Intramolecular Photocycloaddition of the C=C Double Bond to the C≡N Triple Bond Resulting in the Formation of a Novel Cyclic System

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Synopsis. Irradiation of a bichromophoric 1-(*o*-cyanobenzyloxy)-2-(*p*-methoxyphenyl)-2-butene (**1a**) in cyclohexane gave an isoquinoline derivative, 8-methoxy-6-methyl-11,13-dihydro[2]benzoxepino[5,4-*c*]isoquinoline (**2a**). The structure was determined by X-ray analysis. The formation of **2a** can be accounted for by the initial cycloaddition of **1a** in the excited singlet state between the C=C double bond and C≡N triple bond, followed by cleavage of the resulting azetine ring and recyclization.

Introduction of two chromophores into a molecule by linking with an appropriate molecular chain sometimes results in a novel interaction which could not be involved in separate molecules.[1,2] Previously, we reported an enhancement of photoreactivity of the ester carbonyl group in the phenanthrene–styrene reaction brought about by interchromophoric links with the ester group, an oxetane formation through a carbonyl addition.[3—5] During the course of our investigation on the molecular interaction in the excited states, we have found the formation of a new ring system through an intramolecular cycloaddition of the olefinic double bond with the cyano group. In this paper we describe the photochemical and photophysical observations on styrene–benzonitrile linked bichromophoric systems. The cyano group is, usually, photochemically very stable and only a few reports have appeared on photocycloaddition of this group.[6—8]

Experimental

General. Proton and carbon 13 nuclear magnetic resonance (NMR) spectra were recorded on a JEOL JNM-MH-100 or FX-100 (100 MHz) and a JEOL FX-100 (25 MHz) NMR spectrometer, respectively. Infrared spectra (IR) were obtained on a Hitachi 260-50 spectrophotometer and ultraviolet absorption spectra (UV) were taken on a JASCO UVIDEC-600 spectrophotometer.

Fluorescence spectra were obtained on a Hitachi F-4000 fluorescence spectrofluorimeter and fluorescence quantum yields were determined by comparing corrected fluorescence spectra with that of naphthalene ($\phi_f=0.23$).[9] Fluorescence lifetimes were determined with a Horiba NAES-1100 time-resolved fluorescence spectrophotometer (single photon counting).

Materials. Solvents, cyclohexane, tetrahydrofuran, dichloromethane, and acetonitrile, were commercially available and distilled before use.

(*Z*)-1-(*o*-Cyanobenzyloxy)-2-(*p*-methylphenyl)-2-butene (1b). Bromination of 1-(*p*-methylphenyl)-ethanone (25 g, 0.19 mol) with bromine (9.6 cm^3, 0.19 mol) in ether (40 cm^3) in the presence of aluminum chloride (0.25 g) gave 2-bromo-1-(*p*-methylphenyl)ethanone.[10] The crude product was crystallized from methanol (yield 19.6 g, 49%) mp 52—52.5 °C.

2-Bromo-1-(*p*-methylphenyl)ethanone (23 g, 0.11 mol) was allowed to react with acetic acid (51 cm^3, 0.88 mol) in acetone (460 cm^3) in the presence of triethylamine[11] (77 cm^3, 0.55 mol) to give *p*-methylbenzoylmethyl acetate. The crude product was crystallized from methanol (14.1 g, 68%); mp 82—83 °C.

p-Methylbenzoylmethyl acetate (11.5 g, 0.060 mol in 100 cm^3 of THF) was allowed to react with the Wittig reagent prepared from ethyltriphenylphosphonium bromide (25 g, 0.067 mol) and butyllithium[12] (0.073 mol, 60 cm^3 of a hexane solution) in ether (250 cm^3) and the crude product was separated with a silica-gel column ($CHCl_3$). 2-(*p*-Methylphenyl)-2-butenyl acetate was obtained as an oily mixture of the *E*- (23%) and *Z*-isomer (77%) (yield 3.4 g, 28%).

Reduction of 2-(*p*-methylphenyl)-2-butenyl acetate (3.5 g, 0.017 mol) with $LiAlH_4$ (0.49 g, 0.013 mol) in ether (120 cm^3) afforded an oily mixture of the *E*- and *Z*-isomer of 2-(*p*-methylphenyl)-2-buten-1-ol (2.2 g, 80%).

The isomeric mixture (0.4 g) of 2-(*p*-methylphenyl)-2-buten-1-ol was irradiated in benzene in the presence of 2-acetylnaphthalene (0.2 g) with a 400-W high-pressure mercury lamp through a Pyrex jacket wall for 1 h. The reaction mixture was separated by silica gel-column chromatography ($CHCl_3$/ether=20/1) to give (*Z*)-2-(*p*-methylphenyl-2-buten-1-ol (oil, 0.23 g, 58%).

(*Z*)-2-(*p*-Methylphenyl)-2-buten-1-ol (0.23 g, 0.0014 mol) was allowed to react in DMF (10 cm^3) in the presence of sodium hydride (0.1 g, 60% content, washed with hexane and suspended in 5 cm^3 of ether) with *o*-cyanobenzyl bromide (0.28 g, 0.0014 mol) prepared from bromination of *o*-methylbenzonitrile with NBS in CCl_4. The crude product was treated with a silica-gel column (PhH) to give (*Z*)-1-(*o*-cyanobenzyloxy)-2-(*p*-methylphenyl)-2-butene (**1b**) (oil, 0.20 g, 56%) and further purification was made with a Lobar column (Merck, LiChroprep Si60, hexane/ethyl acetate=19/1); purity: more than 98% based on GLPC and HPLC. (*Z*)-**1b**: IR (liquid) 2200 cm^{-1}, $\nu_{C\equiv N}$; ^1H NMR ($CDCl_3$) $\delta=1.69$ (d, 3H, CH_3CH=C), 2.35 (s, 3H, $CH_3\Phi$), 4.29 (bs, 2H, O–CH_2–CH=C), 4.70 (s, 2H, O–CH_2–ΦCN), 5.88 (q, 1H, C=C$H$$CH_3$), 7.16 (bs, 4H, Me$\Phi$–H), 7.3—7.7 (m, 4H, CN$\Phi$–H).

(*Z*)-1-(*o*-Cyanobenzyloxy)-2-(*p*-methoxyphenyl)-2-butene (1a). 2-(*p*-Methoxyphenyl)-2-buten-1-ol was prepared as a mixture of the *E*- (53%) and *Z*-isomer (47%) in a manner similar to that described previously.[3b]

The isomeric mixture of 2-(*p*-methoxyphenyl)-2-buten-1-

ol was irradiated in benzene in the presence of 2-acetylnaphthalene with a 400-W high-pressure mercury lamp through a Pyrex wall for 1 h. The reaction mixture was separated by silica-gel column chromatography ($CHCl_3$/ether=10/1) to give (*Z*)-2-(*p*-methoxyphenyl)-2-buten-1-ol (oil, 0.65 g, 65%).

(*Z*)-2-(*p*-methoxyphenyl)-2-buten-1-ol was allowed to react with *o*-cyanobenzyl bromide in DMF in the presence of sodium hydride. The crude product was treated with a silica-gel column (PhH) to give (*Z*)-1-(*o*-cyanobenzyloxy)-2-(*p*-methoxyphenyl)-2-butene (**1a**) (oil, 1.2 g, 56%); purity: more than 99.3% based on GLPC and HPLC; IR (liquid) 2200 cm^{-1}, $\nu_{C\equiv N}$; ^1H NMR ($CDCl_3$) δ=1.70 (bd, 3H, CH_3CH=C), 3.80 (s, 3H, $CH_3O\Phi$), 4.29 (bs, 2H, O–CH_2–CH=C), 4.70 (s, 2H, O–CH_2–ΦCN), 5.86 (q, 1H, C=C*H*CH_3), 6.8—7.25 (m, 4H, MeOΦ–H), 7.3—7.8 (m, 8H, CNΦ–H).

1-(*o*-Cyanobenzyloxy)-2-phenyl-2-butene (1c). 2-Bromo-1-phenylethanone (phenacyl bromide, 17.2 g, 0.087 mol) was treated with acetic acid (44 cm^3, 0.77 mol) in acetone (400 cm^3) in the presence of triethylamine (67 cm^3, 0.48 mol) to give benzoylmethyl acetate (phenacyl acetate); bp 124 °C/3 mmHg (1 mmHg=133.32 Pa) (yield 8.5 g, 61%).

Benzoylmethyl acetate (8.5 g, 0.048 mol in 100 cm^3 of ether) was allowed to react with the Wittig reagent prepared from ethyltriphenylphosphonium bromide (20.3 g, 0.055 mol) and butyllithium (hexane solution, 0.074 mol) in ether (250 cm^3) and the crude product was separated with a silica-gel column ($CHCl_3$). 2-Phenyl-2-butenyl acetate was obtained as an only mixture of the *Z*- and *E*-isomer (1.8 g, 14%).

The acetate (3.6 g, 0.018 mol) was reduced with $LiAlH_4$ (0.5 g, 0.013 mol) in ether (200 cm^3) to give 2-phenyl-2-buten-1-ol (*Z*+*E* mixture, 2.3 g, 89%).

The butenol (0.9 g, 0.0061 mol) was allowed to react with *o*-cyanobenzyl bromide (1.2 g, 0.0061 mol) in DMF (30 cm^3) in the presence of sodium hydride (0.007 mol, suspended in 20 cm^3 of DMF). The crude product was treated with a silica-gel column ($CHCl_3$) to afford 1-(*o*-cyanobenzyloxy)-2-phenyl-2-butene (**1c**) (oil, 0.21 g, 13%) as a mixture of the *E*- (65%) and *Z*-isomer (35%); ^1H NMR ($CDCl_3$) δ=1.7 (d, 3H, CH_3, *E*), 1.9 (d, 3H, CH_3, *Z*), 4.4 (s, 2H, C=CCH_2, *E*), 4.6 (s, 2H, C=CCH_2, *Z*), 4.8 (s, 2H, OCH_2, *E*+*Z*), 6.0 (q, 1H, C=C*H*CH_3, *E*), 6.2 (q, 1H, C=C*H*CH_3, *Z*), 7.3—7.8 (m, 9H, Ar–H).

(*Z*)-2-(*p*-Methoxyphenyl)-2-butene (3a) and (*Z*)-2-(*p*-Methylphenyl)-2-butene (3b). 1-(*p*-Methoxyphenyl)ethanone and 1-(*p*-methylphenyl)ethanone were, respectively, allowed to react with the Wittig reagent prepared from ethyltriphenylphosphonium bromide and butyllithium in ether. The *Z*- and *E*-isomers were separated from the reaction mixtures with silica-gel column chromatography eluted with hexane. The *E*-isomers obtained were irradiated with 2-acetylnaphthalene in benzene to give isomeric mixtures, from which the *Z*-isomers were separated similarly.

Irradiation of (*Z*)-1-(*o*-Cyanobenzyloxy)-2-(*p*-methoxyphenyl)-2-butene (1a). A solution of (*Z*)-**1a** (44 mg; 3.8×10^{-4} mol dm^{-3}) in cyclohexane (0.4 dm^3) was irradiated in a quartz vessel with a 160-W low-pressure mercury lamp (254 nm) for 2 h (until the starting material was almost completely consumed, as monitored by TLC) under nitrogen atmosphere at room temperature. After evaporation of the solvent, the residue was separated by preparative TLC (SiO_2, 10:1 $CHCl_3$–Et_2O) to afford a solid product; R_f 0.46 (13 mg, 29%). The product was identified as an isoquinoline derivative, 8-methoxy-6-methyl-11,13-dihydro[2]benzoxepino[5,4-*c*]isoquinoline (**2a**) by X-ray crystallographic analysis of single crystals obtained by crystallization from ether.

2a: ^1H NMR ($CDCl_3$) δ=2.97 (s, 3H, CH_3), 3.93 (s, 3H, CH_3O), 4.32 (s, 2H, CH_2–Φ), 4.67 (s, 2H, CH_2–Ar), 7.19—8.17 (m, 7H, Ar–H); ^{13}C NMR ($CDCl_3$) δ=22.9 (CH_3), 55.5 (CH_3O), 60.7 (CH_2), 68.2 (CH_2), 104.4 (CH), 122.7, 123.0 (CH), 125.0 (CH), 127.9, 128.4 (CH), 128.8 (CH) 129.0 (CH), 129.4 (CH), 130.2, 135.5, 141.4, 149.2, 157.3, 158.0.

Similar irradiation of (*Z*)-**1a** in THF ([(*Z*)-**1a**]=4.2×10^{-4} mol dm^{-3}) for 4 h afforded **2a** in 10% yield, as determined with HPLC on a Shimadzu LC-6A equipped with an Otsukadensi MCPD-350PC detector (Solbax ODS column eluted with a MeCN–water (80:20) mixture); however, on irradiation in CH_2Cl_2 ([(*Z*)-**1a**]=2×10^{-3} mol dm^{-3}, 4 h) and MeCN ([(*Z*)-**1a**]=5×10^{-3} mol dm^{-3}, 3 h), formation of **2a** was not detected.

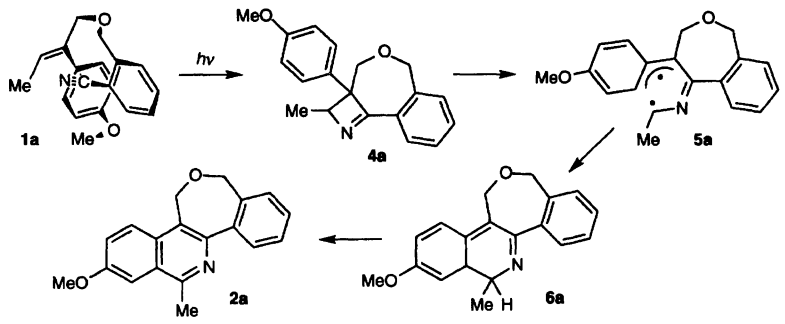
Irradiation of (*Z*)-1-(*o*-Cyanobenzyloxy)-2-(*p*-methylphenyl)-2-butene (1b). A solution of (*Z*)-**1b** (55 mg; 4.9×10^{-4} mol dm^{-3}) in cyclohexane (0.4 dm^3) was irradiated in a manner similar to that for (*Z*)-**1a** for 3 h. After evaporation of the solvent, the residue was separated by preparative TLC (SiO_2, 10:1 $CHCl_3$–Et_2O) to afford a solid product; R_f 0.58 (15 mg, 28%). The product was identified as an isoquinoline derivative of the same ring system as that of **2a**, 6,8-dimethyl-11,13-dihydro[2]benzoxepino[5,4-*c*]isoquinoline (**2b**), by comparing its NMR spectra with those of **2a**.

2b: ^1H NMR ($CDCl_3$) δ=2.53 (s, 3H, CH_3), 2.97 (s, 3H, CH_3), 4.31 (s, 2H, CH_2–Φ), 4.67 (s, 2H, CH_2–Ar), 7.18—8.14 (m, 7H, Ar-H); ^{13}C NMR ($CDCl_3$) δ=21.9 (CH_3), 22.9 (CH_3), 60.7 (CH_2), 68.2 (CH_2), 122.6, 123.1 (CH), 125.3 (CH), 126.8, 128.5 (CH), 129.0 (CH), 129.4 (CH), 132.8 (CH), 133.0, 135.7, 136.6, 153.9, 158.3.

Similar irradiation of (*Z*)-**1b** (4.2×10^{-4} mol dm^{-3}) in THF for 6 h afforded **2b** in 10% yield, as determined with HPLC.

Irradiation of 1-(*o*-Cyanobenzyloxy)-2-phenyl-2-butene (1c). Three portions of a solution of **1c** (a 65:35 *E*/*Z* mixture; 44 mg; 3.3×10^{-4} mol dm^{-3}) in cyclohexane (0.5 dm^3) were irradiated in a manner similar to that for (*Z*)-**1a** for 2 h. After evaporation of the solvent, the combined residue was separated by silica-gel column chromatography eluted with 1:4 ether–chloroform to give a crude product (30 mg, 23%). This was purified by preparative TLC, giving colorless solid, which was identified as 6-methyl-11,13-dihydro[2]benzoxepino[5,4-*c*]isoquinoline (**2c**); MS *m*/*z* 261 (M^+), 232; ^1H NMR ($CDCl_3$) δ=3.1 (s, 3H, CH_3), 4.4 (s, 2H, CH_2–Φ), 4.8 (s, 2H, CH_2–Ar), 7.4—8.3 (m, 8H, Ar–H).

X-Ray Crystallographic Analysis of Isoquinoline 2a. Single crystals were prepared by slow evaporation from ether solution. Intensity data were collected on a Nicolet P3/F four-circle diffractometer with graphite monochromated Mo $K\alpha$ ($2\theta<56°$) radiation. A total of 3556 reflections were collected, of which independent 2987 reflections with $I>3\sigma(I)$ were considered as observed. The structure was solved by the direct method and refined by full-matrix least-squares methods. The weighting scheme applied in the final stage was $w=1/[\sigma(F_o)^2+0.0007(F_o)^2]$.



Scheme 1.

The highest remaining $\Delta\rho$ was 0.18 Å^3. Crystal data for **2a**: $C_{19}H_{17}O_2N$, M.W.=291.34, monoclinic, space group $P2_1/n$, a=13.005(2), b=7.788(1), c=14.867(2) Å, and β=102.60(1)°, V=1469.4(3) Å^3, Z=4, D_c=1.32 g cm^{-3}, R=0.057, R_w=0.066 for 2987 unique reflections with $I>3\sigma(I)$.

Results and Discussion

Bichromophoric (*Z*)-**1a** and (*Z*)-**1b** (Chart 1) exhibit similar absorption spectra in cyclohexane. The absorption maxima (λ_{max}) are at 230 (ε 17800), 274 (3500), and 283 (3000) for (*Z*)-**1a** and at 229 (ε 16000), 274 (1300), and 283 (1200) for (*Z*)-**1b**. The spectra are nearly identical with the sum of the corresponding olefin and nitrile, (*Z*)-2-(*p*-methoxyphenyl)-2-butene ((*Z*)-**3a**) or (*Z*)-2-(*p*-methylphenyl)-2-butene ((*Z*)-**3b**) and *o*-methylbenzonitrile; the absorption tails reach 340 nm, a slightly longer wavelength than that of the butenes. Similar absorption spectra were observed in polar solvents such as dichloromethane, tetrahydrofuran, and methanol. Therefore, no clear interactions between the chromophores were detected in the absorption spectra.

Both of (*Z*)-**1a** and (*Z*)-**1b** showed a weak fluorescence spectrum in the wavelength region of 310—450 nm (λ_{max} 328, 342, 353 nm) in cyclohexane. In tetrahydrofuran, dichloromethane, and acetonitrile, a broad emission appeared probably due to an intramolecular exciplex; the maximum wavelength was dependent upon the solvent, e.g., ca. 380 nm in THF, ca. 400 nm in CH_2Cl_2, and ca. 430 nm in CH_3CN for both derivatives. These observations indicate the intramolecular interaction in these substrates in the excited singlet state.

The fluorescence quantum yield of (*Z*)-**1a** was determined in cyclohexane to be 0.022 by comparing with that of naphthalene (0.23).[9] This value is essentially identical with that of (*Z*)-**3a** (0.027), while (*E*)-**3a** exhibits a strong fluorescence of a quantum yield of 0.28. On repeated measurements, the fluorescence intensity of (*Z*)-**3a** increased markedly but that of (*E*)-**3a** decreased; this might be due to isomerization of the double bonds. On the contrary, the fluorescence intensities of (*Z*)-**1a** and (*Z*)-**1b** did not change appreciably during the fluorescence measurement, indicating that the intramolecular interaction with the cyanophenyl moiety decreased the isomerization efficiency.

The fluorescence lifetime of (*E*)-**3a** was determined

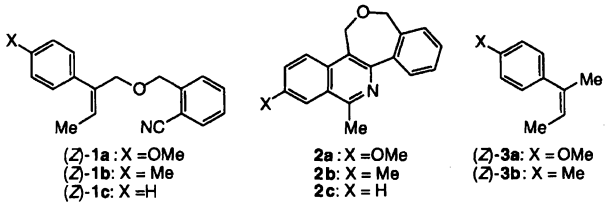


Chart 1.

to be 5.8 ns by single photon counting, whereas those of (*Z*)-**1a**, (*Z*)-**1b**, and (*Z*)-**3a** seem to be shorter than 1 ns but reliable data could not be obtained because of their low fluorescence intensities on selective excitation of the styrene moiety at the absorption edge.

Irradiation of (*Z*)-**1a** in cyclohexane with 254-nm light for 4 h afforded an isoquinoline derivative, 8-methoxy-6-methyl-11,13-dihydro[2]benzoxepino[5,4-*c*]-isoquinoline (**2a**), in 29% yield. The structure of **2a** was determined on the basis of NMR spectra and X-ray analyses of a single crystal. An ORTEP drawing of **2a** is shown in Fig. 1 and the packing of the molecules in

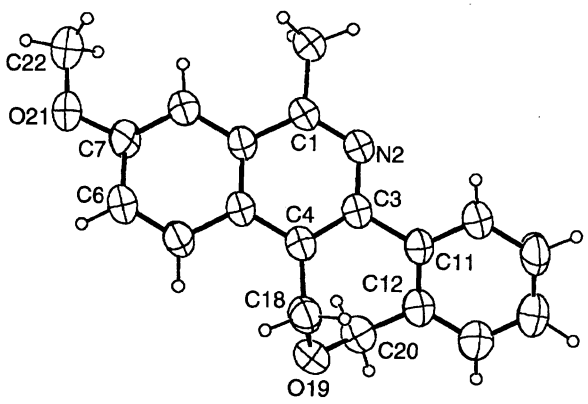


Fig. 1. Perspective drawing of the **2a** molecule with thermal ellipsoid scaled at the 50% probability level. Hydrogen atoms are represented by a circle of radius 1.5 nm. The dihedral angle between the isoquinoline moiety and phenyl ring is 38.9°, whereas the methoxyl group is almost within the plane. The dihedral angles of the C(3)–C(4)–C(18)–O(19), C(4)–C(18)–O(19)–C(20), C(18)–O(19)–C(20)–C(12), and O(19)–C(20)–C(12)–C(11) bonds are −79.1°, 46.1°, 64.6°, and −73.8°, respectively. The dihedral angle of the C(6)–C(7)–O(21)–C(22) bonds is 7.7°.

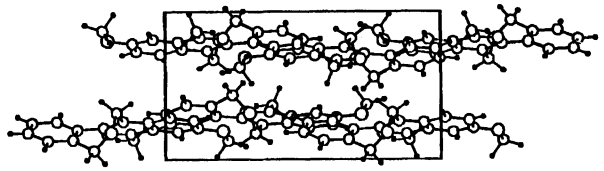


Fig. 2. The crystal structure of **2a** viewed along the *c* axis.

a unit cell is shown in Fig. 2. The crystal data are as follows; monoclinic, space group $P2_1/n$; $a=130.05(2)$, $b=77.88(1)$, $c=148.67(2)$ nm, and $\beta=102.60(1)°$.

Irradiation of (*Z*)-**1b** and **1c** ($E/Z=65:35$) under similar conditions also afforded isoquinoline derivatives, 6,8-dimethyl-11,13-dihydro[2]benzoxepino[5,4-*c*]-isoquinoline (**2b**, 28%) and 6-methyl-11,13-dihydro[2]-benzoxepino[5,4-*c*]isoquinoline (**2c**, 23%), respectively. Their structure was determined by comparing their NMR spectra with those of **2a**.

The formation of the dihydro[2]benzoxepino[5,4-*c*]isoquinoline ring system could be rationalized by the initial cycloaddition of the styryl moiety in the excited singlet state to the cyano group and subsequent rearrangement of the resulting azetine ring, as shown in Scheme 1. Cantrell reported that a 1-azetine derivative formed from photoreaction of benzonitrile and 2,3-dimethyl-2-butene was thermally cleaved to give a conjugated Schiff base.[6] However, a mechanism that the resulting azetine derivative (**4a**) undergoes further photochemistry[7] through an intermediate similar to the biradicaloid, **5a**, is not ruled out.

Measurements of the time development of products by HPLC indicated that on irradiation the starting material, (*Z*)-**1a** or (*Z*)-**1b**, was consumed to give a primary product which showed an absorption maximum around 250 nm, and subsequently, as the primary product decreased, the final product, **2a** or **2b**, was formed. These results are consistent with the mechanism proposed in Scheme 1. The polar solvents tend to decrease the yield of the final products. This may be due to the stabilization of exciplex diminishing the efficiency to overcome the activation barrier for cycloaddition of the exciplexes.[5]

The precedent cycloaddition of nitriles appears to proceed from their excited states.[6—8] In the present reactions, however, it is the olefinic moiety that is in the excited state, where the exciplexes may play an important role.

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