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Aminolysis of Aryl Thiol-2-furoates and Thiol-2-thiophenates in Acetonitrile

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Aminolysis of aryl thiol-2-furoates and thiol-2-thiophenates with benzylamines are investigated in acetonitrile at 50.0 °C. Relatively large selectivity parameters, $\rho_X(\beta_X)$, $\rho_Z(\beta_Z)$ and ρ_{XZ} (> 0) together with the valid reactivity-selectivity principle are consistent with a stepwise acyl transfer mechanism with rate-limiting expulsion of the leaving group, thiophenolate anion, from the tetrahedral intermediate, $T^{\pm}$. The first-order kinetics with respect to the benzylamine concentration and the relatively large secondary kinetic isotope effect involving deuterated benzylamine nucleophiles suggest a four-center type transition state in which concurrent leaving group departure and proton transfer are involved.

Introduction

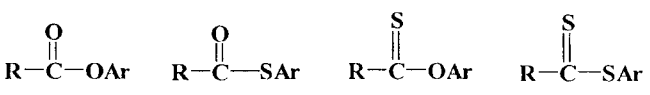
For the past ten years we have been developing the cross-interaction constants, ρ_{ij}, in eqs. 1 where i and j represent substituents in the nucleophile(X), the substrate(Y) or the leaving group(Z), as a mechanistic tool for organic reactions

$$\log(k_{ij}/k_{HH}) = \rho_i\sigma_j + \rho_j\sigma_i + \rho_{ij}\sigma_i\sigma_j \quad (1a)$$

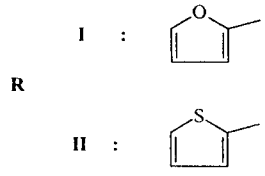
$$\rho_{ij} = \frac{\partial\rho_j}{\partial\sigma_i} = \frac{\partial\rho_i}{\partial\sigma_j} \quad (1b)$$

in solution.[1] The following mechanistic criteria are proposed theoretically[2] and found experimentally[3] to apply to the stepwise mechanism with rate-limiting breakdown of the leaving group in the amionlysis of esters and carbonates: (i) The signs of ρ_{XY} (> 0) and ρ_{YZ} (< 0) are opposite to those for the normal S_N2 processes or for acyl transfer with rate-limiting formation of the tetrahedral intermediate, $T^{\pm}$ ($\rho_{XY} < 0$ and $\rho_{YZ} > 0$). The sign of ρ_{XZ} is always positive unlike for the concerted S_N2 reactions for which ρ_{XZ} can be either positive or negative. (ii) The magnitude of ρ_{XY}, ρ_{YZ} and ρ_{XZ} are greater than those for the S_N2 processes. (iii) The positive ρ_{XZ} invariably leads to a valid reactivity-selectivity principle (RSP).[4]

In contrast to the aminolyses of oxyesters, **a**, their thio-analogs, **b-d**, were found to exhibit mechanistic varieties in the aminolysis reactions. For example, for the aminolysis of



a **b** **c** **d**



thiol derivatives, **b**, with R=CH_3CH_2O a concerted mechanism was found to apply,[5] while for the aminolyses of thiono, **c**, and dithio derivatives, **d**, complex reaction pathways involving rate-limiting proton transfer from the tetrahedral intermediate in aqueous solution have been reported.[6] By comparison the aminolysis of oxyesters and oxycarbonates, **a**, proceeds *via* relatively simple pathways of either rate-limiting breakdown of $T^{\pm}$ with weakly basic amines, or rate-limiting formation of $T^{\pm}$ with basic amines.[7]

In previous works,[8] we have shown that furan (**I**) and thiophene rings (**II**) are relatively strong electron acceptors so that the aminolysis of their oxyesters and dithioesters, **Ia, Id** and **IId**, proceed by the stepwise mechanism with rate-limiting departure of the leaving group in acetonitrile. As a continuation of this series of work, we report here the results of the aminolysis of aryl thiol-2-furoates (**Ib**) and thiol-2-thiophenates (**IIb**) in acetonitrile with benzylamines, eq. 2. The goal of this work is to elucidate the reaction mechanism

$$\underset{\text{R = I or II}}{R-\overset{O}{\overset{\|}{C}}-SC_6H_4Z} + 2XC_6H_4CH_2NH_2 \xrightarrow[50.0\ ^{\circ}C]{MeCN} R-\overset{O}{\overset{\|}{C}}-NHCH_2C_6H_4X + {}^{+}NH_3CH_2C_6H_4X + {}^{-}SC_6H_4Z \quad (2)$$

of aminolysis reaction (2) determining various selectivity parameters, especially, ρ_{XZ}, and also by comparing these with the corresponding values for the reactions of oxygen (**Ia**) and dithio (**Id** and **IId**) analogs. Acetonitrile was used as a reaction medium to alleviate complexities arising from the fast proton transfer step in aqueous solution.

In this works, we adopt a convention of labeling substituents in the nucleophile (benzylamines), substrate and leaving group as X, Y and Z respectively.

Results and Discussion

The reaction follows a general rate law given by eqs. 3, where P is thiophenolate anion and the rate constant in the absence of benzylamine is zero. The k_2 values were obtained

$$\frac{d[P]}{dt} = k_{obs}[\text{substrate}] \quad (3a)$$

$$k_{obs} = k[\text{benzylamine}] \quad (3b)$$

from the slopes of the plots k_{obs} *vs* [benzylamine], and are summarized in Tables 1 and 2. The rates are faster with a stronger nucleophiles (X=*p*-OMe) and a better nucleofuge (Z =*p*-Br) in agreement with the trends for typical nucleophilic substitution reactions. The Hammett $\rho_X(\rho_{nuc})$ and $\rho_Z(\rho_{lg})$ and the Brönsted $\beta_X(\beta_{nuc})$ and $\beta_Z(\beta_{lg})$ values are also shown in Tables 1 and 2. Although each of these selectivity parameters are based on only four rate data, the good linear correlations (correlation coefficient $(r) > 0.996$ in all cases) and relatively small standard deviations suggest that they can provide reliable measures of progress of reaction. We believe that the magnitude of β_x is reasonably reliable although we used the rate data in MeCN with the pK_a values in H_2O, since a constant (pK_a (=pK_{MeCN}-pK_{H_2O}) of *ca.* 7.5[9] was found for various amines. The values of β_Z may be somewhat smaller than the values reported on the basis of aqueous acidities.[9a] However, we are comparing the magnitude of β_Z determined under similar conditions. The trends of changes in the magnitudes of ρ(and β) with substituents are in accord with positive ρ_{XZ} values, eq. 1b with *i, j*=X, Z, and the valid RSP.[10]; a stronger nucleophile ($\delta\sigma_X < 0$) and a stronger nucleofuge ($\delta\sigma_Z > 0$) with a faster rate lead to a smaller magnitude of the selectivity parameter, $\delta\rho_z < 0$ and $\delta(-\rho_X) < 0 \rightarrow \delta\rho_X > 0$. The ρ_{XZ} values determined for the two reaction series with 16 rate data gave ρ_{XZ}=+0.71 ($r > 0.999$) and +0.68 ($r > 0.999$) for the furoates(**I**) and thiophenates(**II**), respectively, which are greater than the corresponding values of 0.65 and 0.59 for the reactions of dithio-compounds in MeCN at 15.0 °C.[8b]

The magnitudes of all selectivity parameters, ρ_X(=−1.3-1.7), β_X(=1.3-1.6), ρ_Z(=3.1-3.5) and β_Z(=-1.3~-1.5) including ρ_{XZ} are much greater than those corresponding values for the reactions of dithio compounds with benzylamines in MeCN at 15.0 °C[8b] (for dithiofuroates, ρ_X=-1.2~-1.5, ρ_Z=1.6-1.9 and ρ_{XZ}=0.65 and for dithiothiophenates ρ_X=-0.8~-1.1, ρ_z=1.1-1.4 and ρ_{XZ}=0.59); for the dithio series a stepwise mechanism with rate limiting breakdown for furoates and partial breakdown for thiophenates of the tetrahedral intermediate, $T^{\pm}$, have been proposed. Thus, the relatively larger magnitudes of selectivity parameters and valid RSP with positive ρ_{xz} values obtained in the present work support a stepwise mechanism with rate-limiting expulsion of thiophenolate anion, k_b in eqs. 4 and 5.

Table 1. Second-order rate constants, k_2 (10^{-3} M^{-1} sec^{-1}), for the reactions of aryl thiol-2-furoates with benzylamines in acetonitrile at 50.0 °C

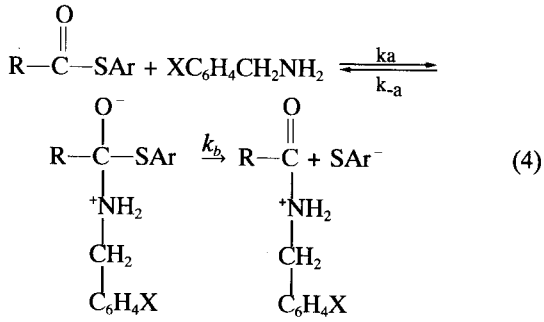
X\Z	p-CH_3	H	p-Cl	p-Br	ρ_Z[a]	β_Z[a]
p-CH_3O	6.33	19.3	107	114	3.14±0.09	-1.32±0.08
p-CH_3	4.07	13.2	75.9	85.7	3.27±0.06	-1.37±0.05
H	2.16	7.51	44.7	51.6	3.39±0.05	-1.41±0.06
p-Cl	0.994	3.54	21.8	25.1	3.50±0.05	-1.46±0.05
ρ_X[a]	-1.56 ±0.04	-1.48 ±0.03	-1.39 ±0.02	-1.33 ±0.02	ρ_{XZ}=-0.71±0.08 b	
β_X[c]	1.57 ±0.03	1.40 ±0.03	1.32 ±0.03	1.26 ±0.05		

[a] Correlation coefficient was better than 0.997 in all cases. [b] Correlation coefficient was 0.999. [c] The pK_a values were taken from Fisher, A.; Galloway, W. J.; Vaughan, J. *J. Chem. Soc.* **1964**, 3591 and pK_a=9.67 was used for X=p-CH_3O which was extrapolated using $pK_a = \rho\sigma + 9.54$ with $\rho = -1.06$.

Table 2. Second-order rate constants, k_2 (10^{-3} M^{-1} sec^{-1}), for the reactions of aryl thiol-2-thiophenates with benzylamines in acetonitrile at 50.0 °C

X\Z	p-CH_3	H	p-Cl	p-Br	ρ_Z[a]	β_Z[a]
p-CH_3O	1.92	6.56	34.1	36.9	3.17±0.08	-1.34±0.07
p-CH_3	1.29	4.25	25.1	26.4	3.28±0.10	-1.39±0.08
H	0.639	2.25	13.5	14.5	3.37±0.09	-1.42±0.08
p-Cl	0.272	1.03	6.62	7.16	3.51±0.09	-1.43±0.09
ρ_X[a]	-1.72 ±0.03	-1.61 ±0.05	-1.45 ±0.04	-1.44 ±0.03	ρ_{XZ}=-0.68±0.06[b]	
ρ_X[a,c]	1.63 ±0.06	1.53 ±0.04	1.38 ±0.07	1.37 ±0.06		

[a] Correlation coefficient was better than 0.997 in all cases. [b,c] Same as those in Table 1.



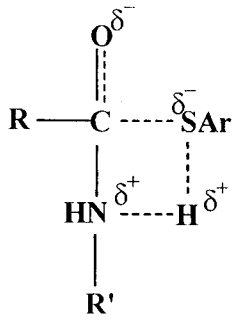
(4)

$$k_2 = \frac{k_a}{k_{-a}} \cdot k_b = K \cdot k_b \quad (5)$$

Comparison of the rate constants shows a change of thiolphenolate (R-C(=O)-SAr) (with X=Z=H, for **I** $k_2=7.5\times10^{-3}$ M^{-1} sec^{-1} and for R=**II** $k_2=2.25\times10^{-3}$ M^{-1} sec^{-1} at 50.0 °C in MeCN) to dithiophenolate[8b] (R-C(=S)-SAr) (with X=Z=H, for **I** $k_2=3.40\times10^{-3}$ M^{-1} sec^{-1} and for R=**II** $k_2=2.56\times10^{-2}$ M^{-1} sec^{-1} at 15.0 °C in MeCN) lead to *ca.* 3.0-4.0 times rate increase considering the temperature difference of 35.0 °C. This is in contrast to the result of Castro *et al.*,[5b,6b] who reported a decrease of rate with change of -C(=O)- to -C(=S)-, but discrepancy may result from the difference in reaction medium, i.e., aprotic *vs* aqueous solution.

There is *ca.* 10 times rate increase by a change of phenolate (OAr) to thiophenolate (SAr), for **Ia**[8a] and **Ib** the k_2 values are $\sim1\times10^{-4}$ and $\sim1\times10^{-2}$ (estimated at 55.0 °C), respectively for X=Z=H. The former reaction series, which was predicted to proceed by a stepwise mechanism with rate-limiting breakdown of the intermediate, was found to have larger magnitude of ρ_X (=-1.0~-2.0) and ρ_{XZ} (= 1.19) but a smaller magnitude of ρ_Z (=1.8-2.5) than corresponding values for the latter series.

We have determined secondary kinetic isotope effects involving deuterated benzylamine nucleophiles. The k_H/k_D values in Table 3 are greater than 1.0 ranging from 1.3 to 1.5 with slightly greater values for thiophenate series. Since the rates are first-order with respect to benzylamine concentration, eq. 3b, general base catalysis by the amine can be safely precluded. Thus, the relatively large k_H/k_D values in Table 3 seem to reflect a four-center type transition state, **III**, where R=**I** or **II** and R'=$C_6H_4CH_2$. Slightly greater k_H/k_D values for a better nucleofuge (Z=p-Br) and a weaker nucleophile (X=p-Cl) support the TS structure, **III**, since a better nucleofuge with a greater negative charge on SAr and a weaker nucleophile with a stronger electron-withdrawing group with a stronger positive charge on N should lead to a longer N···H bond. This type of four-center TS in which there is concurrent thiophenate ion departure and proton transfer has also been proposed previously for the amino-



III

lysis of phenyl dithioacetates,[9a] ethyl aryl carbonates, O-ethyl S-aryl dithiocarbonates,[10] phenyl cyclopropane carboxylates,[11] and aryl dithio-2-furoates and dithio-2-thiophenates[8b] in acetonitrile.

We conclude that the aminolyses of aryl thiol-2-furoates and thiol-2-thiophenates with benzylamine in acetonitrile at 50.0 °C proceed by a stepwise mechanism with rate-limiting expulsion of thiophenolate anion from tetrahedral intermediate. The magnitude of k_H/k_D (> 1.0) values suggests that the TS is a four-center type in which partial deprotonation of an amino hydrogen by the departing group is involved.

Experimental

Materials. Merck GR grade acetonitrile was distilled three times before use and benzylamines were Tokyo Kasei GR grade. Thiophenols, 2-thiophenecarbonyl chloride and 2-furoyl chloride were Aldrich GR grade.

Preparations of phenyl thiol-2-furoate and thiol-2-thiophenate. Thiophenol derivative and 2-thiophenecarbonyl cholride or 2-furoyl cholride were dissolved in anhydrous ether and added KOH carefully keeping the temperature to 0-5 °C. Ice was then added to the reaction mixture and ether layer was separated, dried on $MgSO_4$ and distilled under reduced pressure to remove solvent. The melting points, IR (Nicolet 5BX FT-IR), ^1H and ^{13}C NMR (JEOL 400 MHz) data are as follews:

Phenyl thiol-2-thiophenate. mp 62-63 °C, IR (KBr), 3082 (C-H, thiophene), 1658 (C=O), 1553 (C=C, aromatic), 803 (C-H, aromatic); ^1H NMR ($CDCl_3$) δ 7.96 (1H, dd, *J*=

Table 3. Secondary kinetic isotope effects for the reactions of aryl thiol-2-furoates and thiol-2-thiophenates with deuterated X-benzylamines in acetonitrile at 50.0 °C

R	X	Z	k_H ($dm^3mol^{-1}s^{-1}$)	k_D($dm^3mol^{-1}s^{-1}$)	k_H/k_D
I	p-CH_3O	p-CH_3	$(6.33\pm0.04)^a\times10^{-3}$	$(4.74\pm0.03)^a\times10^{-3}$	1.34 ± 0.01^a
	p-Cl	p-CH_3	$(9.44\pm0.05)\times10^{-4}$	$(6.94\pm0.04)\times10^{-4}$	1.36 ± 0.01
	p-CH_3O	p-Br	$(11.4\pm0.06)\times10^{-2}$	$(8.20\pm0.04)\times10^{-2}$	1.39 ± 0.01
	p-Cl	p-Br	$(25.1\pm0.38)\times10^{-3}$	$(17.8\pm0.25)\times10^{-3}$	1.41 ± 0.03
II	p-CH_3O	p-CH_3	$(19.2\pm0.09)\times10^{-4}$	$(13.7\pm0.08)\times10^{-4}$	1.40 ± 0.01
	p-Cl	p-CH_3	$(2.72\pm0.04)\times10^{-4}$	$(1.91\pm0.03)\times10^{-4}$	1.42 ± 0.03
	p-CH_3O	p-Br	$(36.9\pm0.14)\times10^{-3}$	$(25.8\pm0.25)\times10^{-3}$	1.43 ± 0.01
	p-Cl	p-Br	$(7.61\pm0.02)\times10^{-3}$	$(4.48\pm0.02)\times10^{-3}$	1.47 ± 0.01

[a] Standard deviation.

3.66, 1.47 Hz, thiophene), 7.71 (1H, dd, *J*=5.13, 1.46 Hz, thiophene), 72.48-7.59 (5H, m, phenyl ring), 7.20 (1H, dd, *J* =5.13, 4.40 Hz, thiophene); ^{13}C NMR ($CDCl_3$) δ 181.0 (C=O), 141.4, 135.1, 133.2, 131.6, 129.3, 128.0, 127.0.

p-Methylphenyl thiol-2-thiophenate. mp 68-69 °C, IR (KBr), 3104 (C-H, thiophene), 1659 (C=O), 1552, 1478 (C=C, aromatic), 804 (C-H, aromatic); ^{1}H NMR ($CDCl_3$) δ 7.89 (1H, dd, *J*=3.66 Hz, thiophene), 7.65 (1H, dd, *J*=4.39 Hz, thiophene), 7.39 (2H, d, phenyl ring), 7.25 (1H, d, *J*= 8.06 Hz, phenyl ring), 7.15 (1H, t, *J*=4.40 Hz), 2.43 (3H, s, methyl); ^{13}C NMR ($CDCl_3$) δ 182.5 (C=O), 140.4, 135.0, 133.0, 131.5, 130.0, 127.9, 123.4 (methyl).

p-Chlorophenyl thiol-2-thiophenate. mp 85-86 °C, IR (KBr), 3104 (C-H, thiophene), 1658 (C=O), 11556, 1478 (C=C, aromatic), 809 (C-H, aromatic); ^{1}H NMR ($CDCl_3$) δ 7.89 (1H, dd, *J*=3.66 Hz, 1.47 Hz, thiophene), 7.67 (1H, dd, *J*=4.39 Hz, 1.46 Hz, thiophene), 7.45 (2H, dd, *J*=8.80 Hz, 2.20 Hz, phenyl ring), 7.41 (2H, dd, *J*=8.80 Hz, 2.20 Hz, phenyl ring), 7.16 (1H, dd, *J*=5.14 Hz, 4.40 Hz, thiophene); ^{13}C NMR ($CDCl_3$) δ 181.5 (C=O), 141.0, 136.3, 136.1, 133.5, 131.8, 129.5, 128.1, 125.4.

p-Bromophenyl thiol-2-thiophenate. mp 90-91 °C, IR (KBr), 3110 (C-H, thiophene), 1658 (C=O), 1557, 1462 (C=C, aromatic), 810 (C-H, aromatic); ^{1}H NMR ($CDCl_3$) δ 7.96 (1H, dd, *J*=2.93 Hz, thiophene), 7.68 (1H, dd, *J*=5.13 Hz, 1.47 Hz, thiophene), 7.47 (2H, dt, *J*=8.80 Hz, 2.20 Hz, phenyl ring), 7.38 (2H, dt, *J*=8.80 Hz, 2.20 Hz, phenyl ring), 7.16 (1H, dd, *J*=5.13 Hz, 4.40 Hz, thiophene); ^{13}C NMR ($CDCl_3$) δ 181.3 (C=O), 141.0, 136.4, 133.5, 132.5, 131.8, 128.1, 124.4.

Phenyl thiol-2-furoate. mp 54-55 °C, IR (KBr), 3033 (C-H, furan), 1662 (C=O), 1565 (C=C, aromatic), 751 (C-H, aromatic); ^{1}H NMR ($CDCl_3$) δ 7.61 (1H, s, furan), 7.43-7.51 (5H, m, phenyl), 7.25 (1H, d, *J*=3.42 Hz, furan), 6.59 (1H, dd, *J*=3.42, 1.47 Hz, furan); ^{13}C NMR ($CDCl_3$) δ 178.4 (C=O), 150.1, 146.3, 134.9, 129.5, 129.1, 126.0, 116.1, 112.4.

p-Methylphenyl thiol-2-furoate. mp 77-78 °C, IR (KBr), 3124 (C-H, furan), 1661 (C=O), 1561, 1459 (C=C, aromatic), 768 (C-H, aromatic); ^{1}H NMR ($CDCl_3$) δ 7.61 (1H, s, furan), 7.38 (2H, d, *J*=7.81 Hz, phenyl ring), 7.25 (2H, d, *J*=8.30 Hz, phenyl ring), 7.23 (1H, d, *J*=3.42 Hz, furan), 6.56 (1H, dd, *J*=3.42, 1.47 Hz, furan), 2.39 (3H, s, methyl); ^{13}C NMR ($CDCl_3$) δ 177.7 (C=O), 150.3, 141.1, 139.8, 134.9, 129.9, 122.4, 116.0, 112.3, 21.3 (methyl).

p-Chlorophenyl thiol-2-furoate. mp 102-103 °C, IR (KBr), 3122 (C-H, furan), 1665 (C=O), 1556, 1468 (C=C, aromatic), 767 (C-H, aromatic); ^{1}H NMR ($CDCl_3$) δ 7.63 (1H, s, furan), 7.39-7.43 (4H, m, phenyl ring), 7.27 (1H, d, *J*=3.42 Hz, furan), 6.59 (1H, dd, *J*=3.42, 1.47 Hz, furan); ^{13}C NMR ($CDCl_3$) δ 177.0 (C=O), 149.9, 146.5, 136.2, 136.0, 129.4, 124.5, 116.4, 112.4.

p-Bromophenyl thiol-2-furoate. mp 138-139 °C, IR (KBr), 3105 (C-H, furan), 1662 (C=O), 1561, 1470 (C=C, aromatic), 766 (C-H, aromatic); ^{1}H NMR ($CDCl_3$) δ 7.63 (1H, s, furan), 7.57 (2H, d, *J*=8.30 Hz, phenyl ring), 7.36 (2H, d, *J*=8.30 Hz, phenyl ring), 7.27 (1H, d, *J*=3.91 Hz, furan), 6.59 (1H, dd, *J*=3.42 Hz, 1.47 Hz, furan); ^{13}C NMR ($CDCl_3$) δ 149.9, 146.5, 136.4, 132.3, 125.2, 124.2, 116.4, 112.4.

Kinetic procedure. The reaction were followed conductometrically under pseudo-first-order condition with excess amount of benzylamine, [substrate]$\cong 10^{-3}$ M^{-1} and [benzylamine]$\cong$0.03-0.5 M^{-1}. The rate constants, k_2 in eq. 3, were determined as described previously.[12]

The rate constants reported are averages of more than two determinations and were repducible to $\pm$5%.

Product analysis. Substrate (0.05 mole) and benzylamine (0.5 mole) were added to acetonitrile and reacted at 50.0 °C under the same condition as the kinetic measurements. After more than 15 half lives, solvent was removed under reduced pressure and product was separated by column chromatography. Analytical data are as follows:

$C_4H_3SC(=O)NHCH_2C_6H_5$. mp 75-77 °C, IR (KBr), 3091 (C-H, thiophene), 1629 (C=O), 816 (C-H, aromatic); ^{1}H NMR ($CDCl_3$) δ 4.56 (2H, d, *J*=5.86 Hz, CH_2), 7.01 (1H, br.s, NH), 7.23-7.57 (8H, m, phenyl and thiophene); ^{13}C NMR ($CDCl_3$) δ 43.8, 127.5, 128.2, 128.3, 134.8, 137.7, 138.2, 162.1.

$C_4H_3OC(=O)NHCH_2C_6H_5$. mp 68-71 °C, IR (KBr), 3308 (C-H, furan), 1649 (C=O), 811 (C-H, aromatic); ^{1}H NMR ($CDCl_3$) δ 4.56 (2H, d, *J*=5.86 Hz, CH_2), 6.96 (1H, br. s, NH), 6.44-7.39 (8H, m, phenyl and furan); ^{13}C NMR ($CDCl_3$) δ 48.0, 111.9, 114.3, 127.5, 129.1, 137.7, 143.8, 147.4, 158.2.

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Sensitivity of a Hyperactivated Ras Mutant in Response to Hydrogen Peroxide, Menadione and Paraquat

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We have explored the impact of altering the Ras-cAMP pathway on cell survival upon oxidative exposures. A hyperactivated Ras mutant of *Saccharomyces cerevisiae*, intrinsically more sensitive to heat shock than the wild type, was investigated with regard to oxidative stress. In this paper we report that the response of *ira1, ira2*-deleted mutant (IR2.53) to an oxidant, such as hydrogen peroxide (H_2O_2) or menadione is more sensitive than that of the wild type. IR2.53 showed a dramatic decrease in survival rate when challenged with 0.1 mM H_2O_2 for 30 min. The greater sensitivity of IR2.53 was also noticed with treatment of 0.01 mM menadione. Prior to oxidative stresses by these oxidants, both the wild type and the mutant were preconditioned with a mild heat shock (37 °C, 30 min), resulting in improved survivals against oxidative stresses. Rescue of IR2.53 from menadione stress by heat pretreatment was more clearly demonstrated than that from H_2O_2 treatment. On the other hand, no significant difference was observed between the wild type and the IR2.53 mutant in their survival rates upon paraquat treatments. These findings imply that the mechanism by which H_2O_2 and menadione put forth their oxidative effects may be closely associated with the cAMP-Ras pathway whereas that of paraquat is independent of the Ras pathway. Finally, the level of glutathione (GSH) was measured enzymatically as an indicator of antioxidation and compared with the survival rate. Taken all these together, this study provides an insight into a mechanism of the Ras pathway regulated by several oxidants and suggests that the Ras pathway plays a crucial role in protection of cell damage following oxidative stress.

Introduction

Most living cells are very susceptible to oxygen toxicity, which is mostly caused by a highly reactive superoxide anion radical ($O_2^{\cdot-}$), a hydroxy radical (OH·), hydrogen peroxide (H_2O_2).[1] These reactive oxygen species (ROS) are very reactive and sources of damages to DNA, lipids, and proteins.[2] Aerobic cells have therefore developed multiple defence mechanisms, by which cellular antioxidants and enzymes are capable of removing ROS to avoid oxidative damages. For example, superoxide anions produced in yeast are enzymatically reduced to H_2O_2 by superoxide dismutase (SOD),[3] and subsequently removed by catalase.[4] As an antioxidant, GSH reacts with H_2O_2 and superoxide radicals to protect cells from oxidative stress and xenobiotic toxicity.[5] Glutathione reductase provides sufficient GSH from oxidized glutathione (GSSG) in the presence of NADPH. The yeast strain defective in γ-glutamylcysteine synthetase activity was found to be hypersensitive to H_2O_2 and superoxide anions.[6] Either changes in GSH level or in the ratio of GSH/GSSG

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