



# Diastereoselective formation of cage-type adducts via a novel photoreaction of nicotinic acid esters with furan

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**Abstract**—Irradiation of a benzene solution containing 2-alkoxynicotinic acid esters (0.02 M) and furan (0.2 M) resulted in the formation of cage-type adducts in 73–84% yield. The structure of the adducts was established by X-ray crystallographic analysis. The mechanism involving  $4\pi+4\pi$  photocycloaddition between the pyridine ring and furan was postulated. Two diastereomeric  $4\pi+4\pi$  adducts were detected as intermediates in the <sup>1</sup>H NMR spectroscopy, when the solution was irradiated in the presence of diene as a triplet quencher. © 2002 Elsevier Science Ltd. All rights reserved.

The photochemistry of aromatic compounds is well documented, and the photoaddition of carbon-aromatics is investigated not only for the fundamental photochemical properties but also for a wide range of applications.<sup>1–6</sup> On the other hand, while the valence isomerization of azaaromatic compounds, such as pyridines, was reported three decades ago,<sup>7–9</sup> only a few reports for the photochemical addition with other aromatics or alkenes are known.<sup>10–13</sup> New development of ring transformation of heteroaromatics will result in useful synthesis of heterocyclic compounds. Recently, we found that induction of moderate substituents toward the pyridine ring shows high reactivity toward dimerization and addition reaction.<sup>12–15</sup> Herein we provide a new photochemical addition of nicotinic acid esters with furan leading to cage-type compounds in good yields.

When a 0.02 M of benzene solution of methyl 2-methoxynicotinate **1a** was irradiated in the presence of furan (0.2 M), one isolable photoproduct, 9-methoxy-10-methoxycarbonyl-5-oxa-8-azapentacyclo-[5.4.0.0.2.60.3.110<sup>4,10</sup>]undec-8-ene **2a**, was obtained in 73% yield at 97% conversion.<sup>16</sup> Photolysis of other nicotines **1b–c** under the same conditions also gave the corresponding adducts **2b–c** in good yields as shown in Table 1. No other photoproducts, such as another type of adducts or pyridine dimers,<sup>15</sup> were isolated. The adducts were stable under usual conditions and were

easily isolated by chromatography on silica gel and recrystallization.

The structure was determined on the basis of spectral data. The high-resolution mass spectroscopy (FAB) of **2a** showed a molecular ion peak at 236.0916 (MH<sup>+</sup>), which supported that the product was a 1:1 adduct of **1a** and furan. The <sup>1</sup>H and <sup>13</sup>C NMR spectra strongly suggest the structure of the cage-type adduct. The <sup>1</sup>H NMR spectrum (CDCl<sub>3</sub>) showed new methine protons at  $\delta$  2.83 (11-CH), 3.11 (1-CH), 3.47 (3-CH), 3.55 (2-CH), 4.62 (7-CH), 4.91 (4-CH), and 5.17 (6-CH) in addition to the methyl protons at 3.75 (s, 3H, OCH<sub>3</sub>), and 3.81 (s, 3H, COOCH<sub>3</sub>). The <sup>13</sup>C NMR also showed

**Table 1.** Photoreaction of 2-alkoxynicotinic acid esters **1** with furan

	R <sup>1</sup>	R <sup>2</sup>	Conv. (%)	Yield (%)
a	Me	Me	97	73
b	Et	Me	96	84
c	Me	Et	97	80

A 0.02 M benzene solution of pyridine **1** and 0.2 M furan was irradiated with a high-pressure mercury lamp.

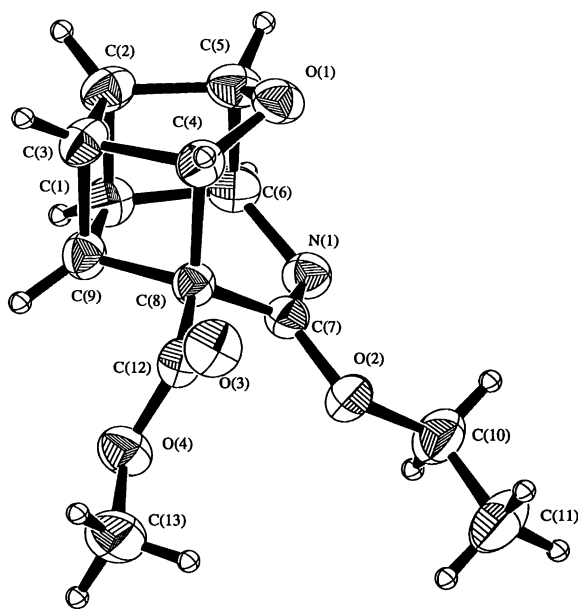
\* Corresponding author.

seven doublet and one singlet  $sp^3$  carbons at  $\delta$  30.3 (d, 11-C), 35.0 (d, 1-C), 42.2 (d, 3-C), 43.8 (d, 2-C), 56.4 (d, 7-C), 57.0 (s, 10-C), 82.5 (d, 6-C), 82.7 (d, 4-C) owing to the cyclobutane rings. The assignment was made using the COSY sequence.

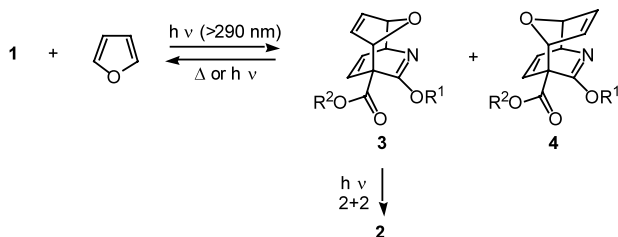
Finally, the cage structure of **2b** was established by X-ray structural analysis (Fig. 1).<sup>17</sup> The cage product **2b** gave colorless prismatic crystals of  $C_{13}H_{15}NO_4$ , monoclinic space group  $P2_1/a$ ,  $a=12.258(8)$  Å,  $b=8.084(9)$  Å,  $c=13.567(9)$  Å,  $\beta=115.64(6)^\circ$ ,  $V=1212(1)$  Å<sup>3</sup>,  $Z=4$ ,  $\rho=1.366$  g/cm<sup>3</sup>,  $\mu(\text{CuK}\alpha)=1.02$  cm<sup>-1</sup>. The structure was solved by the direct method and refined by the full-matrix least-squares method, where the final  $R$  and  $R_w$  were 0.047 and 0.063 for 2534 reflections.

The pyridine-furan adduct **2** is stable at room temperature; however, the starting pyridine **1** and furan were easily regenerated quantitatively by heating (>100°C).

We postulated a mechanism involving a  $4\pi+4\pi$  photocycloaddition of pyridine with furan leading to **3**, followed by  $2\pi+2\pi$  cycloaddition as shown in Scheme 1. We tried to detect the formation of the intermediacy of



**Figure 1.** ORTEP drawing of the adduct **2b**, and selected bond lengths. C(1)–C(2) 1.562(3), C(1)–C(6) 1.546(4), C(1)–C(9) 1.545(3), C(2)–C(3) 1.532(4), C(2)–C(5) 1.536(4), C(3)–C(4) 1.550(3), C(3)–C(9) 1.554(3), C(4)–C(8) 1.574(3), C(5)–C(6) 1.556(4), C(7)–C(8) 1.503(3), C(8)–C(9) 1.570(3).

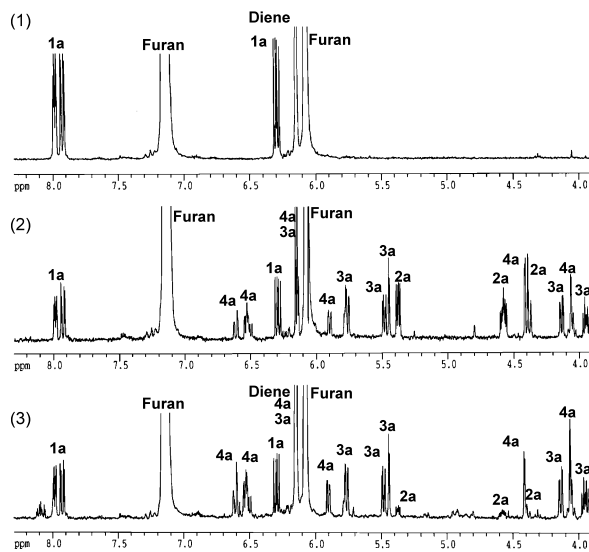


**Scheme 1.**

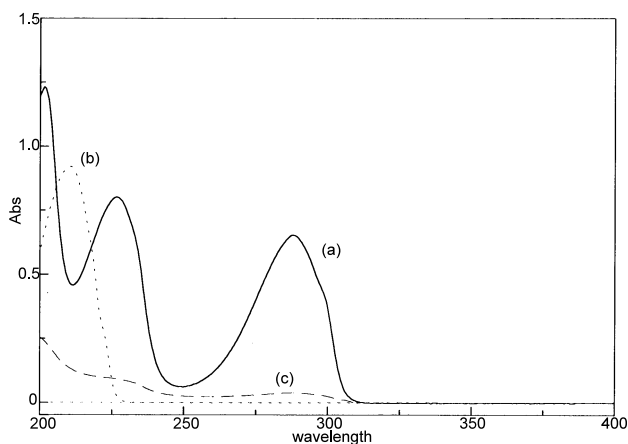
the  $4\pi+4\pi$  adduct with NMR spectroscopy, since  $4\pi+4\pi$  adducts have been detected in the cyanonaphthalene-furan,<sup>18,19</sup> cyanopyridine/furan systems.<sup>20</sup>

Irradiation of a  $C_6D_6$  solution of **1a** (0.02 M) and furan (0.2 M) in a Pyrex NMR tube was followed by <sup>1</sup>H NMR spectroscopy. Fig. 2-(1) shows the spectra of a  $C_6D_6$  solution of **2a** (0.02 M), furan (0.2 M) and 2,5-dimethyl-2,4-hexadiene (0.04 M) as a triplet quencher. Fig. 2-(2) is a spectra after irradiation for 30 min without diene, and Fig. 2-(3) is that after irradiation for 30 min with 0.04 M of diene.

Surprisingly, when the solution was irradiated for 30 min without diene, new peaks assignable to two types of  $4\pi+4\pi$  adduct, **3a** and **4a**, appeared in addition to the peaks derived from cage adduct **2a**. The ratio of **3a:4a:2a** was 28:20:52 (Fig. 2-(2)) at 70% conversion yield.<sup>21</sup> On the other hand, on irradiation of the solution in the presence of 2,5-dimethylhexadiene for 30 min, the formation of **2a** was strictly suppressed. The peaks derived from two  $4\pi+4\pi$  adducts were observed almost predominantly in the ratio of **3a:4a:2a**=47:38:15 (Fig. 2-(3)) at 60% conversion yield. The fact clearly indicates that the initial  $4\pi+4\pi$  cycloaddition was not quenched by triplet quenchers, and subsequent  $2\pi+2\pi$  cycloaddition to **2a** proceeded from the triplet excited state. Almost equally formed diastereomeric  $4\pi+4\pi$  dimer **4a** which cannot cyclize to a cage product is destined to reproduce nicotinate **1** and furan on irradiation as shown in Scheme 1. We tried to isolate these two  $4\pi+4\pi$  adducts. However, the adducts are too unstable to be isolated, because they are easily converted to pyridine **1a**, furan, and a small amount of unidentified compound by the usual work-up process.



**Figure 2.** <sup>1</sup>H NMR spectra of a photolyzed  $C_6D_6$  solution of pyridine **1a** (0.02 M), furan (0.2 M) and 2,5-dimethyl-2,4-hexadiene (0.04 M) in an NMR tube. (1) Before irradiation. (2) Irradiated for 30 min without diene. (3) Irradiated for 30 min with diene.



**Figure 3.** All UV spectra were measured at a concentration of  $1.0 \times 10^{-4}$  mol L<sup>-1</sup> in C<sub>6</sub>H<sub>12</sub>. (a) UV spectrum of **1a**. (b) UV spectrum of furan. (c) UV spectrum of **2a**.

Fig. 3 shows the UV spectra of the pyridine **1a**, furan, and the cage-type adduct **2a** at concentration of each  $1.0 \times 10^{-4}$  mol/L in C<sub>6</sub>H<sub>12</sub>. Furan has no absorption band above 240 nm. Since high pressure mercury lamp with a Pyrex filter was used as the irradiation source, light quantum of 313 nm line was absorbed by the pyridine **1a** ( $\epsilon$  90 at 313 nm). Although we could not measure the UV spectra of  $4\pi+4\pi$ , it seems that the absorbance of nonconjugated intermediates, **3a** and **4a**, is small and most of the light is absorbed by **1a** under these conditions. The cage-type adduct **2** formed from the early stage of the reaction. Furthermore, the quenching experiments indicated the second photocyclization from  $4\pi+4\pi$  adduct **3** to **2** proceeded from the triplet excited state (Fig. 2). These facts indicate that an effective cyclization from **3** to **2** probably promotes efficient energy transfer from the excited state of pyridine **1** to  $4\pi+4\pi$  adduct **3**.

In conclusion, we have provided a new example of the photochemical reaction of nicotinic acid esters with furan leading to 1:1 cycloadducts. This reaction produced two diastereomeric  $4\pi+4\pi$  adducts; however, only one adduct effectively cyclized to a cage-type adduct. Finally, selective formation of the cage-type adduct is performed.

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16. General procedure for the photochemical reaction of 2-alkoxynicotinates **1a–c**. A benzene solution containing 2-alkoxynicotinate **1** was deaerated by bubbling argon for 15 min and was irradiated by Pyrex filtered light with a 1000-W high-pressure mercury lamp at 15–20°C. The consumption of the starting esters was checked by TLC; irradiation time depended on the substituent of esters and needed 1–2 h. After irradiation, the solvent was removed in vacuo and the residual mixture was subjected to chromatography on silica gel (eluant: mixture of *n*-hexane and ethyl acetate). The crystalline photoproducts were recrystallized from a mixture of chloroform and hexane. The structure of photoproducts was determined on the basis of the spectral data.
17. Crystal and data collection parameters, relevant structure refinement parameters, atomic coordinates for the non-hydrogen atoms, positional and isotropic displacement coefficients for hydrogen atoms, a list of anisotropic displacement coefficients for the non-hydrogen atoms and a full list of bond distances and bond angles have been deposited with the Cambridge Crystallographic Data Center. The crystallographic data will be sent on quoting the CCDC numbers 181815 for **2b** (e-mail: deposit@ccdc.cam.ac.uk).
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21. The <sup>1</sup>H NMR spectra of  $4\pi+4\pi$  adducts; **3a**: (C<sub>6</sub>D<sub>6</sub>)  $\delta$  3.53 (s, 3H), 3.84 (s, 3H), 3.95 (m, 2H), 4.13 (dd, *J*=5.7 and 1.8 Hz, 1H), 5.43 (d, 1.8 Hz, 1H), 5.48 (dd, *J*=5.7 and 1.8 Hz, 1H), 6.20 (m, 1H). The adduct **4a**: (C<sub>6</sub>D<sub>6</sub>)  $\delta$  3.45 (s, 3H), 3.58 (s, 3H), 4.07 (m, 2H), 4.40 (m, 1H), 5.91 (dd, *J*=1.3 and 5.8 Hz, 1H), 6.20 (m, 1H), 6.59 (m, 1H), and 6.62 (m, 1H).