ORGANIC LETTERS

2011
Vol. 13, No. 10
2694–2697

Solvent Polarity Affects H Atom Abstractions from C−H Donors

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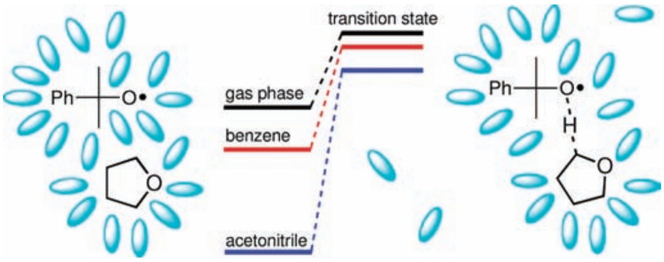
Received March 25, 2011

ABSTRACT



Kinetic solvent effects on hydrogen abstractions involving C−H donors (dienes, ethers, alkylbenzenes) have been corroborated by experiment and theory (UB3LYP/6-311++G, polarized continuum model). To single out the effect of solvent polarity, rate constants for scavenging of the cumyloxyl radical and fluorescence quenching of 2,3-diazabicyclo[2.2.2]oct-2-ene were obtained in binary aprotic mixtures of ethylacetate and acetonitrile. Polar solvents result in a selective stabilization of the reactants (see TOC graphic), which results in slower rate constants.**

Hydrogen atom abstraction (H abstraction) is one of the most fundamental and, besides electron transfer, most intensively studied elementary reactions. H abstractions can proceed in the ground state, where they are important for radical scavenging by antioxidants, or in the excited state, for which photoreduction reactions are prime examples. Accordingly, much research effort has been dedicated to their detailed mechanistic study from an experimental and theoretical point of view. In particular, kinetic solvent effects (KSEs) continue to intrigue the community due to their fundamental appeal,[1−7] and in limiting cases they are potentially of practical relevance.[8,9] For phenols and amines as hydrogen donors[6,7,10−13] and hydroxyl radicals as H-abstracting species[14] KSEs in protic solvents are known to be pronounced. However, a controversial discussion has arisen on whether solvent polarity effects on H abstraction reactions with C−H donors (haloalkanes, ethers, alkylbenzenes, dienes) are experimentally significant or even pronounced,[5,6] or perhaps in special cases masked by a competitive reactivity of tautomers.[4,15]

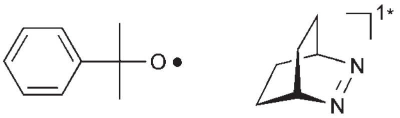


Figure 1. Structures of the hydrogen-abstracting species cumyloxyl radical and singlet-excited DBO.

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10.1021/ol2007956

Recently, we reported two comprehensive experimental data sets, which led us to the conclusion that there exist small, but significant effects of the solvent polarity on the rate constants of H abstractions from C−H donors, which for specific reactive intermediates and relative to the gas phase can become large.[5] In detail, we observed a *slower* reaction rate with *increasing* solvent polarity. This effect was confirmed not only for *tert*-butoxyl and cumyloxyl radicals as hydrogen acceptors, but also for n,π*-excited 2,3-diazabicyclo[2.2.2]oct-2-ene (DBO), a model for the persistent 2,2-diphenyl-1-picrylhydrazyl radical (DPPH).[15−17] The "inverted" nature of this KSE as compared to that for electron transfer, where faster reactions in polar solvents are common, has also been observed by others, for example, by Lanzalunga and co-workers in the scavenging of DPPH by *N*,*N*-dimethylaniline derivatives.[2] Newcomb and co-workers made similarly supportive observations of a KSE for intramolecular H abstractions from benzylic C−H by alkyl radicals.[3] Perhaps the first detailed study of solvent effects is that of Sakurai and Hosomi, which revealed slower reactions of *tert*-butoxyl radicals with toluenes in more polar solvents;[18] the comparison of the gas-phase reactivity of the same radical with toluene (9.6×10^5 M^{-1} s^{-1})[19] versus that in (nonpolar) solution (1.9×10^5 M^{-1} s^{-1})[20] exposes the same trend.

Although several data sets on solvent effects, spanning more than 1 order of magnitude variation in rate constants with invariably inverted signature, have become available,[2−5] the notion that H abstractions from C−H donors show no environmental dependence persists. Recently, Bietti and Salamone have remeasured 1 out of our originally reported 18 donor/acceptor pairs,[5] namely cumyloxyl/1,4-cyclohexadiene,[6] and found no KSE for this pair. Herein, we validate the existence of KSEs on H abstractions from C−H donors experimentally and, for the first time, through high-level calculations.

Table 1. Scavenging Rate Constants for Cumyloxyl Radicals

	k_H (10^7 M^{-1} s^{-1})[a]	
scavenger	EtOAc	CH_3CN
1,4-cyclohexadiene	6.5	6.2
2,5-dihydrofuran	6.5	6.0
tetrahydrofuran	0.72	0.55
hexamethylbenzene	1.1	0.80

[a] Error ±5% (±σ); data reproducibility ±10%; at 295 K.

The choice of the H-abstracting species (cumyloxyl radical and singlet-excited DBO, Figure 1), as well as the experimental approach, were identical with our previous work.[5] Also the selection of the hydrogen donors (dienes, ethers, and an alkylbenzene) purposefully overlaps. To exclude that the previous observation of slower reactions in polar solvents was due to a combination of experimental inaccuracy and a statistical error, as recently suggested,[6] corroborative experimental data in a binary solvent mixture were obtained. This allowed the continuous variation of solvent polarity. We selected acetonitrile (CH_3CN) and ethylacetate (EtOAc), because (i) these two nonviscous solvents are miscible in all proportions, (ii) the intrinsic lifetime ($\tau_0 = 1/k_0$) of the hydrogen-abstracting species is comparable in these two solvents (620 versus 670 ns for singlet-excited DBO and 0.97 versus 1.20 μs for cumyloxyl radicals in EtOAc and CH_3CN, respectively; this work), thereby minimizing artifacts from measurements on different instrumental time scales and/or on quencher concentrations, (iii) they differ significantly in solvent polarity ($E_T(30) = 38.1$ for EtOAc and 45.6 for CH_3CN),[21] (iv) their polarizability is comparable (refractive index, $n_D = 1.372$ for EtOAc and 1.344 for CH_3CN),[21] and (v) they are both *aprotic* and possess essentially the same hydrogen-bond acceptor properties ($\beta_2^H = 0.45$ for EtOAc and 0.44 for CH_3CN);[22] variations of the latter have been held responsible for the KSE in H abstractions from phenols.[7,10−12,22] Our present aim is not to exaggerate the solvent effects, because this has been attempted elsewhere by including the gas phase, nonpolar solvents, as well as protic solvents.[5−7,10−13] Instead, we intend to clearly pinpoint the effects, even if expectedly subtle, and to relate them directly to the solvent *polarity*.

Table 2. Fluorescence Quenching Rate Constants for DBO

	k_q (10^7 M^{-1} s^{-1})[a]		
quencher	EtOAc	EtOAc/CH_3CN (50/50)	CH_3CN
1,3-cyclohexadiene	5.5	4.3	3.6
1,4-cyclohexadiene	2.4	2.0	1.8
2,3-dihydrofuran	1.8	1.4	1.2
2,5-dihydrofuran	2.3	1.9	1.5
hexamethylbenzene	2.2	1.7	1.4

[a] Error ±5% (±σ); data reproducibility ±10%; at 295 K.

Indeed, the data in Tables 1 and 2 expose consistently a lower reactivity toward H abstraction in the distinctly more polar acetonitrile. For cumyloxyl radicals and the most reactive C−H donors, the values (obtained by

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transient absorption spectroscopy) fall within the reproducibility limit (±10%, the typical variation when the experiment is conducted by different operators or in different laboratories); the statistical error ($\pm\sigma$ from the regression analysis of the kinetic plots) is smaller (±5%). More convincing than the error analysis of individual couples is, of course, the statistics of the combined data sets (consisting of 9 entries), which afford a probability of less than 0.2% that the observed trend is the result of random error. It is therefore the internal consistency of the global data set for largely different hydrogen donors and entirely different reactive species that establishes the broader validity of the proposed KSE.[5] The trend can be visually inspected from the kinetic raw data (Figure 2). The systematic dependence obtained upon continuous variation of the solvent polarity (Figure 3 and 50/50 entries in Table 2) provides further circumstantial evidence.

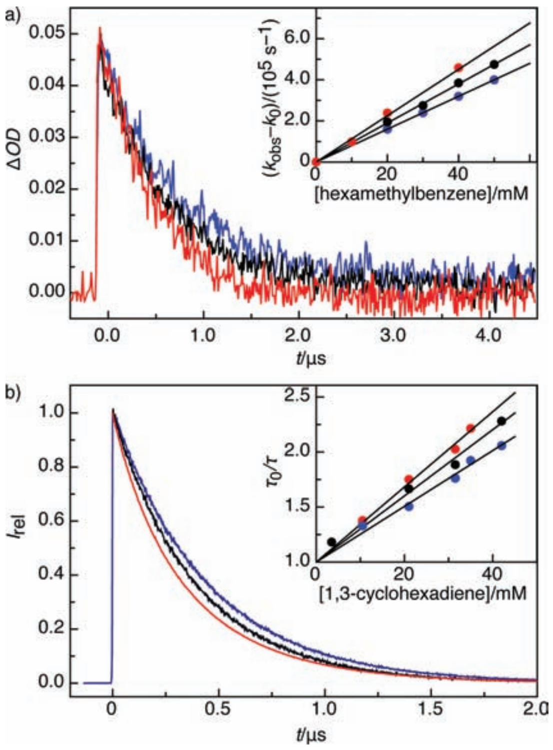

Figure 2. Kinetic measurements in CH_3CN (blue), EtOAc/CH_3CN (50/50, black), and EtOAc (red) at 295 K. (a) Transient absorption decays of cumyloxyl radicals in the presence of hexamethylbenzene (40 mM). (b) Fluorescence decays of DBO in the presence of 1,3-cyclohexadiene (31 mM). The insets show the corresponding kinetic plots.

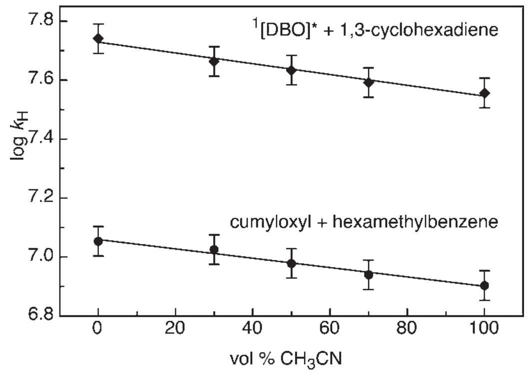

Figure 3. Plots of log*k* versus the composition of a binary EtOAc/CH_3CN mixture at 295 K.

Chemical intuition suggests that any chemical reaction is sensitive to the medium.[21] For H abstractions from C−H bonds the effects are small, but in favor of a higher reactivity in nonpolar solvents. Recently, we have attributed this KSE to a selective stabilization of the reactants.[5,23] To theoretically corroborate our previous explanation, we have now performed high-level quantum-chemical calculations, which were most conveniently accessible for the ground-state reactions of the cumyloxyl radical. We selected density-functional theory (UB3LYP) due to its known robust performance for treating radical reactions.[24,25] A high basis set (6-311++G**) was chosen to achieve high accuracy;[19,24−26] in particular, diffuse functions are indispensable to reproduce solvation effects, and those for H were included since this atom is being transferred.[24,26]

The transition states for H abstraction in the gas phase were optimized (Figure 4) and their identity verified through the occurrence of a single imaginary frequency (that for stretching along the O−H−C coordinate for H abstraction). The resulting activation energies in the gas phase (relative to the individual reactants) are shown in Table 3. Solvation energies were calculated by a continuum description of the solvent based on the self-consistent reaction field (SCRF) method; the polarized continuum model (PCM)[24,26] with a UAHF cavity (see the Supporting Information) was employed. Values were obtained (including geometry optimization at the stationary points) for nonpolar benzene ($E_T(30) = 34.3$)[21] and polar acetonitrile (Table 3), two solvents for which also a significant amount of experimental reactivity data exist.

The obtained barriers were small (1.3−4.3 kcal mol^{-1}). Experimental activation energies for C−H abstractions are scarce and limited to the *tert*-butoxyl radical, mostly in nonpolar benzene/di-*tert*-butyl peroxide (1/2) solution.[19,20,27,28] The absolute order-of-magnitude agreement between calculated values and reported experimental activation energies (e.g., 2.5 and 3.5 kcal mol^{-1} for tetrahydrofuran[28] and toluene[20]) was nevertheless gratifying to observe.

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Table 3. Calculated Activation Energies[a] for Cumyloxyl Radical Scavenging in Different Solvents

scavenger	calcd $E_a^{\ddagger}$ (kcal mol^{-1}) gas phase	benzene	acetonitrile
1,4-cyclohexadiene	1.42	1.72	1.91
2,5-dihydrofuran	1.28	1.77	2.23
tetrahydrofuran	2.59 [1.16][b]	2.98 [1.90][b]	4.08 [2.84][b]
hexamethylbenzene	2.86	3.29	4.29

[a] UB3LYP/6-311++G** level of theory; values include zero-point energy and thermal enthalpy corrections at 298.15 K, plus *RT*, to convert from activation enthalpies. [b] Values for *tert*-butoxyl in brackets.

The calculated solvation effects are compelling in that they reveal without a single exception an increase in activation energy upon going from the gas phase to benzene to acetonitrile. Most importantly, the close inspection of the solvation energies for each hydrogen donor reveals invariably larger values for the reactants than the transition states (Figure 4 and the Supporting Information). The reactants do therefore experience a selective stabilization by the (polar) solvent, which accounts adequately for the observed trend in absolute activation energies as well as rate constants. A comparative calculation for H abstraction from tetrahydrofuran by the extensively investigated *tert*-butoxyl radical[4,20,27] revealed the same trends in activation energies (Table 3) *and* solvation effects (Figure 4c). The theoretical findings do therefore fully support our originally tentative explanation based on the Kirkwood continuum model.[5,21,23]

The trend of the calculated activation energies is fully consistent with the observed lower reactivity toward H abstraction in polar solvents (inverted effect). Also the order of magnitude of the solvent effects is well-reproduced: if one assumes constant pre-exponential factors for a particular H donor,[29] the absolute variation of the activation energies in dependence on the medium would correspond to about a factor of 2–5 difference between the different media (ca. 0.5–1 kcal mol^{-1}). DBO has a higher dipole moment than alkoxyl radicals (ca. 3.5 versus 1.6 D),[5] with an expectedly larger solvent stabilization, which accounts for the larger solvent effects in Table 2. Theoretical predictions and experimental measurements expose therefore jointly that KSEs on H abstractions by alkoxyl radicals from C–H donors are small, but significant, and, whenever observed, they are inverted. The effects, which originate from a selective stabilization of the reactants, become more obvious in protic solvents with phenolic H donors,[6,7,10–13] but they are offset only in exceptional cases, in which a specific solvation of the transition state competes.[14]

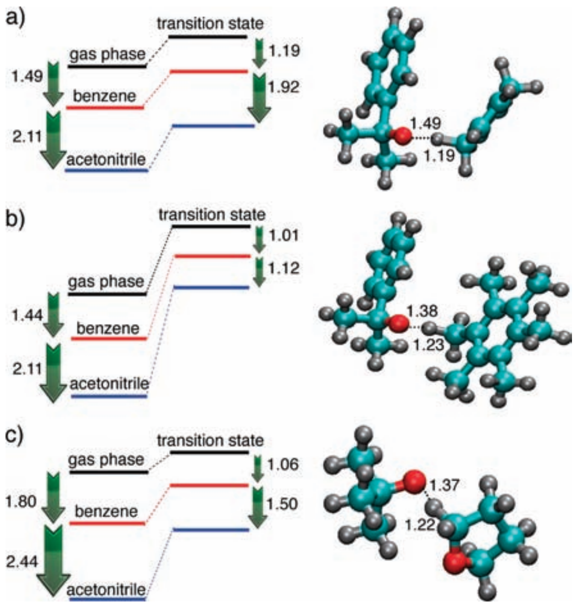

Figure 4. Optimized (B3LYP/6-311++G**) transition-state structures and solvation energies of the reactants and the transition state for the scavenging of the cumyloxyl radical by (a) 1,4-cyclohexadiene and (b) hexamethylbenzene as well as (c) for the scavenging of the *tert*-butoxyl radical by tetrahydrofuran.

With respect to the practical relevance of the presently described small but inverted solvent effects, they can be—and already have been—used to pinpoint a direct C–H abstraction as reaction mechanism.[2] They also contribute their share to the pronounced solvent effects for H abstractions from phenols and amines, which have been previously exclusively attributed to the hydrogen-bond accepting or donating properties of the solvent.[6,7,10–12] In general, solvent effects on radical reactions are presently experiencing a renaissance, and their importance, even for synthesis, has just recently been highlighted.[9]

Acknowledgment. Financial support by the Deutsche Forschungsgemeinschaft (DFG NA 686/5), the Fonds der Chemischen Industrie, the Spanish Ministry for Science and Innovation, Madrid (CTQ2008-06777-C02-02/BQU), and the Egyptian Government (doctoral fellowship for H.S.E.) is gratefully acknowledged.

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

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