PROXIMITY EFFECT IN THE HYDROGEN-DEUTERIUM EXCHANGE AND DEETHOXYCARBONYLATION OF PERI-SUBSTITUTED NAPHTHALENE WITH THE 1,2,3-TRIAZOLE RING

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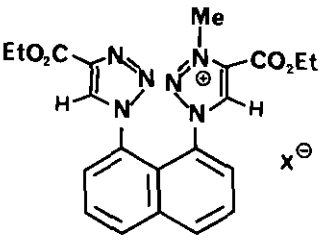
Abstract - The H-D exchange reaction and the deethoxycarboxylation in D_2O of 1-[8-(4-ethoxycarbonyl-1H-1,2,3-triazol-1-yl)-1-naphthyl]-3-methyl-4-ethoxycarbonyl-1H-1,2,3-triazolium salts (**1**) were studied by ^1H nmr spectroscopy and compared with those of 1-(1-naphthyl)-3-methyl-4-ethoxycarbonyl-1H-1,2,3-triazolium salts (**2**). The reaction rates of **1** are found to be much faster than those of **2**. The results suggest that the triazole ring in 1 interacts sterically with the N-methylated triazole ring to accelerate the reactions.

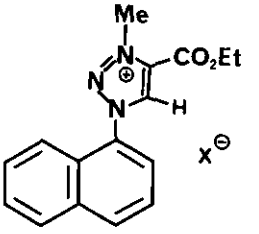
1,8-Disubstituted naphthalenes exhibit unique properties in both structure and reactivity,[1] because two substituents locate *in close proximity each other*. A typical example of the properties is an unusual basicity observed in 1,8-bis(dimethylamino)naphthalene ("proton sponge") and related compounds.[2] A few studies on the peri-interaction of the two aromatic rings of 1,8-diarylnaphthalenes have been reported from the viewpoints of the restricted rotation[3] and charge transfer.[4] However, the chemical reactions in these compounds have not yet been investigated from the standpoint of the effect of *peri-substituents*. Recently, we have synthesized novel 1,1'-(1,8-naphthylene)di-1H-1,2,3-triazoles,[5] which are the first prepared 1,8-diheteroarylnaphthalenes, and expected to undergo unique reactions rooted in the heteroaromatic ring. We have compared the reactivity of quaternized salts of these compounds with that of the corresponding monotriazolyl ones. In this paper, we describe the H-D exchange reaction and deethoxycarbonylation of

these compounds, and report the acceleration of these reactions by the adjacent triazole ring at the peri-position of the naphthalene ring.



1a: X=tosyl
1b: X=Cl
1c: X=Br
1d: X=I

Controlled N-methylation of diethyl 1,1'-(1,8-naphthylene)di-1H-1,2,3-triazole-4-carboxylate with methyl p-toluenesulfonate gave selectively the mono N-methyltriazolium tosylate salt (**1a**), and treatment of **1a** with ion exchange resins afforded the corresponding triazolium halides (**1b-1d**). The monotriazolium salts (**2a-2d**) were synthesized similarly from ethyl 1-(1-naphthyl)-1H-1,2,3-triazole-4-carboxylate.



2a: X=tosyl
2b: X=Cl
2c: X=Br
2d: X=I

In the ^{1}H nmr spectrum of **1a**, two singlet signals appearing at 8.92 and 9.28 ppm in deuterium oxide are assigned to the 5-position hydrogens of the triazole and N-methylated triazole rings, respectively. The assignment is based on the comparison with the spectrum of **2a**. The triazolium proton signal of 9.28 ppm gradually decreased in intensity and finally disappeared within 2 hours at 20 °C and pD 4.6, while other proton signals including signal of 8.92 ppm showed no measurable change. This indicates that a hydrogen-deuterium exchange reaction occurred at the 5-position of the N-methylated triazole ring. At pD 7.4, the exchange reaction occurred more rapidly than at pD 4.6 and only 5 minutes was enough for the disappearance of the signal. The acceleration of the rate at higher pD shows that the exchange reaction of **1** is a nucleophilic process.

In the case of **2a**, the H-D exchange reaction rate was very slow at 20 °C and pD 4.6 and became comparable with that of **1a** only when the reaction temperature was raised to 70 °C. These results indicate that the H-D exchange reaction of the quaternized triazole ring in 1 is promoted by the triazole ring at the peri-position. The nitrogen atom of the 3-position in triazole ring is the "pyridazine" type and shows weak basicity.[6] The basicity of **1** seems to be so weak because this compound has an electron withdrawing ester group at the 4-position. Thus, in the H-D exchange reaction of the N-methylated triazole ring of **1**, the adjacent triazole ring may not act as a base. According to our

studies on the molecular structure of 1,1'-(1,8-naphthylene)di-1H-1,2,3-triazoles by X-ray structure analyses,[7] the two triazole rings are almost parallel and in trans conformation. This fact suggests that the triazole and triazolium rings of **1** are face-to-face each other and the former interacts with the latter to stimulate the H-D exchange reaction. A similar situation is observed in paracyclophanes in which the face-to-face phenyl ring affects the acetolysis.[8]

The pseudo first order kinetic constants for the H-D exchange reaction of **1** and **2** were obtained from the decay rate of the ^1H nmr signal. The results are summarized in Table 1 with the previously reported data on several azolium salts.

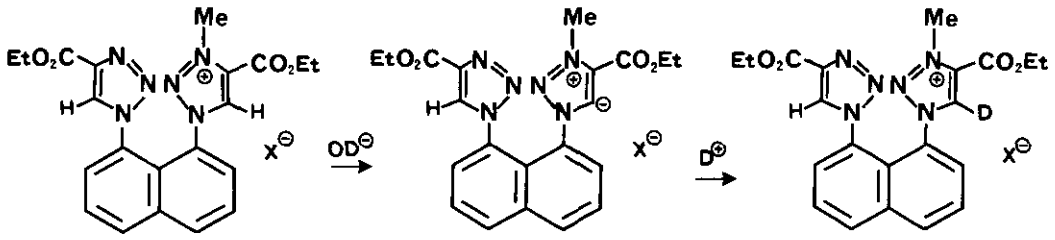
Table 1. Rates of H-D exchange for some azolium salts

Azolium salt	pD	T (°C)	10^4 k (sec^{-1})	$t_{1/2}$ (min)
1a	4.6	20	4.4	26
1b	4.6	20	12	9.9
1c	4.6	20	6.7	17
1d	4.6	20	3.3	35
2a	4.6	70	5.0	23
2b	4.6	70	18	6.5
2c	4.6	70	5.8	20
2d	4.6	70	4.4	26
DMPI[a)]	12.9	31	---	14
DMTT[b)]	9.9	34	---	13

a) DMPI:1,2-dimethylpyrazolium iodide.[9]

b) DMTT:1,3-dimethyl-1H-1,2,3-triazolium p-toluenesulfonate.[10]

The exchange rates of **1** are relatively faster than not only the rates of **2** but also those of the other azolium compounds. In the nucleophilic H-D exchange reaction of azolium salts, the rate determining step is the deprotonation one with a base, as shown in Scheme 1.

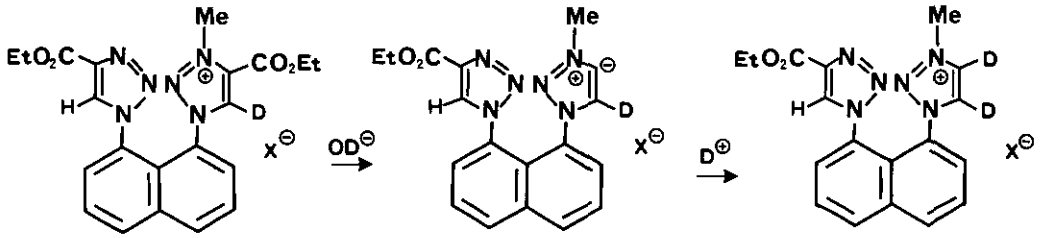


Scheme 1.

Thus, the H-D exchange reaction should become faster when the intermediate is more stabilized.[11] In the case of **1**, the faced triazole ring, as described before, might stabilize the zwitter ionic intermediate by the through space interaction.

The counter ions influence the H-D exchange reaction as shown in Table 1. Comparison of the rate constants of **1b**, **1c** and **1d** shows that the reaction becomes slower as the atomic number of halides becomes larger. Similar trend was observed in the case of **2b**, **2c** and **2d**. The ion radius and/or electronegativity of the halide ions might affect the stabilization of the zwitter ionic structure in the triazole ring.

When the deuterium oxide solution of **2a** was heated up to 100 °C, decomposition of **2a** to N-methylated 1-(1-naphthyl)-1H-1,2,3-triazole occurred gradually. This compound and ethanol were observed by ^{1}H nmr spectroscopy. There was no signal of other reaction product in the ^{1}H nmr spectrum. A similar reaction occurred more rapidly in the case of **1a**. These indicate that an elimination reaction of the ethoxycarbonyl group occurs at the 4-position of the triazolium ring as shown in Scheme 2.



Scheme 2.

Concerning the elimination of the substituent from the azole ring, Begtrup reported that the debromination of 4-bromo-1,3-dimethyl-1H-1,2,3-triazolium p-toluenesulfonate occurred in 1N aqueous sodium hydroxide at room temperature.[12] However, deethoxycarbonylation under these mild conditions has not yet been observed for azolium systems. The rates of deethoxycarbonylation for 1 and 2 were determined by ^{1}H nmr and the results were given in Table 2.

Table 2. Rates of deethoxycarbonylation for triazolium salts at 100°C

Triazolium salt	10^5k (sec^{-1})	Triazolium salt	10^5k (sec^{-1})
1a	5.6	**2a**	2.3
1b	5.3	**2b**	2.1
1c	5.3	**2c**	1.8
1d	5.6	**2d**	2.4

Although the deethoxycarbonylation rates are slower than those of H-D exchange reaction, **1** also reacts more rapidly than **2** in the deethoxycarbonylation. The rates for the H-D exchange reactions of **1** are about twenty times as fast as those of **2**, but the differences of the deethoxycarbonylation rates between **1** and **2** are only about three times. The effect of the counter ion noticed in the H-D exchange reactions as described before was not observed for the deethoxycarbonyl reaction. In this reaction, there are two possibilities for the reaction mechanism. One is direct attack of a base to the carbonyl group to release ethyl carbonate, while the other is the hydrolysis of the ester group by a base followed by the decarboxylation of the formed carboxylic acid. At the present time, it is difficult to tell which is the correct mechanism, but the former may be likely since the direct formation of the ylide type intermediate indicated in Scheme 2 is favorable.

In conclusion, the interactions between the triazole ring and the quaternized triazole ring located at peri-positions in close proximity, are observed in the H-D exchange reaction and deethoxycarbonylation in **1**. This is the first observation in which the interaction of the two aromatic rings at peri-position in the naphthalene moiety affects the chemical reaction.

EXPERIMENTAL

All melting points were determined on a Mettler FP61 instrument and were uncorrected. ^{1}H Nmr spectra were obtained by a JEOL GX-400 spectrometer(399.65 MHz for ^{1}H) using sodium 4,4-dimethyl-4-silapentanesulfonate(DSS) as an internal standard. All fast atom bombardment(FAB) mass spectra were recorded on a JEOL JMS-SX102 instrument, equipped with its own standard FAB source. Xenon was used as the bombarding gas with an energy of 4 keV. High resolution positive FAB spectra were obtained from glycerol solutions of the compounds, while diethanolamine was used as the matrix at negative FAB spectra. Ir and uv spectra were measured on a JASCO 5MP and a Shimadzu MPS-2000 spectrophotometer, respectively.

1-[8-(4-Ethoxycarbonyl-1H-1,2,3-triazol-1-yl)-1-naphthyl]-3-methyl-4-ethoxycarbonyl-1H-1,2,3-triazolium p-toluenesulfonate (1a).

A mixture of diethyl 1,1'-(1,8-naphthylene)di-1H-1,2,3-triazole-4,5-dicarboxylate(500 mg, 1.2 mmol) and a large excess of methyl p-toluenesulfonate(5 g, 27 mmol) was allowed to react at 50 °C for 30 min. To the reaction mixture was added 100 ml of ether, and left 12 h at 5 °C. The resulting precipitate was collected by filtration and washed with ether. The precipitate was dissolved in water and filtered. Evaporation of water in vacuo gave a white residue, which was recrystallized from acetone and water to give 200 mg (28 %) of **1a**, mp 159-160 °C(dec.); ^{1}H nmr(deuterium oxide): δ 1.42-1.46(m, 6H), 2.38(s, 3H), 4.47-4.58(m, 4H), 4.54(s, 3H), 7.34(d, J=7.9 Hz, 2H), 7.66(d, J=7.9 Hz, 2H), 7.85-7.98(m, 4H), 8.48(d, J=8.1 Hz, 1H), 8.56(d, J=8.2 Hz, 1H), 8.92(s, 1H), 9.28(s, 1H). High resolution positive mass: Found 421.1621, Calcd for $C_{21}H_{21}N_6O_4$ 421.1625. Negative mass: 171($C_7H_7SO_3^-$); ir(potassium bromide): ν 1745(C=O), 1730(C=O) cm^{-1}; uv(methanol): λ 289, 220 nm.

Counter ion was changed by passing **1a** through amberlite IRA-400 anion exchange resin in the appropriate form.

1-[8-(4-Ethoxycarbonyl-1H-1,2,3-triazol-1-yl)-1-naphthyl]-3-methyl-4-ethoxycarbonyl-1H-1,2,3-triazolium chloride (1b).

This compound was obtained as colorless crystals from acetone and water, mp 92-93 °C(dec.); ^{1}H nmr(deuterium oxide): δ 1.42-1.45(m, 6H), 4.48-4.55(m, 4H), 4.55(s, 3H), 7.86-7.99(m, 4H), 8.49(d, J=7.9 Hz, 1H), 8.57(d, J=8.2 Hz, 1H), 8.94(s, 1H), 9.31 (s, 1H). High resolution positive mass: Found 421.1606, Calcd

for $C_{21}H_{21}N_6O_4$ 421.1625. Negative mass: 37, 35(Cl^-); ir(potassium bromide): ν 1750(C=O), 1740(C=O) cm^{-1}; uv(methanol): λ 290, 221 nm.

1-[8-(4-Ethoxycarbonyl-1H-1,2,3-triazol-1-yl)-1-naphthyl]-3-methyl-4-ethoxycarbonyl-1H-1,2,3-triazolium bromide (**1c**).

This compound was obtained as pale yellow crystals from acetone and water, mp 90-91 °C(dec.); ^1H nmr(deuterium oxide): δ 1.42-1.47(m, 6H), 4.49-4.56(m, 4H), 4.54(s, 3H), 7.83-7.99(m, 4H), 8.46(d, J=8.0 Hz, 1H), 8.54(d, J=8.2 Hz, 1H), 8.92(s, 1H), 9.28(s, 1H). High resolution positive mass: Found 421.1646, Calcd for $C_{21}H_{21}N_6O_4$ 421.1625. Negative mass: 81, 79(Br^-); ir(potassium bromide): ν 1750(C=O), 1735(C=O) cm^{-1}; uv(methanol): λ 290, 221 nm.

1-[8-(4-Ethoxycarbonyl-1H-1,2,3-triazol-1-yl)-1-naphthyl]-3-methyl-4-ethoxycarbonyl-1H-1,2,3-triazolium iodide (**1d**).

This compound was obtained as pale yellow crystals from acetone and water, mp 88-89 °C(dec.); ^1H nmr(deuterium oxide): δ 1.42-1.46(m, 6H), 4.49-4.56(m, 4H), 4.55(s, 3H), 7.86-7.99(m, 4H), 8.49(d, J=7.9 Hz, 1H), 8.57(d, J=8.2 Hz, 1H), 8.94(s, 1H), 9.30(s, 1H). High resolution positive mass: Found 421.1639, Calcd for $C_{21}H_{21}N_6O_4$ 421.1625. Negative mass: 127(I^-); ir(potassium bromide): ν 1750(C=O), 1730(C=O) cm^{-1}; uv(methanol): λ 291, 220 nm.

Similarly, the reaction of ethyl 1-(1-naphthyl)-1H-1,2,3-triazole-4-carboxylate (500 mg, 1.9 mmol) with about ten times as much excess of methyl p-toluenesulfonate gave **2a**, and counter ion was changed in a similar manner of **1**.

1-(1-Naphthyl)-3-methyl-4-ethoxycarbonyl-1H-1,2,3-triazolium p-toluenesulfonate (**2a**).

This compound was obtained as colorless crystals from acetone and water, mp 137-138 °C(dec.); ^1H nmr(deuterium oxide): δ 1.45(t, J=7.1Hz, 3H), 2.38(s, 3H), 4.60(q, J=7.1 Hz, 2H), 4.73 (s, 3H), 7.34(d, J=7.9 Hz, 2H), 7.65-7.78(m, 6H), 7.88(d, J=7.3 Hz, 1H), 8.18(m, 1H), 8.33(d, J=8.4 Hz, 1H), 9.65(s, 1H). High resolution positive mass: Found 282.1213, Calcd for $C_{16}H_{16}N_3O_2$ 282.1243. Negative mass: 71 ($C_7H_7SO_3^-$); ir(potassium bromide): ν 1750(C=O) cm^{-1}; uv(methanol): λ 283, 218 nm.

1-(1-Naphthyl)-3-methyl-4-ethoxycarbonyl-1H-1,2,3-triazolium chloride (**2b**).

This compound was obtained as colorless crystals from acetone and water, mp 129-130 °C(dec.); ^1H nmr(deuterium oxide): δ 1.46(t, J=7.2 Hz, 3H), 4.60(q, J=7.2 Hz, 2H), 4.74(s, 3H), 7.67-7.79(m, 4H), 7.89(d, J=7.4 Hz, 1H), 8.18(m, 1H), 8.34(d, J=8.4 Hz, 1H), 9.67(s, 1H). High resolution positive mass: Found

282.1213, Calcd for $C_{16}H_{16}N_3O_2$ 282.1243. Negative mass: 37, 35(Cl^-); ir(potassium bromide): ν 1740(C=O) cm^{-1}; uv(methanol): λ 284, 218 nm.

1-(1-Naphthyl)-3-methyl-4-ethoxycarbonyl-1H-1,2,3-triazolium bromide (**2c**).

This compound was obtained as pale yellow crystals from acetone and water, mp 128-129 °C(dec.); ^1H nmr(deuterium oxide): δ 1.46(t, J=7.2 Hz, 3H), 4.60(q, J=7.2 Hz, 2H), 4.74(s, 3H), 7.67-7.79(m, 4H), 7.89(d, J=7.3 Hz, 1H), 8.18(m, 1H), 8.34(d, J=8.4 Hz, 1H), 9.67(s, 1H). High resolution positive mass: Found 282.1280, Calcd for $C_{16}H_{16}N_3O_2$ 282.1243. Negative mass: 71, 69(Br^-); ir(potassium bromide): ν 1740(C=O) cm^{-1}. uv(methanol): λ 284, 219 nm.

1-(1-Naphthyl)-3-methyl-4-ethoxycarbonyl-1H-1,2,3-triazolium iodide (**2d**).

This compound was obtained as pale yellow crystals from acetone and water, mp 125-126 °C(dec.); ^1H nmr(deuterium oxide): δ 1.47(t, J=7.2 Hz, 3H), 4.61(q, J=7.2 Hz, 2H), 4.74(s, 3H), 7.67-7.79(m, 6H), 7.89(d, J=7.0 Hz, 1H), 8.18(m, 1H), 8.34(d, J=8.2 Hz, 1H), 9.67(s, 1H). High resolution positive mass: Found 282.1217, Calcd for $C_{16}H_{16}N_3O_2$ 282.1243. Negative mass: 127(I^-); ir(potassium bromide): ν 1740(C=O) cm^{-1}; uv(methanol): λ 284, 218 nm.

Kinetic measurements were performed as follows. The triazole salt(0.02 mmol) was placed in an nmr tube and 0.5 ml of buffer deuterium oxide solution(potassium hydrogenphthalate for pD 4.6 and phosphate for pD 7.4) was added. The sample was rapidly placed in the temperature-controlled nmr probe, and the ^1H nmr spectra was measured at appropriate intervals. For H-D exchange reactions, the extent of the exchange was determined by comparison of the ^1H nmr peak area of the 5-proton at triazole ring with that of the 4- and 5-protons at naphthalene ring. For deethoxycarbonylation, the progress of the reaction was determined by comparison of the ^1H nmr peak area of the methyl groups.

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