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Stereoselectivity of the Hydrogen-Atom Transfer in Benzophenone–Tyrosine Dyads: An Intramolecular Kinetic Solvent Effect

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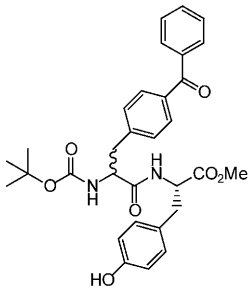
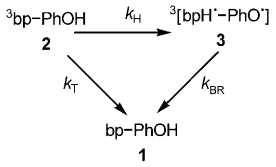
Intramolecular quenching of excited states by successful electron transfer (ET) or hydrogen-atom transfer (HAT) is known to produce covalently connected radical–ion pairs[1] or biradicals (BR) in high yields with a high selectivity.[2] For instance, tyrosyl radicals (Tyr(O•)) that are instrumental in biochemical metabolism and pathogenesis,[3] can be obtained by the intramolecular quenching of ketone-triplet states by remote tyrosine. In a recent study we have provided evidence that the efficiency of the tyrosyl-radical formation by HAT in short peptide-bound benzophenone∪Tyr dyads (bp∪Tyr) is generally governed by regiochemical and by stereochemical constraints of the peptide chain.[4] Notably, the HAT rates and the degrees of stereoselectivity were significantly solvent dependent. The high selectivity of an intramolecular HAT reaction in a related bp∪Tyr dyad has been recently used to address the nature of the long-range ET reactions of ribonucleotide reductase with external Tyr(O•) radicals.[5] This approach underlines the potential of ketone∪Tyr dyads as model systems for biologically relevant questions of radical-site formation and radical transport.

In the current work we address the solvent dependence of the intramolecular HAT quenching in a pair of diastereomeric bp∪Tyr dyads **1** by nanosecond laser flash photolysis. The stereoselectivity of the quenching of the triplet states **2** (Scheme 1) was studied in fifteen different solvents. As a result, significant stereoselectivity, as measured by the ratio of the HAT rate constants $S_D = k_H(\mathbf{1b})/k_H(\mathbf{1a})$, is induced by specific solvent-solute interactions, that is, by hydrogen-bond formation between the dyad and the solvent. A kinetic model is proposed which accounts for the solvent dependence and the intramolecular dynamics and that exhibits strong parallels to the Ingold et al. kinetic solvent effect (KSE)[6] in bimolecular HAT reactions (Scheme 1).



Boc-(*S*)-bpa-(*S*)-Tyr-OMe (**1a**)
Boc-(*R*)-bpa-(*S*)-Tyr-OMe (**1b**)



Scheme 1. a) Chemical structure of the dyads **1a**,**b**; b) reaction scheme for the deactivation of the triplet excited state **2**, and of the biradical **3**.

Excitation of the bp chromophores of the dyads **1** with 355 nm pulses yields the excited triplet states **2** with unit quantum yields within the duration of the laser flash. Resolution of the transient spectra after the flash revealed that the biradicals **3** (bpH•∪Tyr(O•)) are formed during the decay of **2** by HAT from the Tyr residue with quantum yields close to unity in inert solvents. Biradical decay cleanly returns the ground-state dyads. Details of this process will be discussed elsewhere. The dyad concentrations were such that contributions from bimolecular quenching of **2** by ground-state **1** remained below 5%. In inert solvents the experimentally observed rate constant of the triplet decay k_D then simply equals the rate constant of the intramolecular H-atom transfer k_H. In solvents with labile H-atoms the competitive HAT from the solvents as an additional decay channel was taken into account (see Supporting Information). The obtained kinetic data for the decay of **2a**,**b** in fifteen solvents are sum-

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marized in Table S1 (Supporting Information). The influence of the solvent on the value of k_H (s^{-1}) that covers a range of 10^6–10^8 for both compounds can be separated into bulk effects and specific solvent effects.

One effect of the solvent is referred to the influence of the bulk viscosity η_{solv}. In particular, plots of $1/k_H$ are linear with the viscosity, provided that different solvent classes are analyzed separately. This is shown in Figure 1 for five alcohol solvents and three chlorohydrocarbons. Strikingly, stereoselection between **1a** and **1b** seems to be insignificant in chlorohydrocarbon solutions ($S_D < 1.3 \pm 0.3$; circles in Figure 1), whereas alcohol solvents give rise to significant selectivity ($S_D \approx 3.0 \pm 0.3$; squares in Figure 1).

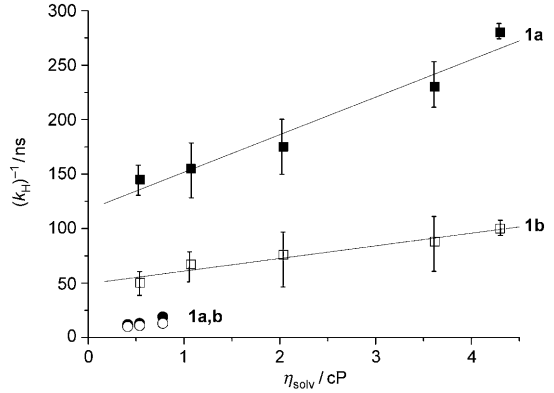
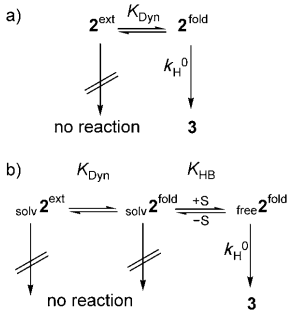


Figure 1. Viscosity dependence of the reciprocal H-atom transfer rate constants; squares: alcoholic solvents; circles: chlorohydrocarbon solvents; lines: linear fits to the data.

Scheme 2a serves to rationalize the viscosity dependence of the decay of **2** within a two-step kinetic model. Therein k_H^0 is the rate constant of the elementary HAT step. $K_{Dyn} = k_{Dyn}^f/k_{Dyn}^b$ denotes the molecular-*dyn*amics equilibrium between folded and extended conformations of the dyads ($\mathbf{2}^{fold}$ and $\mathbf{2}^{ext}$). The rate constants of folding and unfolding, k_{Dyn}^f and k_{Dyn}^b, carry a viscosity dependence. A similar model has been found adequate to describe the viscosity dependence of intramolecular quenching of excited tryptophan by remote cysteine.[7]

$$\frac{1}{k_H} = \frac{1}{K_{Dyn} \cdot k_H^0} + \frac{1}{k_{Dyn}^f} = \frac{1}{K_{Dyn} \cdot k_H^0} + \frac{\eta_{solv}}{k_{Dyn}^{f0}} \quad (1)$$

In terms of Equation (1) the striking difference between the intercepts of the "chlorohydrocarbon" and the "alcohol" plots might be attributed to a substantial impact of the solvent on the molecular conformation, that is, on the equilibrium K_{Dyn}. Such an effect on the equilibrium conformation is well established for the side-chain rotamers of aromatic amino acids, that are sensitive to the bulk solvent permittivity,[8] and has been recently found to apply also for a set of structurally related dyads.[4] Provided that this is an important factor, solvents of similar viscosity *and* permittivity



Scheme 2. Kinetic schemes of the intramolecular H-atom transfer in a) a two-step mechanism and b) a three-step mechanism including H-bonding to the solvent.

should give rise to similar stereoselectivity. However, experiments in other low-permittivity solvents like pyridine and 1,4-dioxane exhibit a significant stereoselection ($3.0 < S_D < 4.0$) together with a substantial decline of the overall reactivity. This is in stark contrast to the results obtained for the chlorohydrocarbons. Although we cannot rule out bulk solvent effects on the molecular conformation, we attribute the failure of equation of Equation (1) to adequately describe the quenching data in alcohol solvents to neglected specific solvent–solute interactions.

The importance of specific solvent–solute interactions as a source of kinetic solvent effects is borne out by a linear free energy relationship with a solvation-parameter model introduced by Abraham et al. [Eq. (2)].[9] The solvent descriptors are the solvent's dipolarity/dipolarizability π_2^H, the solvent's effective hydrogen-bond acidity $\Sigma\alpha_2^H$, and the solvent's effective hydrogen-bond basicity $\Sigma\beta_2^H$. The respective data are compiled in Table S1 (Supporting Information). The rate constants for HAT of **1a**,**b** in twelve solvents (three highly viscous alcohols were not considered) were subjected to multi-linear regression in terms of Equation (2). The fit-parameters are given in Equations (3) and (4). Error analysis in terms of reduced χ^2 gave values of 2.41 and 4.34 for **1a** and **1b**, respectively. It is noted, that these values substantially improve (reduced $\chi^2 \approx 1.6$) when data for ethanol and benzonitrile are not considered. A plot of the fitted rate constants versus the experimental rate constants is convincingly linear with a slope of 0.98 ± 0.03 (Figure S1, Supporting Information).

$$\ln k_H = \ln k_0 + s\pi_2^H + a\Sigma\alpha_2^H + b\Sigma\beta_2^H \quad (2)$$

$$\ln k_H\ (\mathbf{1a}) = 18.50(\pm 0.13) - 0.15(\pm 0.17)\pi_2^H - 0.69(\pm 0.21)\Sigma\alpha_2^H - 4.86(\pm 0.17)\Sigma\beta_2^H \quad (3)$$

$$\ln k_H\ (\mathbf{1b}) = 18.62(\pm 0.18) - 0.15(\pm 0.23)\pi_2^H - 0.41(\pm 0.28)\Sigma\alpha_2^H - 3.06(\pm 0.22)\Sigma\beta_2^H \quad (4)$$

The fits essentially predict identical HAT rate constants k_0 in the absence of solvent effects for both dyads. The fit parameters *s*, *a*, and *b* are all of negative sign, that is, the inter-

action of the solute with a solvent induces a reactivity loss. However, the effects of π_2^H and $\Sigma\alpha_2^H$ are small so that the reactivity loss and, equivalently, the increase of the free energy of activation $\Delta G^{\neq}$ is mainly attributable to H-bonding of the dyad to the solvent, with the solvent being the acceptor. Interestingly, the dependence on the solvent's H-bond basicity is significantly smaller for the (*R*,*S*)-diastereomer **1b**. This difference appears to be the dominant source of the stereoselectivity $S_D = k_H(\mathbf{1b})/k_H(\mathbf{1a})$, which is observed for the decay of **2**. In particular, a semilogarithmic plot of S_D is linear with $\Sigma\beta_2^H$ over the complete set of fifteen solvents (Figure 2), irrespective of viscosity effects.

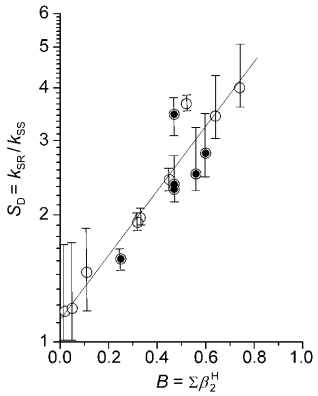


Figure 2. Stereoselectivity of the H-atom transfer in the dyads **1a**,**b** as a function of the solvents' H-bond basicity; filled symbols: alcoholic solvents.

The propensity of phenols to act as an H-bond donor is well known,[10] so that the Tyr-phenol moiety can be assumed to be an important source of the specific interaction with the solvent. Accordingly, a specific ground-state solvation of Tyr has been observed for related compounds.[4,11] The loss of reactivity in strongly H-bonding environments is in agreement with earlier observations in the bimolecular HAT from phenols.[6] We therefore attribute this retardation in H-bond accepting solvents to the reversible masking of the phenol by the solvent S in an HB-equilibrium with $K_{HB} = [PhOH\cdots S]/([PhOH][S])$. What results for the special case of strong H-bonding is a three-step kinetic Scheme for the intramolecular quenching of **2** (Scheme 2b), with the different triplet species ${}_{solv}\mathbf{2}^{ext}$ (solvated/extended) ${}_{solv}\mathbf{2}^{fold}$ (solvated/folded), and ${}_{free}\mathbf{2}^{fold}$ (unsolvated/folded). With the assumption of fast H-bond equilibration of ${}_{solv}\mathbf{2}^{fold}$ and ${}_{free}\mathbf{2}^{fold}$,[12] the observed quenching rate constant in this model is given by Equation (5). A detailed derivation can be found in the Supporting Information. Equation (5) predicts a linear relationship between the reciprocal HAT rate constant and the equilibrium constant for the H-bonding of the phenol to the solvent (multiplied by the solvent's molarity [S]) as is implied also by Ingold et al. KSE model for bimolecular HAT reactions.[6]

As shown in Figure 3, this prediction is satisfyingly fulfilled for five solvents of similar viscosity. The analysis is limited by the availability and the uncertainty of the H-bond equilibrium constants (box in Figure 3 highlights the uncertainty in pyridine).[13] Irrespective of these limitations, the

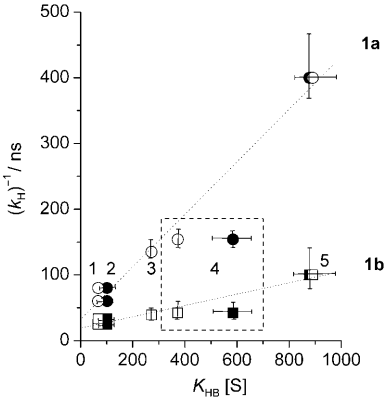


Figure 3. Plot of the H-atom transfer rate constants for **1a** (squares) and **1b** (circles) in terms of Equation (5); filled symbols: range of "thermochemically" derived values for K_{HB}, compiled in ref. [6]; open symbols: "kinetically" determined values for K_{HB}, taken from ref. [6]; lines: linear trends of the "kinetically" derived data set; solvent code: 1 = acetonitrile; 2 = ethyl acetate; 3 = methanol; 4 = pyridine; 5 = dimethylformamide.

slopes of the plots for **1a** (0.40 ns) and **1b** (0.09 ns) differ considerably. Provided that solvent-dependent changes of the dyad conformations are insignificant (i.e., $K_{Dyn} \approx$ const.), this finding points to different solvation of the diastereomeric dyads. Based on the current results, it cannot be decided yet, whether the discriminating factor can be attributed to differential solvation of the triplet excited dyads **2a** and **2b** before the HAT step and/or in the diastereomeric transition states of the transfer reaction.

$$\frac{1}{k_H} = \frac{1}{k_{Dyn}^f} + \frac{K_{HB}[S]}{K_{Dyn} \cdot k_H^0} \qquad (5)$$

We conclude that the rates of the intramolecular HAT reaction are delicately dependent on the H-bonding between the H-atom donor and the solvent, which shields the donor from reactive approach of the H-abstracting moiety. In the present case of diastereomeric dyads, this intramolecular kinetic solvent effect induces solvent-dependent stereoselection ($1.2 < S_D < 4.0$).

Experimental Section

The dyads **1a**,**b** were synthesized by standard techniques of peptide coupling. Synthetic procedures and characterization of the compounds are given in the Supporting Information. The laser flash photolysis equipment has been described in detail previously.[14] The excitation light source was the 355 nm output of a Nd/YAG laser (7–9 ns fwhm; 3–7 mJ pulse^{-1}). Spectral analysis and data processing have been described in detail before.[4]

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Keywords: biradicals · hydrogen bonds · ketones · photochemistry · solvent effects

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