CRYSTAL AND MOLECULAR STRUCTURES OF 2-AMINO-3-METHYLIMIDAZO-[4,5-*f*] QUINOLINE, A NOVEL POTENT MUTAGEN FOUND IN BROILED FOOD

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1. Introduction

Mutagenicity has been found in smoke condensates from broiling fish and beefsteak [1]. We have isolated two major active components from the neutral fraction of broiled sardines [2]. They are novel mutagens, and their structures have been characterized to be 2-amino-3-methylimidazo[4,5-*f*]-quinoline (IQ) and 2-amino-3,4-dimethylimidazo[4,5-*f*]quinoline (methyl-IQ) [2,3]. IQ has been chemically synthesized, and its mutagenic activity towards *Salmonella typhimurium* TA98 has been found to be even higher than aflatoxin B_1 (433 000 revertants/μg) [4]. A mutagen isolated from heated beef extract is identical to IQ [5]. IQ has also been found in hamburger [6]. Thus, it is likely that IQ is widely distributed in a variety of broiled foods. This finding leads one to consider the possibility of IQ causing human cancer, although the carcinogenicity of IQ is yet to be tested. As a basis for elucidating the mode of action of IQ on the molecular level, it is important to study the three-dimensional molecular structure of IQ. In this letter, we report on the crystal and molecular structures of IQ obtained by X-ray crystallography. The precise bond lengths and bond angles will be useful for studies on the interactions of DNA and IQ, as expected from the planar structure of this mutagen molecule.

2. Materials and methods

The sample of IQ was synthesized as described in [4]. The crystals were grown in an aqueous methanol solution as pale yellow bipyramid. The lattice constants and intensity data were collected on a Philips four-circle diffractometer. The intensities of 1882 reflections were obtained as above the 2σ (τ) level within the 2θ angle of 156°.

3. Results and discussion

The crystal data of IQ ($C_{11}H_{10}N_4$, M_r = 198.08) are: monoclinic system; a = 12.056(6) Å; b = 10.944(6) Å; c = 7.491(4) Å; β = 99.05(1)°; space group, $P2_1/a$; and Z = 4. The crystal structure was solved by the direct method utilizing the MULTAN program [7]. The atomic parameters were subjected to the block-diagonal least square refinement. Anisotropic thermal vibrations were assumed for the carbon and nitrogen atoms but isotropic thermal vibrations were assumed for the hydrogen atoms. The hydrogen atoms were located on the difference electron density map and their atomic parameters were also refined. The R-value was thus reduced to 0.057 for 1882 structure factors. The final values of atomic parameters and temperature factors are listed in table 1.

The skeletal molecular structure of IQ is shown in fig.1. The 6–6–5 membered ring system takes a planar conformation; any carbon or nitrogen atom deviates, by no larger than 0.028 Å, from the best-fit plane of 13 ring atoms. The bond lengths and bond angles are listed in table 2, together with standard deviations in parentheses. As for the quinoline moiety of IQ, the bond lengths and bond angles are much the same as those of quinoline and quinoline derivatives.

The crystal structure of IQ is shown in fig.2. Within a monoclinic unit cell, a pair of IQ molecules are

Table 1
Final atomic parameters

Atom	x	y	z	B_{eq}
N(1)	3631(1)	4285(1)	8850(2)	2.52(0.02)
C(2)	3774(1)	3692(2)	10430(2)	2.66(0.02)
N(2)	4609(2)	3876(2)	11818(2)	3.09(0.02)
N(3)	2936(1)	2859(1)	10532(2)	3.01(0.02)
C(3)	2822(2)	2078(2)	12055(3)	4.42(0.03)
C(4)	1213(2)	2283(2)	8300(3)	3.21(0.03)
C(5)	666(2)	2525(2)	6597(3)	2.82(0.03)
N(6)	501(2)	3574(2)	3778(3)	3.16(0.03)
C(7)	889(2)	4391(3)	2755(3)	4.14(0.04)
C(8)	1857(2)	5090(2)	3261(3)	4.58(0.03)
C(9)	2476(2)	4921(2)	4922(3)	3.54(0.03)
C(10)	2200(2)	2925(2)	8908(3)	2.76(0.02)
C(11)	1090(2)	3411(2)	5478(3)	2.70(0.02)
C(12)	2101(2)	4066(2)	6121(3)	2.64(0.02)
C(13)	2649(1)	3806(1)	7887(2)	2.49(0.02)
Atom	x	y	z	B
H(2A)	480(2)	322(2)	1252(3)	4.5(0.6)
H(2B)	513(2)	437(2)	1164(3)	4.0(0.5)
H(3A)	344(4)	153(4)	1227(6)	9.7(1.1)
H(3B)	277(3)	256(3)	1317(5)	7.2(0.8)
H(3C)	194(3)	203(2)	1213(4)	5.6(0.6)
H(4)	92(3)	179(3)	925(5)	7.2(0.9)
H(5)	-7(2)	205(2)	609(3)	4.1(0.5)
H(7)	48(3)	447(3)	154(5)	7.8(0.9)
H(8)	211(3)	564(3)	235(4)	6.1(0.7)
H(9)	322(2)	538(2)	524(3)	4.0(0.5)

Dimensionless coordinates of non-hydrogen atoms are multiplied by 10^4 and those of hydrogen atoms by 10^3. The values of B_{eq} and B are given in unit of Å^2

nearly coplanar and form two intermolecular hydrogen bonds, N(2)–H(2B) . . N(1). The N(2)H_2 group is also involved in another intermolecular hydrogen bond N(2)–H(2A) . . N(6). The hydrogen bond dis-

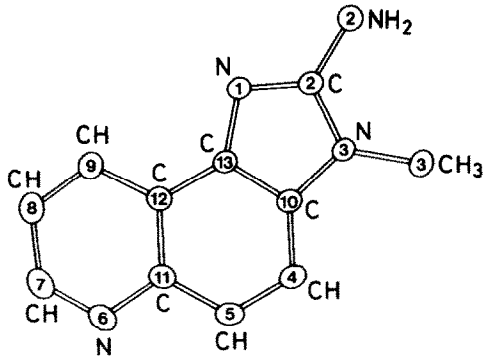

Fig.1. The skeletal molecular structure of IQ.

Table 2
Bond lengths (Å) and bond angles (°)

N(1)-C(2)	1.337(2)	C(2)-N(3)-C(3)	126.7(2)
C(2)-N(2)	1.344(2)	C(3)-N(3)-C(10)	126.3(2)
C(2)-N(3)	1.372(2)	C(10)-N(3)-C(2)	106.9(1)
N(3)-C(3)	1.450(3)	N(3)-C(10)-C(4)	130.8(2)
N(3)-C(10)	1.390(2)	C(4)-C(10)-C(13)	123.7(2)
C(10)-C(13)	1.392(3)	C(13)-C(10)-N(3)	105.5(2)
C(10)-C(4)	1.395(3)	C(10)-C(4)-C(5)	118.0(2)
C(4)-C(5)	1.366(3)	C(4)-C(5)-C(11)	121.0(2)
C(5)-C(11)	1.428(3)	C(5)-C(11)-N(6)	117.0(2)
C(11)-C(12)	1.432(3)	N(6)-C(11)-C(12)	122.5(2)
C(11)-N(6)	1.368(3)	C(12)-C(11)-C(5)	120.5(2)
N(6)-C(7)	1.311(4)	C(11)-N(6)-C(7)	116.9(2)
C(7)-C(8)	1.397(4)	N(6)-C(7)-C(8)	125.1(2)
C(8)-C(9)	1.360(3)	C(7)-C(8)-C(9)	119.2(2)
C(9)-C(12)	1.418(3)	C(8)-C(9)-C(12)	119.1(2)
C(12)-C(13)	1.412(2)	C(9)-C(12)-C(13)	125.3(2)
C(13)-N(1)	1.389(2)	C(13)-C(12)-C(11)	117.5(2)
C(13)-N(1)-C(2)	104.9(1)	C(11)-C(12)-C(9)	117.2(2)
N(1)-C(2)-N(2)	126.1(2)	C(12)-C(13)-N(1)	130.2(2)
N(2)-C(2)-N(3)	121.7(2)	N(1)-C(13)-C(10)	110.5(2)
N(3)-C(2)-N(1)	112.2(2)	C(10)-C(13)-C(12)	119.4(2)

tances and angles are: N(2) . . . . N(1) = 3.023 Å, H(2B) . . N(1) = 2.16 Å, ∠N(2)–H(2B) . . N(1) = 176°, N(2) . . . . N(6) = 3.163 Å, H(2A) . . N(6) = 2.28 Å and ∠N(2)–H(2A) . . N(6) = 166°. Van der Waals contacts are found between a methyl group and pyridine moiety of adjacent molecules. Only partial stacking is observed around the C(7)–N(6)–C(11) moiety of two adjacent IQ molecules.

A number of quinoline derivatives have been found to be mutagenic and carcinogenic [8–10]. However,

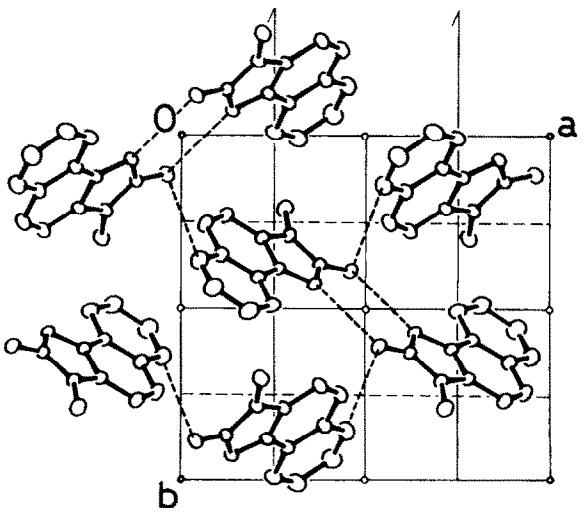

Fig.2. The projection of crystal structure along the c axis. Hydrogen bonds are shown with heavy broken lines.

the mutagenicity of IQ is by far stronger than the mutagenicity of those quinoline derivatives. The molecular mechanism of the potent mutagenicity of IQ is now being studied in our laboratory. However, most mutagens are known to form adducts with DNA and such reactions appear to be involved in mutagenesis [11]. Because of the planar skeletal structure (fig.1), the molecule of IQ is possibly intercalated between DNA bases, thus promoting the adduct-forming reactions between DNA and the final metabolite of IQ. The molecular structure (bond lengths and bond angles) of IQ as elucidated here will be the basis for some detailed quantum-theoretical studies on the electronic structure of IQ and also for model-building studies on the interactions between DNA and IQ molecules.

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References

[1] Nagao, M., Honda, M., Seino, Y., Yahagi, T. and Sugimura, T. (1977) Cancer Lett. 2, 221–226.
[2] Kasai, H., Yamaizumi, Z., Wakabayashi, K., Nagao, M., Sugimura, T., Yokoyama, S., Miyazawa, T., Spingarn, N. E., Weisburger, J. H. and Nishimura, S. (1980) Proc. Jap. Acad. 56B, 278–283.
[3] Kasai, H., Yamaizumi, Z., Wakabayashi, K., Nagao, M., Sugimura, T., Yokoyama, S., Miyazawa, T. and Nishimura, S. (1980) Chem. Lett. 11.
[4] Kasai, H., Nishimura, S., Wakabayashi, K., Nagao, M. and Sugimura, T. (1980) Proc. Jap. Acad. 56B, 382–384.
[5] Spingarn, N. E., Kasai, H., Vuolo, L. L., Nishimura, S., Yamaizumi, Z., Sugimura, T., Matsushima, T. and Weisburger, J. H. (1980) Cancer Lett. 9, 177–183.
[6] Wakabayashi, K., Nagao, M., Kawachi, T., Yamaizumi, Z., Shiomi, T., Kasai, H., Nishimura, S. and Sugimura, T. (1981) in preparation.
[7] Germain, G., Main, P. and Woolfson, M. M. (1971) Acta Cryst. A27, 368–376.
[8] Nagao, M., Yahagi, T., Seino, Y., Sugimura, T. and Ito, N. (1977) Mut. Res. 42, 335–342.
[9] Hollstein, M., Talcott, R. and Wei, E. (1978) J. Natl. Cancer Inst. 60, 405–410.
[10] Hirao, K., Shinohara, Y., Tsuda, H., Fukushima, S., Takahashi, M. and Ito, N. (1976) Cancer Res. 36, 329–335.
[11] Freese, E. (1971) in: Chemical Mutagens (Hollaender, A. ed) vol. 1, pp. 1–56, Plenum, New York.