The Photochemical Magnetic Field Effect of Isoquinoline *N*-Oxides

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The irradiation of isoquinoline *N*-oxide in ethanol resulted in the formation of lactam in a *ca.* 67% yield *via* the S_1 state (Process I). When the photochemical isomerization was carried out in the presence of a magnetic field, the chemical yield of lactam was found to show a minimum at approximately 1T. In order to interpret this new phenomenon, Process I was assumed to be initiated by electron transfer from the excited singlet *N*-oxide to the hydrogen-bonded ethanol (the formation of a singlet hydrogen-bonded radical ion pair). Thus, the new type of magnetic-field effect was excellently explained in terms of an electron-nuclear hyperfine interaction mechanism including the electron-exchange interaction in the radical-ion pair (the magnetic-field effect due to HFI-J mechanism). This implies that the magnetic-field effect is unambiguous evidence that Process I (*N*-oxide→lactam) does not involve the oxaziridine intermediate, but proceeds *via* the singlet hydrogen-bonded radical-ion pair (radical-ion-pair mechanism of Process I). The irradiation of 1-cyanoisoquinoline *N*-oxide in ethanol resulted in the formation of 1,3-oxazepine in a *ca.* 66% yield *via* the S_1 state (Process II). The photochemical isomerization was not affected at all by an external magnetic field. This is consistent with the idea that Process II (*N*-oxide→oxazepine) does not involve a field-sensitive intermediate, but occurs with the intervention of oxaziridine (the oxaziridine mechanism of Process II).

It is one of the most interesting and challenging problems in chemistry to determine whether or not a magnetic field has an effect on chemical reactions. Although a number of studies of this subject had been made over a long period, corroborating evidence for the existence of an external magnetic-field effect upon chemical reactions in a liquid solution had never been obtained until 1970.[1] In 1971, on the basis of the radical-pair model of CIDNP (Chemically Induced Dynamic Nuclear Polarization),[2,3a] Lawler and Evans predicted the influence of a magnetic field on radical-pair reactions in solution.[4] In 1972 and later, as was expected from the radical-pair model, the magnetic-field effect arising from electron-nuclear hyperfine interaction (HFI mechanism) or electronic Zeeman interaction (Δg mechanism) was observed by Molin's group in the thermal reaction of pentafluorophenylmethyl chloride or decafluorodiphenylchloromethane with butyllithium.[5] Such magnetic-field effects (HFI and Δg mechanisms) were also observed in several photochemical systems by Tanimoto *et al.*,[6a] Schulten *et al.*,[6b] and Michel-Beyerle *et al.*,[6c] in 1976.

In that same year (1976), the present author found a very interesting and unexpected effect of the magnetic field which was quite different from the above two types of magnetic-field effects;[7] when the photochemical isomerization of isoquinoline *N*-oxide in ethanol was carried out in either the absence or presence of a magnetic field, the chemical yield of the product (1-isoquinolone) was observed to show a minimum at approximately 1T. In 1978 this new phenomenon was successfully interpreted in terms of a hyperfine interaction mechanism including an electron-exchange interaction in the singlet hydrogen-bonded radical-ion pair assumed to be a transient intermediate of this reaction;[8] thus, it has been termed the magnetic-field effect due to the HFI-J mechanism. These studies were partly reported in preliminary form.[7-10] The purpose of the present and succeeding papers is to present further details of the new type of external magnetic-field effect, together with a novel mechanism of the photochemical isomerization of isoquinoline *N*-oxide.

Experimental

The isoquinoline *N*-oxide **1** used as a sample was synthesized by treating isoquinoline with 35% aqueous hydrogen peroxide and acetic anhydride according to the method given in the literature;[11] it was then purified by vacuum distillation, followed by alumina-column chromatography (the eluent, chloroform–ethanol (40:1)); mp 103—105 °C. The 1-cyanoisoquinoline *N*-oxide **4** used as the other sample was prepared from 1-isoquinolinecarbonitrile according to Ochiai's method[12] and recrystallized from ethanol three times; mp 205—206 °C.

A 50-cm^3 portion of ethanolic solution containing 35 mg of isoquinoline *N*-oxide **1** (or 20 mg of 1-cyanoisoquinoline *N*-oxide **4**) in a quartz vessel was placed in an electromagnet (EEO-1815) supplied by the Maezumi Electric Company and subsequently, illuminated with a 500W Ushio Super-high-pressure Mercury Lamp (USH-500D) equipped with a Toshiba filter UV-31 (or a Toshiba filter UV-35) for 10 min (or 15 min) at room temperature while nitrogen was being bubbled in. The ethanol used as the reaction medium was a reagent-grade product (99.5%) of Wako Pure Chemical Industries. The photoproduct **2** (or **5**) and unreacted *N*-oxide **1** (or **4**) were separated by means of silica-gel TLC (Merck silica-gel plate $60F_{254}$; layer thickness, 2 mm; the eluent, benzene–ethanol–diethyl ether (5:1:2) for **1** and **2**, or hexane–diethyl ether (1:2) for **4** and **5**), and the amounts were determined spectrophotometrically. The UV absorption spectra were taken with a Shimadzu recording spectrophotometer, UV-220.

Results

The irradiation of isoquinoline *N*-oxide **1** in ethanol resulted in the formation of lactam **2** (1-isoquinolone)[13] in a *ca.* 67% yield (Eq. 1). Figure 1 shows the results when the reaction was carried out

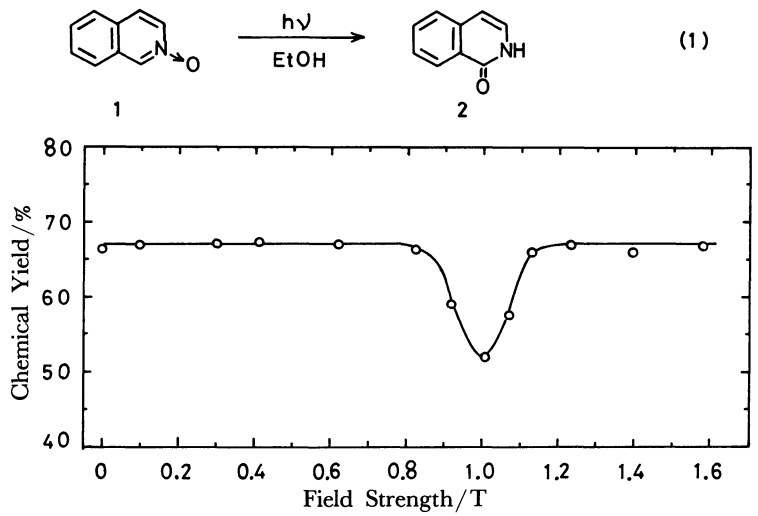


Fig. 1. The magnetic-field dependence of the chemical yield of lactam **2** in the photochemical reaction of isoquinoline *N*-oxide **1**. [*N*-oxide **1**]=4.82×10^{-3} mol dm^{-3}. Conversion: *ca.* 17%. Solvent: 50 cm^3 of ethanol.

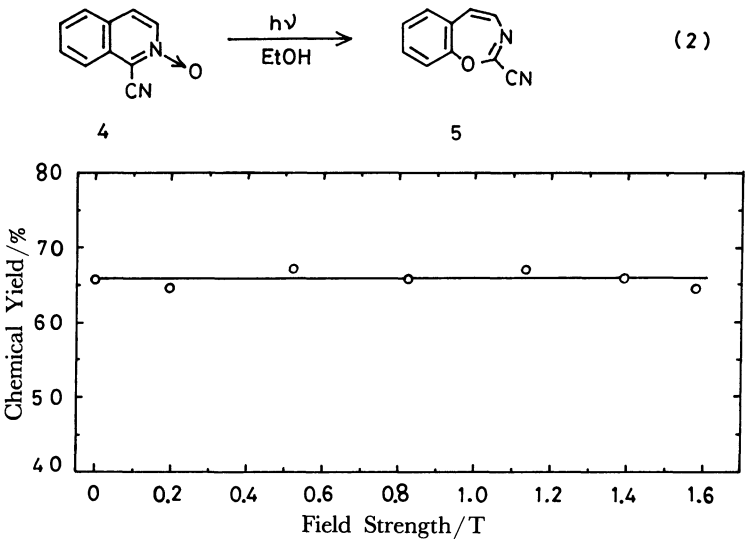


Fig. 2. The chemical yield of oxazepine **5** *vs.* magnetic-field strength in the photochemical reaction of 1-cyanoisoquinoline *N*-oxide **4**. [*N*-oxide **4**]=2.35×10^{-3} mol dm^{-3}. Conversion: *ca.* 30%. Solvent: 50 cm^3 of ethanol.

in the absence and in the presence of a magnetic field; the chemical yield of lactam **2** was determined as a function of the field strength. As can be seen from the figure, the chemical yield of lactam **2** was *ca.* 67% at a magnetic field below 0.8T, but it decreased steeply with an increase in the field strength to be *ca.* 52% at about 1T. A further increase in the magnetic field resulted in a steep increase in the chemical yield until it approached an approximately constant value (*ca.* 67%). The conversion remained almost constant (*ca.* 17%).

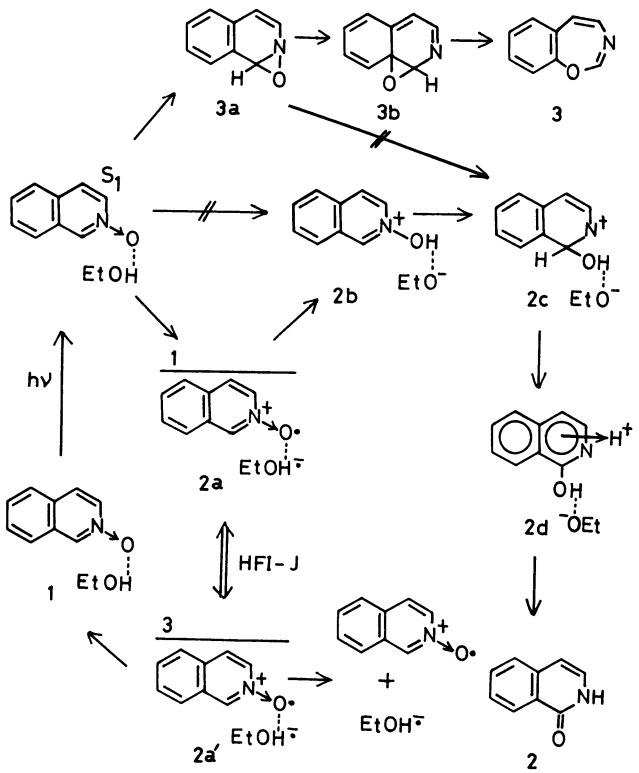
In the case of 1-cyanoisoquinoline *N*-oxide **4**, unlike the case of isoquinoline *N*-oxide **1**, the oxazepine **5** (2-cyano-1,3-benzoxazepine)[14] was obtained in the yield of *ca.* 66% (Eq. 2). Figure 2 shows a plot of the chemical yield of oxazepine **5** against the field strength, from which the chemical yield was proved to be independent of an external magnetic field. Here, also, the conversion remained almost constant (*ca.* 30%).

Discussion

It is well known that, the irradiation of isoquinoline *N*-oxide as well as that of quinoline *N*-oxide in solution results in the formation of a lactam and/or 1,3-oxazepine, depending on the nature of the reaction medium or the substituent group;[15] the photochemical isomerization of the *N*-oxides into lactam and oxazepine are referred to as Process I and Process II respectively. In non-hydroxylic solvents, the *N*-oxide is predominantly transformed into its oxazepine (Process II), whereas in hydroxylic solvents (ROH), Process I

(*N*-oxide→lactam) becomes much more important than Process II (*N*-oxide→oxazepine). When *N*-oxide has a CN or CF_3 group at the carbon atom adjacent to the ring nitrogen, however, only Process II occurs to yield the 1,3-oxazepine, independent of the nature of the reaction medium. Both Processes I and II have been revealed to proceed through the lowest excited singlet state (S_1), whereas the deoxygenation products (the parent amines) are formed from the lowest triplet state (T_1) in only a trace or in a yield of a few percent.[15-17]

Reactive Intermediate. In order to account for Processes I and II, oxaziridine **3a** has been custamarily postulated as the primary photoproduct (reactive intermediate) from which all the products (lactam **2** and oxazepine **3**) are derived[15a] (*cf.* Scheme 1). Since 1972, however, several experimental data conflicting with this idea have been documented in the literature.[11,15b,15c,16-18] We ourselves have demonstrated that the photochemical isomerizations are closely related to whether or not the *N*-oxide oxygen atom forms hydrogen bond with a solvent molecule;[18] that is, such a hydrogen-bonding interaction turns out to be essential for the photochemical rearrangement to the lactam **2** (Process I), but not for the photoisomerization into the oxazepine **3** (Process II). On the basis of these facts, as is shown in Scheme 1, Process I has been assumed to proceed *via* the hydrogen-bonded ion pair **2b** which is formed by the protonation of the N→O group with the hydrogen-bonded solvent molecule (EtOH) in the S_1 state (ion-pair mechanism of Process I), whereas Process II occurs with the formation of the oxaziridine intermediate **3a** from the S_1 state (oxaziridine mechanism of Process II). Such reaction mechanisms have been strongly supported by the studies of quenching by inorganic anions.[19] However, there has still been considerable doubt as to the ion-pair mechanism of Process I; the formation of the ion-pair **2b** through the hydrogen-bonding interaction was not considered to be favorable from the S_1 state, because a hydrogen-bonding ability of the oxygen atom of the N→O group was much lower in the S_1 state than in the S_0 state.[20]

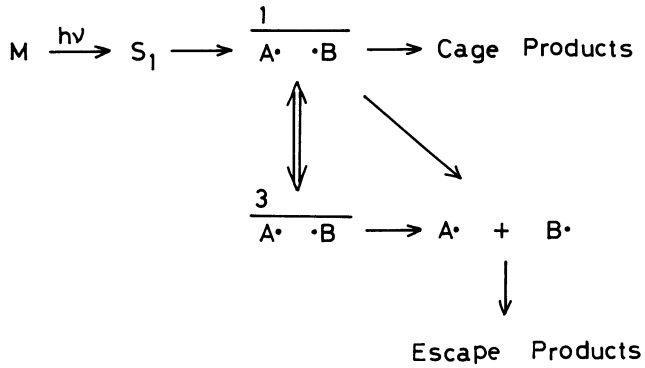


Scheme 1.

As a general rule, if a chemical reaction in solution is subject to a magnetic-field effect, then it may be taken as definite evidence that the reaction proceeds *via* a radical-pair intermediate.[3] As has been described in the Experimental section, the photochemical rearrangement of isoquinoline *N*-oxide **1** to the lactam **2** (Process I) showed an unexpected magnetic-field effect (Fig. 1), whereas the photoisomerization of 1-cyanoisoquinoline *N*-oxide **4** into the 1,3-oxazepine **5** (Process II) was not at all affected by an external magnetic field (Fig. 2). The results indicate unambiguously that Process I involves a field-sensitive radical pair as a reactive intermediate, while Process II does not. Hence, as will be described below, some modifications are required for the ion-pair mechanism of Process I.

Isoquinoline *N*-oxide molecule has two pairs of 2p non-bonding electrons on the oxygen atom of the N→O group; one of them is in conjugation with the π-electron system of the isoquinoline ring (πO:), while the other remains as a nonbonding pair (σO:). The photoelectron spectrum of this molecule shows the first band at 7.98 eV to be due to πO:,[21] indicating that the *N*-oxide cation radical is a π-radical with a radical center at the oxygen atom of the N→O group. Therefore, as is shown in Scheme 1, if an electron (πO:) is transferred from the excited singlet *N*-oxide (S_1) to the hydrogen-bonded ethanol to form the singlet hydrogen-bonded radical-ion-pair **2a** in a solvent cage, the following reactions will take place between the two radical ions constituting the pair; the *N*-oxide cation radical attributable to an odd π-electron on the oxygen atom will abstract hydrogen from the hydrogen-bonded ethanol anion radical, resulting in the formation of the hydrogen-bonded ion-pair **2b** responsible for Process I. This idea makes it possible to explain clearly not only the formation of the ion-pair **2b** which is not explicable by the ion-pair mechanism, but also the observed magnetic field effect. Hereafter, the above reaction mechanism postulated the initial formation of hydrogen-bonded radical ion pair **2a** will be termed the radical ion pair mechanism of Process I.

Magnetic-field Effect. An external magnetic-field effect can generally be expected for chemical reactions proceeding *via* radical-pair intermediates in solution, becuase an external magnetic field may influence the rate of the intersystem crossing of a radical pair.[3]



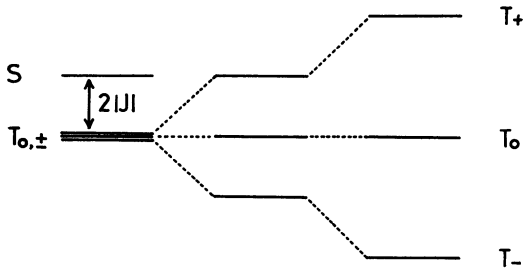
Scheme 2.

Scheme 2 shows the case of a compound M in solution absorbing light and so being exctied into the S_1 state, thus forming a singlet radical-pair intermediate. The radical pair, because of its singlet character, mostly undergoes recombination or disproportionation within a solvent cage to give a cage product. The transition of the singlet radical pair to the triplet, however, results in the formation of an escape product. If the intersystem crossing undergoes an external magnetic perturbation, the chemical yield of the cage product or the escape product can be expected to show a magnetic-field dependence.

If the exchange interaction between the unpaired electrons in a radical pair is disregarded, the following two mechanisms are currently accepted for the magnetic-field effect upon the rate of the intersystem crossing of a radical pair:[3] (i) The external magnetic field causes the intersystem crossing of a radical pair by virtue of the different g-values of the component radicals; therefore, the chemical yield of the cage product (or of the escape product) decreases (or increases) quadratically with an increase in the field strength (the magnetic-field effect due to the Δg mechanism). (ii) The external magnetic field results in a reduction in the number of effective working channels for the hyperfine-induced intersystem crossing of a radical pair. As a result, the chemical yield of the cage product (or of the escape product) increases (or decreases) remarkably at a very low field (the magnetic-field effect due to the HFI mechanism).

The magnetic-field effect observed in the present photochemical system (Fig. 1) is quite different from the above two cases; it can not be interpreted in terms of either the Δg or the HFI mechanism. As is shown in Scheme 1, however, if we assume the singlet hydrogen-bonded radical-ion pair **2a** as a reactive intermediate of Process I, the observed magnetic-field effect can be reasonably explained as follows:

The exchange interaction between the unpaired electrons in the radical ion-pair **2a** may be considered to be much greater than the electron-nuclear hyperfine energy because the radical centers are in close proximity as a result of hydrogen-bonding interaction between the two radical ions; as is shown in Scheme 3,



Scheme 3.

the singlet (S) and triplet ($T_{0,\pm}$) levels of the pair are nondegenerate, having an energy gap of $2|J|$, where J denotes the electron-exchange integral. Therefore, the singlet-triplet mixing due to hyperfine interaction does not occur in the zero field. However, the triplet level is resolved into three sublevels, T_0, T_+, and T_-, by the application of the magnetic field to this system; the T_+ level approaches the S level as the field strength increases. Consequently, the S–T_+ mixing becomes possible at the field strength in which the S–T_+ energy gap is of the order of the hyperfine interaction. The S–T_+ mixing is maximal at the magnetic field in which the singlet level (S) is in resonance with the T_+ level. A further increase in the field strength results in an increase in the separation between the levels of S and T_+; consequently, the mixing of S and T_+ decreases steeply. Thus, the chemical yield of lactam **2** comes to show a minimum at the resonance magnetic field (*ca.* 1T) in which the intersystem crossing of the singlet radical ion-pair **2a** is most favorable.

As has been mentioned above, the new type of magnetic-field effect observed in the present investigation was proved to be explicitly accounted for by an electron-nuclear hyperfine interaction mechanism including electron-exchange interaction in the singlet hydrogen-bonded radical ion-pair **2a** assumed as a reactive intermediate. Hereafter, this will be referred to as the "magnetic-field effect due to the HFI-J mechanism." Needless to say, if the electron-exchange interaction in a pair is neglected (J=0), the magnetic-field effect due to the HFI or Δg mechanism can be expected in lieu of the HFI-J magnetic-field effect.

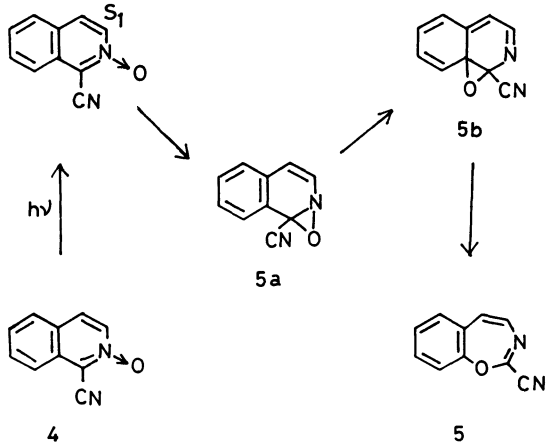
The magnetic-field effect due to the HFI-J mechanism is thought to be particularly interesting and important from the viewpoint of mechanistic photochemistry, because it can be expected when a photoexcited molecule in solution undergoes chemical interaction with the hydrogen-bonded species to form an appropriate hydrogen-bonded radical pair or radical ion-pair intermediate in a solvent cage.[22]

Reaction Mechanism. An examination of the photochemical magnetic-field effect of isoquinoline *N*-oxide **1** or 1-cyanoisoquinoline *N*-oxide **4** in ethanol leads to the conclusion that Process I (*N*-oxide→lactam) is initiated by the formation of the singlet hydrogen-bonded radical ion-pair **2a** from

the S_1 state, while Process II (*N*-oxide→oxazepine) proceeds through the formation of oxaziridine **3a** (or **5a**) from the S_1 state, as is shown in Schemes 1 and 4.

In the case of isoquinoline *N*-oxide **1** (Scheme 1), the primary photochemical step is an electron (πO:) transfer from the excited singlet *N*-oxide (S_1) to the hydrogen-bonded ethanol to produce the singlet hydrogen-bonded radical ion-pair **2a** which is sensitive to the external magnetic field. Subsequently, hydrogen transfer takes place from the ethanol anion radical to the hydrogen-bonded *N*-oxide cation radical, the hydrogen-bonded ion-pair **2b** responsible for Process I being produced. The oxaziridine intermediate **3a** which is involved in Process II is also formed from the S_1 state in competition with the formation of the radical ion-pair **2a**. The conversion of the ion-pair **2b** to the lactam **2** may be supposed to follow the carbonium-ion rearrangement mechanism proposed by Kaneko,[23] because the *N*-oxide bearing a CN or CF_3 group at the carbon atom adjacent to the ring nitrogen does not undergo Process I. Kaneko has assumed the oxaziridine **3a** to be a precursor of the ion-pair **2c** and proposed the oxaziridine mechanism (**3a**→**2c**→**2d**→**2**) for Process I.[23] However, it is now clear, from the observation of HFI-J magnetic-field effect, that Process I does not involve the oxaziridine intermediate **3a**, but proceeds according to the radical ion-pair mechanism (**2a**→**2b**→**2c**→**2d**→**2**). This mechanism has been also supported by the examination of the quenching of the photochemical isomerization of 4-methylquinoline *N*-oxide by inorganic anions.[19]

In the case of 1-cyanoisoquinoline *N*-oxide **4** (Scheme 4), the formation of the oxaziridine intermediate **5a** occurs first from the S_1 state, followed by isomerization into the oxazepine **5** (Process II). Unlike the case of isoquinoline *N*-oxide **1**, no electron transfer occurs between the excited singlet *N*-oxide (S_1) and the solvent molecule; therefore, Process I does not occur. This is probably because the strong electron-withdrawing CN group at the 1-position of an isoquinoline nucleus may cause a lowering of the hydrogen-bonding ability of the oxygen atom of the N→O group and an increase in the ionization potential; also, it may render the carbonium-ion rearrangement unfeasible, even though a radical ion-pair responsible for Process I is formed. The intervention of an oxaziridine in Process II has been demonstrated, in the case of 2-cyanoquinoline *N*-oxide, from the quenching studies using inorganic anions.[19]



Scheme 4.

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