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Correlation of the Chemical Reactivity of Some Tetrazine Derivatives with Their Reactivity toward Ortho-positronium Atoms and Their LUMO Energies

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Chemical reaction rate constants of the nucleophilic ortho-positronium (o-Ps) atom with a series of tetrazine derivatives were determined in dimethylformamide (DMF) solutions by positron annihilation lifetime spectroscopy. The observed rate constants are in the range that corresponds to that of the diffusion-controlled reactions. It was shown that this pronounced reactivity of tetrazines toward o-Ps stems from the electron-deficient tetrazine core. The introduction of electron-donating substituents onto the tetrazine ring, as expected, decreases the reactivity of the molecule toward o-Ps. The measured reaction rate constants of o-Ps resulted in a good linear correlation with the calculated LUMO energies of the tetrazines. The reactivity of tetrazines toward o-Ps correlated well also with their reactivity toward classical nucleophiles.

I. Introduction

When a high-energy positron (e^+), the antiparticle of an electron (e^-), enters a condensed medium, it will thermalize in a few picoseconds by losing its kinetic energy via ionization of the molecules of the medium. After thermalization, the positron annihilates with an electron into γ quanta either via a free annihilation process or from a bound state, which is known as a positronium (Ps) atom.[1−3] Ps is the simplest hydrogen-like exotic atom which can be considered as the lightest, "0 mass number isotope" of hydrogen, where the heavy proton has been exchanged by the much lighter positron. Due to the different spin combinations of a positron and an electron, there are two possible Ps states, the para-positronium (p-Ps) with antiparallel (singlet) spin state and the ortho-positronium (o-Ps) with parallel (triplet) spin state. The intrinsic lifetimes of p-Ps and o-Ps are 0.125 and 140 ns, respectively.

According to the basic idea of the spur model of positronium formation,[4] a thermalized positron can form a Ps atom with an electron which is freed by the positron itself in its ionization track or spur. Through its different decay modes Ps can be used as an efficient microprobe of various physical or chemical properties of matter.

In condensed medium the long lifetime of o-Ps is shortened to a few nanoseconds due to the so-called pick-off annihilation, whereby the positron in the o-Ps atom seeks out an electron in the surrounding molecules with opposite spin and annihilates with it instead of its own electron. No special chemical interactions between the o-Ps atom and the surrounding medium are involved in this process.

On the other hand, if the o-Ps atom takes part in chemical reactions (e.g., substitution, oxidation, complex formation) with certain molecules of the system, its annihilation characteristics will depend strongly on the physical and chemical structure of these molecules. In solution the chemical interactions (due to the increased proximity of electrons with opposite spin) will shorten the mean o-Ps lifetime as compared to the characteristic pick-off lifetime of the pure solvent. These processes are called "quenching" of o-Ps.

Certain groups of compounds such as diamagnetic nitroaromatics, electron-deficient olefins such as maleic anhydride and quinones, and also nitriles proved to be very effective o-Ps quenchers.[5−7] All these molecules are known as good electron acceptors, and o-Ps reacts with them via donor−acceptor interaction.[8] The study of a series of substituted nitrobenzenes revealed a clear correlation between their reactivity and Hammett's σ constant of the corresponding substituents.[8] It was also demonstrated that the positively charged carbon atoms of the benzene ring are the reactive centers where the nucleophilic o-Ps attacks the molecule.[5,9−10]

In our previous papers[10−12] we reported that positron annihilation lifetime spectroscopy can provide information also on subtle structural changes in the molecules[10,11] or on fine differences in their chemical reactivity,[12] if an appropriate model system is selected and the comparison is based on a series of molecules with a common framework.

The aim of the present work was to use positron annihilation lifetime spectroscopy to determine the relevant factors responsible for the differences in the reactivity of a series of molecules with a similar framework toward the nucleophilic o-Ps atom. We wanted also to compare the results with the differences existing in the chemical reactivity of the same molecules.

As a model system for this 2-fold aim, a series of tetrazines that bear π-donor amine and alkoxy substituents in positions 3 and 6 were selected (**1**−**8** in Figure 1). These compounds are easily accessible and provide a representative selection for which the influence of electronic factors on the reactivity of the tetrazine core can be established. For reference, 1,4-dihydro-3,6-bis(dimethylpyrazolyl)tetrazine (**9**), a nonaromatic analogue of **1**, was also examined (Figure 1).

Tetrazines possess four nitrogen atoms in their heterocyclic core, which makes their aromatic system electron deficient and leads to low-lying LUMO orbitals. This in turn results in a

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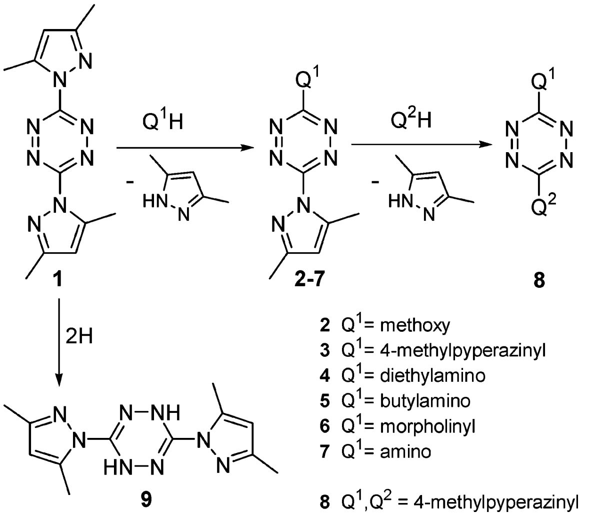

Figure 1. The investigated tetrazine derivatives.

unique reactivity—participation in “inverse electron demand” Diels—Alder reactions and facile nucleophilic substitution—that makes tetrazines useful building blocks in organic synthesis. The primary factor influencing the reactivity of tetrazines in these processes is the energy of their LUMO orbital. The lower the energy of the orbital, the higher the reactivity of the tetrazine; therefore, any physical measurement that could provide information on the LUMO energy would be of significant importance.[13] It was demonstrated recently[12] that the chemical reaction rate constant the of o-Ps atom toward electron-deficient heterocyclic compounds can be a measure of their electron deficiency. Analogously, Kobayashi and co-workers demonstrated[14,15] that in the case of nitrogen heterocycles the results of the same measurements give a linear correlation with calculated LUMO energies of the investigated systems. These findings encouraged us to investigate whether the reactivity of o-Ps atoms toward tetrazines could provide a tool for the prediction of the reactivity of tetrazines (determination of their LUMO energies).

II. Experimental Section

Preparation of the Tetrazine Derivatives. The preparation of the model compounds started from the conveniently accessible 3,6-bis(3′,5′-dimethylpyrazol-1′-yl)tetrazine (**1**).[16] **1** was reacted with the appropriate amine in toluene at room temperature[17] to give **3**−**7** as red crystalline solids.[18] **2** was prepared from the reaction of **1** with methanol in pyridine at room temperature.[19] To achieve disubstitution, 3,6-dichlorotetrazine was treated with 4-methylpiperazine, and after the completion of the reaction and removal of the volatiles in a vacuum, **8** was recrystallized from cyclohexane.

Compounds **1**−**7** and **9** were already known from the literature,[16,18,19] while compound **8** is reported for the first time.

*3,6-Bis(4′-methylpiperazin-1′-yl)-tetrazine (**8**).* To 1 mL (0.903 g, 9.01 mmol) of *N*-methylpiperazine 151 mg (1 mmol) of 3,6-dichlorotetrazine was added in small portions at 25 °C over 15 min. The reaction mixture was quenched with 5 mL of 1 M K_2CO_3 solution and extracted four times with 10 mL of dichloromethane. The combined organic layers were dried over $MgSO_4$ and filtered, and the solvent was evaporated. The remaining deep red solid was recrystallized from cyclohexane, giving 230 mg of pure product.

Yield: 82.6%. mp: 142−143 °C. ^1H NMR ($CDCl_3$, 250 MHz, $CDCl_3$): δ 3.83 (t, 8H, $J = 4.75$ Hz), 2.52 (t, 8H, $J = 5.25$ Hz), 2.34 (s, 3H). ^{13}C NMR ($CDCl_3$, 62.5 MHz, $CDCl_3$): δ: 159.9, 54.4, 46.3, 43.9. MS (EI, 70 eV) m/z (relative intensity,%): 279 (21), 278 (66), 208 (31), 125 (28), 124 (41), 99 (18), 98 (49), 71 (100), 57 (44), 43 (89). IR (KBr) ν_{max}: 2956, 2924, 2801, 1498, 1445, 1370, 1306, 1268, 1150, 1036, 1009, 951, 784 cm^{-1}. HRMS m/z Calcd for $C_{11}H_{16}N_5O_2$: 279.2045 $[M + H]^+$. Found: 279.2032.

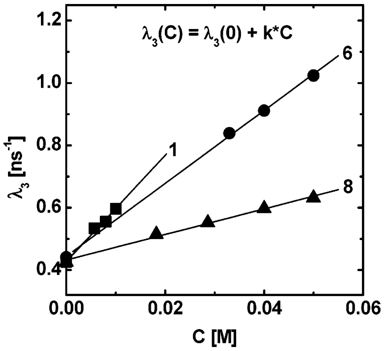

Figure 2. Decay rate constants of the o-Ps atom (λ_3) measured at 20 °C in DMF solutions of compounds **1**, **6**, and **8** plotted as a function of solute concentration. The reaction rate constants (k) were calculated by eq 1 as the slope of the least-squares-fit lines and are presented in Table 1 together with the results found for the other investigated compounds. (The experimentally observed uncertainties of λ_3 expressed as the standard deviations for the mean values of three parallel measurements are less than the dimensions of the symbols for the data points in the figure.)

Positron Lifetime Measurements. The positron source consisted of about 1 MBq of ^{22}Na thermally diffused into a sodium glass film of 2.5 mg/cm^2 thickness, resulting in a source correction of 9%. The source was fixed in an all-glass sample holder. The solution to be studied was thoroughly deoxygenated in the sample holder by pure nitrogen gas. A vacuum-tight Teflon screw stopper closed the sample holder, and the sample was kept under atmospheric pressure of nitrogen during the measurement. The holder was immersed into a thermostat, which was controlled with an accuracy of ±0.05 °C.

The positron annihilation lifetime spectra were recorded by a fast−fast coincidence spectrometer with BaF_2 scintillators. The time resolution of the setup was fwhm = 300 ps. A total of 10^6 counts were recorded in each spectrum. The measurements were carried out in DMF solutions in the temperature range of 15−65 °C. Three spectra were collected for each concentration. The spectra were analyzed by the RESOLUTION computer program[20] in terms of three exponential components with lifetimes/decay rates $\tau_i = 1/\lambda_i$ and relative intensities I_i, where $i = 1, 2, 3$ corresponds to p-Ps, free positron, and o-Ps, respectively. The experimentally observed uncertainties of the results expressed as the standard deviations for the mean values of the three parallel measurements were only a little higher than the standard deviation of the individual measurements estimated by the RESOLUTION computer program.

III. Results and Discussion

Reaction Rate Constants. The rate constants (k) for the chemical reactions of the o-Ps were calculated by the well-known eq 1[1] from the o-Ps decay rate constants (λ_3) measured as a function of the solute concentration (C):

$$\lambda_3(C) = \lambda_3(0) + kC \tag{1}$$

$\lambda_3(C)$ and $\lambda_3(0)$ are the o-Ps decay rate constants measured in the solutions and in the pure solvent, respectively.

In Figure 2, as an example, the decay rate constants of o-Ps atom measured at 20 °C in DMF solutions of compounds **1**, **6**,

TABLE 1: Measured o-Ps Reaction Rate Constants and Calculated[21] LUMO Energies and Charge Distribution for Different Tetrazine Derivatives

tetrazine	k (10^{10} M^{-1} s^{-1})	E_{LUMO} (eV)	q (C3)	q (C6)
1	1.73 ± 0.05	−1.616	0.583	0.583
2	1.53 ± 0.13	−1.312	0.355	0.343
3	1.37 ± 0.04	−1.067	0.551	0.598
4	1.24 ± 0.03	−1.012	0.568	0.620
5	1.22 ± 0.06	−0.962	0.479	0.533
6	1.18 ± 0.13	−1.154	0.562	0.604
7	1.17 ± 0.02	−1.015	0.579	0.622
8	0.39 ± 0.02	−0.514	0.637	0.637
9	0.099 ± 0.005	na	na	na

and **8** are plotted as a function of the solute concentration. The data points fit well to straight lines, demonstrating the validity of eq 1. The rate constants (k) for the chemical reactions of o-Ps atom were calculated as the slopes of the least-squares-fit lines. The complete series of the chemical reaction rate constants for compounds **1**−**9** measured at 20 °C are presented in Table 1. There are three important conclusions that we established after comparing the data in Table 1:

(i) The reaction rate constants, with the exception of that for **9**, are in the range that corresponds to that of the diffusion-controlled reactions.

(ii) The pronounced reactivity of tetrazines toward o-Ps stems from the aromatic tetrazine core. It is convincingly demonstrated by a nearly 200-fold decrease in reactivity on the reduction of the tetrazine core (cf. **1** and **9**) destroying its aromatic bond system.

(iii) The introduction of electron-donating substituents onto the tetrazine ring, as expected, decreases its reactivity toward o-Ps. The effect is most pronounced in the case of compound **8**, where both substituents of **1** are replaced.

Activation Parameters. In the cases of compounds **1**, **3**, and **7** the temperature dependence of the reaction rate was also investigated. The rate constants were determined at five different temperatures in the range of 15−65 °C.

Figure 3 shows that the temperature dependence of the reaction rate constants can be well described by the Arrhenius equation:

$$k/T = R/(N_A h)\ \exp(\Delta S^{\ddagger}/R)\ \exp(-\Delta H^{\ddagger}/RT) \qquad (2)$$

The average activation parameters ($\Delta S^{\ddagger}$ and $\Delta H^{\ddagger}$) are presented in Table 2.

The results show that the average activation parameters are very similar in all three cases. Thus the mechanism of the reactions and the structure of the activated complexes are similar and are not affected very much by the properties of the substituents. The relatively small negative value found for the activation entropy is reasonable for polar solvents. For diffusion-controlled reactions one may expect that $\Delta H^{\ddagger}$ has a value similar to that of the activation energy of the viscosity (ΔE_{η}) of the solvent. ΔE_{η} = 7.6 kJ/mol was calculated for DMF from viscosity data taken from the literature.[22] This value is somewhat higher than that found by us for $\Delta H^{\ddagger}$. A reasonable explanation for the lower activation energy might be the long wavelength and tunneling property of a nearly thermalized o-Ps atom.[23]

LUMO Energies. The LUMO energies as well as the charge distribution of compounds **1**−**8** were calculated by the Gaussian 98[21] package at the AM1 level following a full geometry optimization. The results are presented in Table 1.

By plotting the measured o-Ps reaction rate constants against the calculated LUMO energies, similarly to other heterocyclic systems,[14,15] we observed a linear relationship with a good correlation of the data shown in Figure 4.

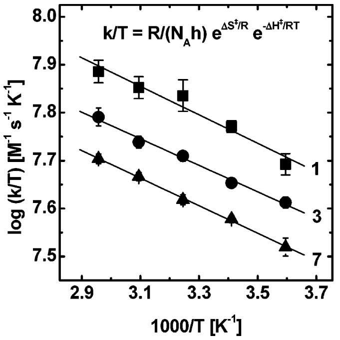

Figure 3. log(k/T) vs 1/T Arrhenius-type plots for diffusion-controlled reactions of the o-Ps atom with tetrazine derivatives **1**, **3**, and **7** measured in DMF solutions in the temperature range of 15−65 °C. The parameters of the least-squares-fit lines, i.e., the average activation entropies ($\Delta S^{\ddagger}$) and enthalpies ($\Delta H^{\ddagger}$), are presented in Table 2.

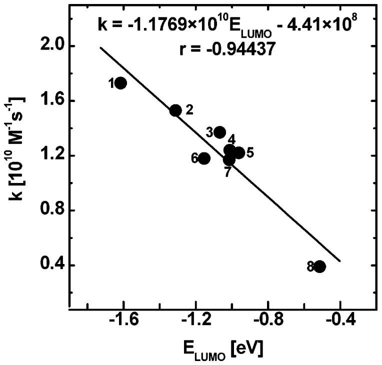

Figure 4. Chemical reaction rate constants (k) of o-Ps plotted against calculated LUMO energies (E_{LUMO}) of tetrazines **1**−**8**.[21]

TABLE 2: Average Activation Parameters for the Reactions of o-Ps with Tetrazine Derivatives for the 15−65 °C Temperature Range from the Least-Squares Fits of the Arrhenius-Type Plots Shown in Figure 3

tetrazine	$\Delta S^{\ddagger}$ (J mol^{-1} K^{-1})	$\Delta H^{\ddagger}$ (kJ/mol)
1	−30.0 ± 2.0	5.6 ± 0.6
3	−33.2 ± 1.1	5.2 ± 0.3
7	−34.1 ± 0.5	5.4 ± 0.2

Chemical Reactivity. The established reactivity order of the investigated tetrazines is in good agreement with our synthetic experiences, too.

In nucleophilic substitutions **1** is the most reactive of the listed tetrazines and reacts readily with nucleophiles at room temperature. A similar reactivity is observed for **2**. Of the other tetrazines **3**−**7** also undergo nucleophilic substitution but only under more forcing conditions,[17−19] requiring longer reaction times, use of an excess of the nucleophile (usually used as solvent), and/or increased temperature. **8** is by far the least reactive and gives only partial conversion even under forcing conditions.

In the "inverse electron demand" Diels−Alder reactions of tetrazines the same trend is observed. **1** is known to react with electron-rich olefins,[24] and the reaction of **2** was also reported.[25] The other tetrazines **3**−**8** on the other hand did not react with the same reagents even under forcing conditions.[17]

IV. Summary

A series of tetrazine derivatives were synthesized and their reactivity toward o-Ps was determined by positron annihilation lifetime spectroscopy. The reaction rate constants of o-Ps were found in the range that corresponds to that of the diffusion-controlled reactions. We have shown that the nucleophilic o-Ps attacks the molecules at their electron-deficient aromatic tetrazine cores and the introduction of electron-donating substituents onto the ring decreases the reactivity of the molecules. The measured reaction rate constants of o-Ps showed a good correlation with the calculated LUMO energies of the same tetrazines and their observed reactivity in nucleophilic substitution reactions and inverse "electron-demand" Diels−Alder reactions.

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