Abstraction from the CH/CD Group, and Mixed Primary and α-Secondary Kinetic Isotope Effects for Hydrogen/Deuterium Abstraction from the CH_3/CD_3 Groups in Isopropanol

phenyl radical	EFF_{CH}/EFF_{CD} = isotope effect	$EFF_{(CH3)2}/EFF_{(CD3)2}$ = isotope effect
a - EA = 4.87 eV	0.14%/0.049% = 2.9	0.012%/0.0020% = 6.0
b - EA =5.08 eV	0.86%/0.45% = 1.9	0.11%/0.022% = 5.0
c - EA = 5.11 eV	0.32%/0.14% = 2.3	0.039%/0.0086% = 4.5
d - EA = 5.40 eV	1.2%/0.52% = 2.3	0.27%/0.072% = 3.8
e - EA = 5.78 eV	7.9%/4.6% = 1.7	2.9%/0.81% = 3.6
f - EA = 6.11 eV	11%/8.2% = 1.3	8.4%/2.4% 3.5
g - EA = 6.18 eV	7.8%/4.8% = 1.6	5.4%/2.3% = 2.3
h - EA = 6.28 eV	15%/12% = 1.3	12%/5.0% = 2.4

relationship, the ratio of the selectivity of a phenyl radical toward CH/CH_3 group can be predicted by the radical's calculated vertical EA.

Comparison of the Selectivity Trends of Hydrogen Atom Abstraction from Isopropanol and Ethanol. The above selectivity trend was also observed in our previous study on phenyl radicals' reactions with ethanol.[32] Figure 6 shows a plot of the selectivity of hydrogen atom abstraction from unlabeled ethanol vs the total hydrogen atom abstraction efficiency based on the data published before.[32] The five phenyl radicals (**b**, **d**, **e**, **f**, and **g**) studied prefer to abstract a hydrogen atom from the CH_2 group over the CH_3 group and the OH group. Generally, the slower the reaction, the greater the selectivity toward the CH_2 group. Figure 7 shows a plot of the selectivity of hydrogen atom abstraction from each site in unlabeled ethanol vs the vertical electron affinity of the radical. The preference of the CH_2 group for the five radicals (**b**, **d**, **e**, **f**, and **g**) decreases as the vertical electron affinity increases from radical **b** (5.08 eV) to **g** (6.18 eV), which resembles the trend observed for hydrogen atom abstraction from isopropanol.

Kinetic Isotope Effect. The combined kinetic isotope effect for the CD_3 group, which consists of the primary and the α-secondary isotope effects, is given by $EFF_{(CH3)2}/EFF_{(CD3)2}$. The primary kinetic isotope effect for the CD group is given by EFF_{CH}/EFF_{CD}. The kinetic isotope effects for all eight phenyl radicals toward CD and CD_3 groups in labeled isopropanol are given in Table 3. The kinetic isotope effects for the CD_3 groups in labeled isopropanol in reactions with radicals **b** (5.0), **e** (3.6), **f** (3.5), and **g** (2.3) are comparable to those for the CD_3 group in labeled ethanol[32] in reactions with radicals **b** (5.2 ± 0.6), **e** (4.4 ± 1.0), **f** (4.1 ± 0.5), and **g** (2.3 ± 0.4). However, it should be noted that a large relative error is associated with the kinetic isotope effects for the CD_3 group determined in this study since hydrogen atom abstraction from the CH_3 and CD_3 groups is a minor reaction channel. The kinetic isotope effect for the CD_3 groups in isopropanol upon reaction with radical **d** (3.8) is not comparable to that for the CD_3 group in ethanol (6.2 ± 2.4). This finding further suggests that large experimental errors are associated with the value estimated here for the minor reaction channel involving the CH_3 and CD_3 groups. As the vertical electron affinity increases from radical **a** (4.87 eV), **b** (5.08 eV), **c** (5.11 eV), **d** (5.40 eV), **e** (5.78), **f** (6.11 eV), **g** (6.18 eV), to **h** (6.28 eV), the hydrogen atom abstraction efficiency increases (EFF_{CH} from 0.14% to 15% and $EFF_{(CH3)2}$ from 0.012% to 12%), and the isotope effect decreases from 2.9 to 1.3 for the CD group, and from 6.0 to 2.4 for the CD_3 group.

Interestingly, the efficiencies of hydrogen atom abstraction by the reactive phenyl radicals (**e**: 7.9%, **f**: 11%, **g**: 7.8%) from the CH group in isopropanol are comparable to the efficiency measured in solution for hydrogen atom abstraction by the 4-dehydrobenzoate and 4-dehydrotoluene aryl radicals (10%, estimated from the reaction rate[5] relative to diffusion rate[43]) from the SnH group in tri-*n*-butyltin hydride. Further, the kinetic isotope effects measured for the positively charged radicals (**e**: 1.7, **f**: 1.3, **g**: 1.6) for deuterium atom abstraction from the thermodynamically favored CD-site in deuterium-labeled isopropanol also are comparable to the isotope effects reported for aryl radicals (1.6,[5] 1.4,[5,6] and 1.3[7]) for deuterium atom abstraction from the SnD group in Bu_3SnD.[5] On the other hand, the KIE value of 2.9 reported here for the least reactive radical **a** for deuterium atom abstraction from the CD group in deuterium-labeled isopropanol is close to the KIE value of 2.8 for deuterium atom abstraction by aryl radicals from perdeuterated tetrahydrofuran in solution, estimated here based on the previously measured[5] reaction rates for tetrahydrofuran (0.375×10^7 M^{-1} s^{-1}) and perdeuterated tetrahydrofuran (0.132×10^7 M^{-1} s^{-1}).[5]

For a given radical, the kinetic isotope effect for the CD_3 group is larger than for the CD group in labeled isopropanol. This result is consistent with findings obtained for the CD_3 and CD_2 groups in ethanol.[32] In addition, the kinetic isotope effects

for the CD_2 group in ethanol are larger than for the CD group in isopropanol. Therefore, we conclude that the kinetic isotope effects follow the order of CD_3 group > CD_2 group > CD group. This result implies that the extent of C−D or C−H bond breaking in the transition state is in the order of CD_3 group > CD_2 group > CD group or CH_3 group > CH_2 group > CH group.

Conclusions

The selectivities of eight phenyl radicals toward different hydrogen atom donor sites in unlabeled isopropanol were determined by using partially labeled isopropanol isotopologues. The results suggest that the selectivity of phenyl radicals toward alcohols is controlled by their vertical electron affinity, which also controls their reactivity. The lower the vertical affinity of a radical, the lower its reactivity, and the greater the preference for the thermodynamically favored CH group over the CH_3 group or the OH group. This trend is useful in predicting the selectivity of other charged phenyl radicals. The kinetic isotope effect for the CD_3 group was found to be larger than for the CD group. As the radical's vertical electron affinity increases, the kinetic isotope effect for both the CD_3 group and the CD group decreases (from 6.0 to 2.4 and 2.9 to 1.3, respectively). These results imply that the conclusions of the earlier ethanol study[32] apply to other alcohols, as well.

Acknowledgment. The National Institutes of Health are thanked for financial support provided to this work.

Supporting Information Available: This material is available free of charge via the Internet at http://pubs.acs.org.

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JP802257M