A Stable Monosubstituted Isoindole Derivative: The Crystal Structure of 1-(1,2,3-1*H*-Benzotriazol-1-yl)-2-(4-methylphenyl)-2*H*-isoindole

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1-(1,2,3-1*H*-benzotriazol-1-yl)-2-(4-methylphenyl)-2*H*-isoindole (1a) is a stable isoindole derivative in the crystalline state. On the basis of the results of X-ray crystallographic analysis, this exceptional stability was explained as follows: the presence of a typical *anti*-parallel face-to-face stacking between isoindole rings deprives the two reactive centers of an intermolecular approach.

Keywords 2*H*-isoindole; X-ray analysis; crystal structure; face-to-face stacking; *o*-xylylene structure; 1,2,3-1*H*-benzotriazole

2*H*-isoindoles are compounds which attract interest as reactive units in the synthesis of electrically conductive polymers.[2)] The high reactivity of this heterocycle is presumably due to its *o*-xylylene character as is found in isobenzofuran,[3)] although the compound satisfies the Hückel $4n+2$ rule for aromaticity. Thus, it has been believed that isoindoles are stably isolable only when they possess bulky substituents at both the 1- and 3-positions (*e.g.*, 2,5-dimethyl-1,3-diphenyl-2*H*-isoindole).[4)] Position 1- or 3-unsubstituted and mono-substituted derivatives were only obtained *in situ* in the preparation from the corresponding isoindolines.[5)]

However, the authors have recently found that 1-(1,2,3-1*H*-benzotriazol-1-yl)-2-(4-methylphenyl)-2*H*-isoindole (**1a**), though it lacks a substituent at the 3-position, is exceptionally stable in the crystalline state. It was prepared in a moderate yield, together with the 1,3-disubstituted isoindoline derivative (**3a**), by a condensation of *o*-phthalaldehyde with *p*-toluidine in the presence of 1,2,3-1*H*-benzotriazole (Bt-H).[6)] The purified crystals of **1a** are storable for a year in an open vessel at room temperature under room light without any noticeable deterioration. By contrast, in a $CDCl_3$ solution, on exposure to room light, **1a** changed the color from lemon-yellow to deep green within a few minutes, indicating that a rapid polymerization reaction took place.[7)] These facts suggest the presence of special stabilization factor(s) in the crystals of **1a**. Thus, we conducted an X-ray analysis study on a single crystal of **1a**.

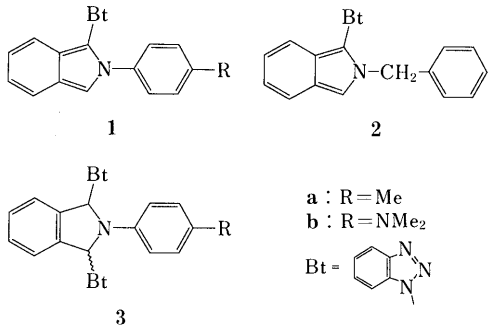

Chart 1

Experimental

1-(1,2,3-1*H*-Benzotriazol-1-yl)-2-(4-methylphenyl)-2*H*-isoindole (**1a**)[6)] was crystallized from diethyl ether as pale orange prisms of mp 164—166 °C. A single crystal of this specimen was subjected to an X-ray analysis.

All measurements were made on a Rigaku AFC-5R four-circle diffractometer controlled by the MSC/AFC program package, using MoK_α radiation monochromated by a graphite monochromator (λ= 0.71069 Å) at 296 K. The approximate crystal size was $0.7\times0.5\times0.3$ mm. The data were collected using a ω–2θ scan mode for $3°<2\theta<55°$ with a scan speed of 6.0°/min. Of the total 4067 reflections collected, 2690 with $I>3\sigma(I)$ were used for calculations. The structure was solved by direct methods using MITHRIL[8)] and refined by the full-matrix least-squares method. Non-hydrogen atoms were refined anisotropically and all hydrogen atoms were located on a difference Fourier map and

TABLE I. Positional Parameters with Thermal Parameters B_{eq} for Non-hydrogen Atoms

Atom	x	y	z	B_{eq}
N(1)	1.0927 (1)	0.5576 (1)	0.2900 (2)	3.12 (4)
N(2)	0.9980 (1)	0.7672 (1)	0.3205 (2)	3.42 (4)
N(3)	0.9375 (2)	0.8125 (1)	0.4548 (2)	4.37 (5)
N(4)	0.8401 (2)	0.8920 (1)	0.4234 (2)	4.82 (6)
C(1)	0.8340 (2)	0.5072 (1)	0.1140 (2)	3.63 (6)
C(2)	0.9542 (2)	0.4883 (1)	0.2379 (2)	3.07 (5)
C(3)	0.7031 (2)	0.4372 (2)	0.0635 (2)	4.08 (6)
C(4)	0.6886 (2)	0.3477 (1)	0.1339 (2)	3.97 (6)
C(5)	0.8113 (2)	0.3288 (1)	0.2547 (2)	3.88 (6)
C(6)	0.9431 (2)	0.3982 (1)	0.3077 (2)	3.40 (5)
C(7)	0.5445 (3)	0.2728 (2)	0.0776 (4)	6.1 (1)
C(8)	1.2273 (2)	0.5050 (1)	0.3113 (2)	3.43 (5)
C(9)	1.1138 (2)	0.6848 (1)	0.3228 (2)	3.28 (5)
C(10)	1.2635 (2)	0.7121 (1)	0.3637 (2)	3.45 (5)
C(11)	1.3360 (2)	0.5973 (1)	0.3560 (2)	3.44 (5)
C(12)	1.4918 (2)	0.5967 (2)	0.3878 (2)	4.24 (6)
C(13)	1.5681 (2)	0.7056 (2)	0.4267 (3)	5.36 (8)
C(14)	1.4950 (2)	0.8194 (2)	0.4358 (3)	5.78 (8)
C(15)	1.3464 (2)	0.8252 (2)	0.4062 (3)	4.76 (7)
C(16)	0.9373 (2)	0.8234 (1)	0.2025 (2)	3.52 (5)
C(17)	0.8353 (2)	0.9019 (1)	0.2679 (2)	4.00 (6)
C(18)	0.7488 (2)	0.9736 (2)	0.1775 (3)	5.46 (8)
C(19)	0.7686 (3)	0.9614 (2)	0.0240 (4)	6.3 (1)
C(20)	0.8730 (3)	0.8818 (2)	−0.0403 (3)	6.1 (1)
C(21)	0.9598 (2)	0.8117 (2)	0.0474 (3)	4.83 (7)

refined with an isotropic temperature factor. The final R values are $R=0.040$ and $R_w=0.049$.

Crystal data: $C_{21}H_{16}N_4$, M.W.=324.38; triclinic; space group $P\bar{1}$; $a=9.458(4)$ Å, $b=11.360(2)$ Å, $c=8.710(3)$ Å, $\alpha=110.55(2)°$, $\beta=107.13(3)°$, $\gamma=86.71(2)°$; $V=836.2(5)$ Å^3; $D_{calc}=1.288$ g cm^{-1}; $Z=2$; $F(0\,0\,0)=340$.

The final positional parameters for non-hydrogen atoms are given in Table I. Dihedral angles between aromatic rings, of which the Least-squares planes are calculated by the Hamilton method,[9] are as follows: phenyl−isoindole=136.84°; phenyl−benzotriazole=108.06°; isoindole−benzotriazole=76.07°. Intermolecular distances between non-hydrogen atoms less than 3.6 Å are listed in Table II.[10]

Results and Discussion

Molecular Structure The bond lengths and angles of non-hydrogen atoms are shown in Fig. 1. The bond lengths of C–H are from 0.94 to 1.01 Å. Each of three planes defined by phenyl, isoindole, and benzotriazole groups was almost planar but deviated slightly (less than 0.01 Å) from the ideal planes. The bond lengths and angles in the benzotriazole moiety are compatible to those of 1-(1,2,3-1*H*-benzotriazole)-acetic acid[11] and those in the isoindole moiety show similar trends with the values reported for benzotriazole-2-acetic acid,[11b] indicating a cyclohexadienoid character of the latter ring.

The most remarkable feature of this molecule is its doubly twisted structure (Fig. 2). Three planes (phenyl, isoindole and benzotriazole rings) form dihedral angles to one another as 137°, 76° and 108°, so as to gain maximum steric relief between these groups. This doubly twisted structure assists the compact packing of the moelcules in a crystalline state, as shown below.

Crystal Structure In a unit cell of **1a** (Fig. 3), the molecules exist with *anti*-parallel face-to-face stacking between two isoindole moieties (related by an inversion center). The average distance between the two isoindole planes is 4.4 Å. Although there are several other intermolecular contacts less than 3.6 Å in the crystals (Table II), which may play a role in a compact molecular packing, they are not concerned with the distance of the reactive centers. The shortest distance between the reactive centers, C(8) and C(8′) or C(9′), in the crystal is 5.2 Å.

Explanation of the Stability of 1a in a Crystalline State The detailed polymerization mechanism of 2*H*-isoindoles has not yet been settled. In the related isobenzofuran system, a caged dimer has been proven as an intermediate of polymerization.[12] Therefore, it would be reasonable to assume that the reaction is initiated by a biradical creation at the 1- and 3-positions [C(8) and C(9) in the present work] and proceeds through an intermolecular coupling between them. Thus, the remarkable stability of **1a** in a crystalline state is attributable to the presence

TABLE II. Intermolecular Distances between Non-hydrogen Atoms Less than 3.60 Å (e.s.d. Values in Parentheses)

Original molecule	Another molecule	Molecular code[a]	Length (Å)
N(1)	C(6)	A	3.477 (2)
N(1)	C(5)	A	3.555 (3)
N(4)	C(13)	C	3.437 (3)
N(4)	C(14)	C	3.453 (3)
C(1)	C(8)	B	3.530 (3)
C(2)	C(6)	A	3.545 (3)
C(3)	C(11)	B	3.443 (3)
C(5)	C(9)	A	3.594 (3)
C(6)	C(6)	A	3.233 (3)
C(6)	C(21)	B	3.512 (3)
C(8)	C(12)	D	3.596 (3)
C(12)	C(12)	D	3.387 (4)
C(20)	C(20)	E	3.450 (5)

a) When the coordinates of the original molecule are defined as (x, y, z), molecules A, B, C, D, and E correspond to the coordinates of $(2a-x, b-y, c-z)$, $(x-a, y, z)$, $(2a-x, b-y, -z)$, $(3a-x, b-y, c-z)$, and $(2a-x, 2b-y, -z)$, respectively.

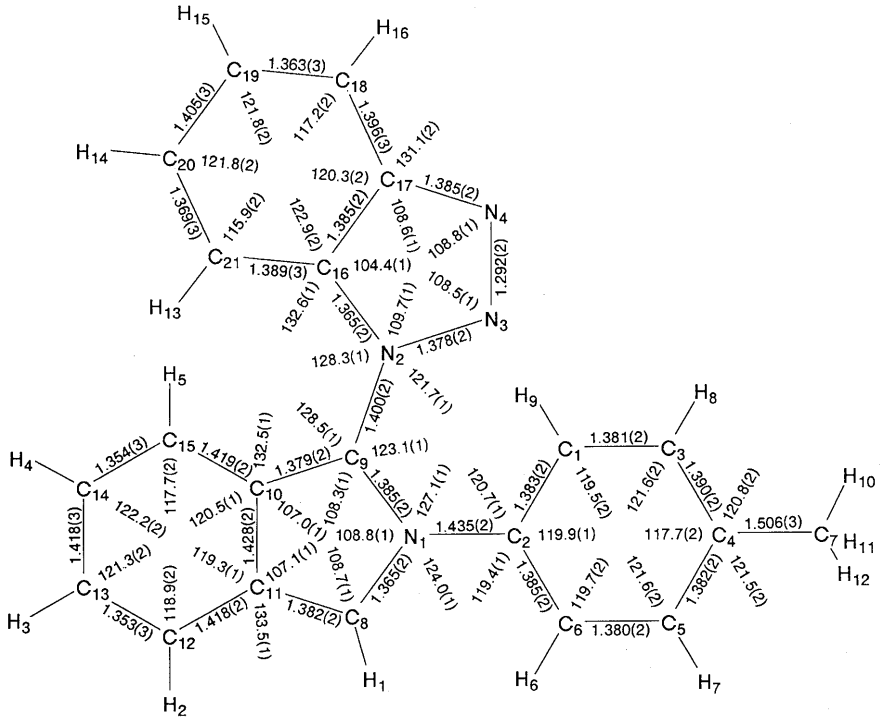

Fig. 1. The Bond Lengths and Angles for Non-hydrogen Atoms of **1a**

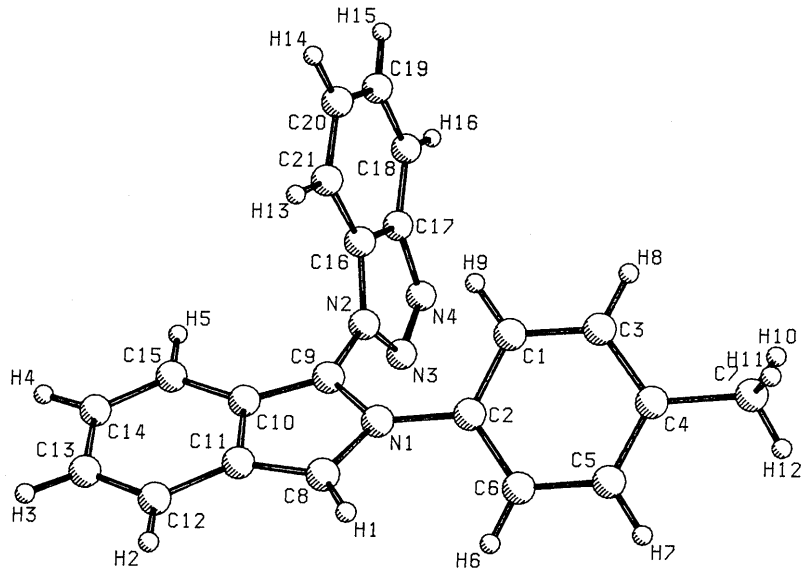

Fig. 2. The ORTEP Drawing of **1a**

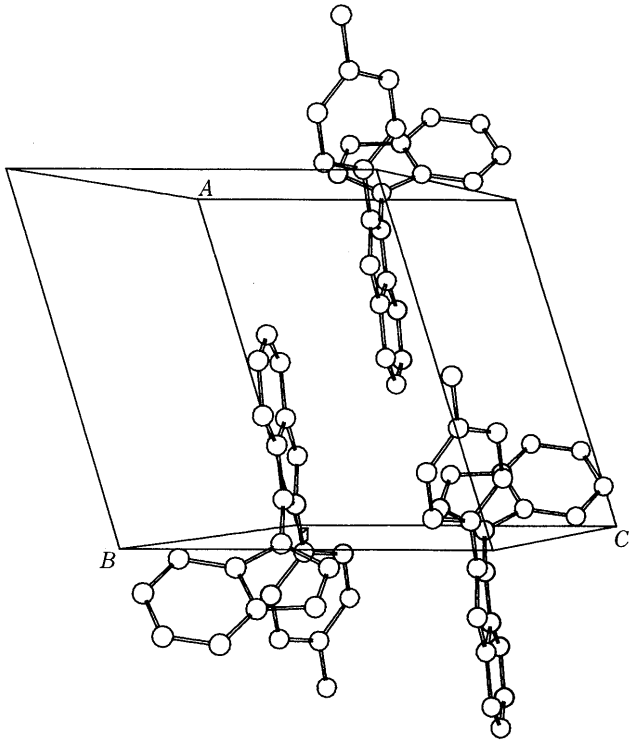

Fig. 3. Packing of **1a** in a Unit Cell

of *anti*-parallel isoindole-isoindole stacking. This effect enforces two reactive centers in two molecules, preventing them from approaching each other (>5.2 Å), thus preventing the new C–C bond formation, and therefore, the polymerization. On the other hand, in solutions, a random array of the molecules would bring two reactive centers close enough for the bond formation. As a support for this consideration, **1a** in a non-crystalline solid state[13] was found to undergo partial polymerization[7] in a few weeks at room temperature under room light.

The mono-substituted isoindoles (**1b** and **2**) were also preparable with moderate yields[6b] in a manner similar to **1a**, and they were also stable in crystalline states. The reason for the stability of these compounds would also be explained as mentioned above.

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References and Notes

1) Deceased December 25, 1991.
2) F. Kubota, Japan Kokai Tokkyo Koho, JP 02263824, 02263825 (1990) [*Chem. Abstr.*, **115**, 20292*t*, 20293*u* (1991)].
3) J. Moursounidis, D. Wege, *Aust. J. Chem.*, **41**, 235 (1988).
4) *a*) A. R. Katritzky, "Handbook of Heterocyclic Chemistry," Pergamon Press, Oxford, 1985, Chapter 3.3; *b*) M. P. Carmody, M. J. Cook, N. L. Dassanayake, A. R. Katritzky, P. Linda, R. D. Tack, *Tetrahedron*, **32**, 1767 (1976).
5) *a*) R. P. Kreher, N. Kohl, *Angew. Chem., Int. Ed. Engl.*, **23**, 517 (1984); G. Simig, *Synlett.*, **1990**, 425; *b*) A. M. El-Khawaga, M. R. Hoffmann, *ibid.*, **1990**, 519. See also: Y. Watanabe, S. C. Shim, H. Uchida, T. Mitsudo, Y. Takegami, *Tetrahedron*, **35**, 1433 (1979).
6) *a*) I. Takahashi, M. Tsuzuki, H. Kitajima, *Chem. Express*, **7**, 701 (1992); *b*) I. Takahashi, M. Tsuzuki, H. Yokota, H. Kitajima, S. Hosoi, Y. Tsuda, unpublished work.
7) Formation of polymeric materials was ascertained by the broad signals at δ 7.0—6.0 and 2.2—1.8 in the ^{1}H-NMR spectra ($CDCl_3$/TMS).
8) C. J. Gilmore, *J. Appl. Cryst.*, **17**, 42 (1984).
9) J. A. Ibers, W. C. Hamilton, *Acta Cryst.*, **17**, 781 (1964).
10) Other tables such as "$F_O - F_C$" and "U_{ij} matrix" are available upon request.
11) *a*) F. Giordano, A. Zagari, *Acta Cryst.*, **B33**, 1288 (1977); *b*) *Idem*, *J. Chem. Soc., Perkin Trans. 2*, **1978**, 312. See also: A. R. Katritzky, F.-B. Ji, W.-Q. Fan, J. K. Gallos, J. V. Greenhill, R. W. King, *J. Org. Chem.*, **57**, 190 (1992).
12) p. 269 of reference 5*a*.
13) Deposited solid in a 2-week reaction in acetonitrile. The ^{1}H-NMR spectrum in $CDCl_3$ was identical with that of **1a**.