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Structure of Rutin Pentamethanol

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The crystal structure of rutin, 3-[(6-*O*-(6-deoxy-α-L-mannopyranosyl)-β-D-glucopyranosyl)oxy]-2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-4*H*-1-benzopyran-4-one, has been determined by the X-ray diffraction method. The crystals are orthorhombic with $a=8.748(3)$, $b=23.567(10)$, $c=36.052(12)$ Å and the space group is $C222_1$. The final R value is 0.102 for 1789 observed reflections after full-matrix least-squares refinement. The dihedral angle between the benzopyran and the phenyl rings is 19.0(7)°, and the quercetin and the rutinose portions are linked together with the torsion angles of 114.1(18)° and 143.1(15)°, around the C(3)–O(3) and O(3)–C(1′) bonds, respectively. There are two kinds of intramolecular hydrogen bonds between the quercetin and glucose moieties. The structure–function relationship of the flavonoids involving rutin as inhibitors of aldose reductase is also discussed.

Keywords rutin; flavonoid; X-ray diffraction; structure–function relationship; aldose reductase inhibitor

Rutin, one of the typical glucoside in the flavonoids, consists of two porsions, quercetin and rutinose (D-glucose and L-rhamnose), as shown in Chart 1, and is widely distributed in natural plants, especially in the buckwheat plant (Fagopyrum esculentum Moench., Polygonaceae) which contains rutin amounting to about 3%(w/w) of the dried sample.[1]

Pharmacologically, rutin is characterized as a preventer capillary bleeding and fragility associated with scurvy.[2,3] Recently, biological activities of flavonoids including rutin as potent inhibitors of lens aldose reductase (potentially useful for prevention of diabetic cataracts) were reported.[4]

In this paper, we describe the three-dimensional structure of rutin determined by the X-ray diffraction method, and discuss how the activities as a potent inhibitor of enzymes are related to its molecular structure, based on a comparison with related compounds previously reported.[4]

Experimental

Single crystals suitable for X-ray diffraction experiments were grown by slow evaporation from methanol solution containing a small amount of water at 6 °C within one or two weeks. The intensity data were measured at 10 °C with a yellow needle crystal (0.6 × 0.3 × 0.08 mm) sealed in a 1.0 mm diameter glass capillary.

The crystal of rutin ($C_{27}H_{30}O_{16}\cdot 5CH_3OH$; $M_r=770.83$) is orthorhombic, and belongs to the space group $C222_1$, and the crystallographic data are: $a=8.748(3)$, $b=23.567(10)$, $c=36.052(12)$ Å, $V=7432(5)$ Å^3, $z=8$, $D_m=1.426(2)$, $D_c=1.378$ Mgm,$^{-3}$, $F(000)=3280$, $\mu(\text{Cu } K_\alpha)=0.956$ mm^{-1}.

Unit-cell parameters and the intensity data were measured on a Rigaku automatic four-circle diffractometer using Cu K_α radiation ($\lambda=1.5418$ Å) generated with Rigaku RU-300 rotating anode device. The lattice parameters were refined by the least-squares method to fit the measured 2θ value for 44 reflections in the range $30° < 2\theta < 40°$. The intensities were measured by using the ω–2θ scan technique, and intensity fluctuation was estimated by monitoring a standard reflection after every 100 reflections. A total of 2244 unique reflections with $2\theta < 120°$ (the maximum of $\sin\theta/\lambda$ is 0.56 Å^{-1}) were recorded, of which 1789 were above the 2σ (F_O) level, and they were used for structure determination. The intensities were corrected for Lorentz, polarization and absorption.[5]

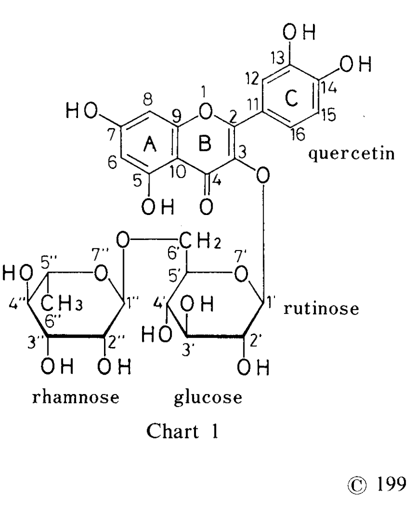

Chart 1

The structure was solved by direct methods using the program MULTAN 78.[6] The structure was refined by the full-matrix least-squares method with anisotropic thermal parameters for the non-hydrogen atoms except four disordered ones, the O(13-I) and O(13-II) in the rutin molecule and the O(6M) and C(6M) in the solvent molecule. The hydrogen atoms linked to carbon atoms were fixed at theoretical positions (C–H = 1.08 Å) with all the same isotropic temperature factor of 5.0 Å^2 and those joined to oxygen atoms were not considered, because of ambiguity in the direction of the hydrogen atom. The final refinement cycle reduced the R value to 0.102 ($R_w=0.095$) for the 1789 observed reflections. The function minimized is $\Sigma w(|F_O|-k|F_C|)^2$, where the weight w is given as $1/\sigma^2(F_O)$ and k is the scale factor. The highest residual in the final difference Fourier map is 0.16 eÅ^{-3}. The relatively high R value after the final refinement is due to the poor quality and large mosaic spread of the crystal, that may be caused by loss of solvent on exposure to air. All the numerical calculations using the UNICS programs[7] and RFINE[8] were carried out on an ACOS 930 computer at the Crystallographic Research Center, Institute for Protein Research, Osaka University. The atomic scattering factors cited in "International Tables for X-Ray Crystallography," (1974)[9] were used.

Results

The final positional and thermal parameters for non-hydrogen atoms are given in Table I.

Crystal Packing and Stacking Interactions The crystal packing in the unit cell is indicated by a stereo packing

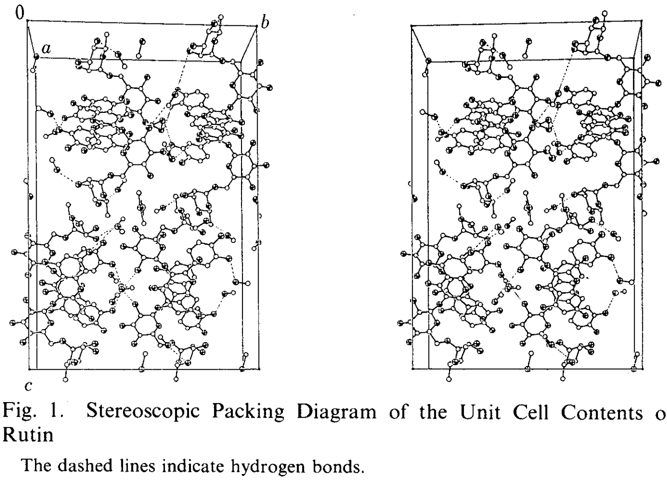

Fig. 1. Stereoscopic Packing Diagram of the Unit Cell Contents of Rutin

The dashed lines indicate hydrogen bonds.

TABLE I. Atomic Coordinates and Thermal Parameters of Non-hydrogen Atoms

Atom	x	y	z	B_{eq}/B_{iso} (Å^2)
O(1)	0.2777 (14)	0.7798 (5)	0.2389 (3)	5.3 (4)
C(2)	0.3538 (19)	0.8157 (8)	0.2150 (5)	4.7 (5)
C(3)	0.3469 (20)	0.8728 (8)	0.2194 (5)	5.1 (6)
O(3)	0.4305 (14)	0.9082 (5)	0.1977 (3)	5.7 (4)
C(4)	0.2631 (27)	0.8966 (8)	0.2510 (5)	6.5 (6)
O(4)	0.2621 (19)	0.9496 (5)	0.2573 (4)	7.1 (4)
C(5)	0.0849 (25)	0.8743 (9)	0.3052 (5)	6.3 (6)
O(5)	0.0861 (21)	0.9322 (7)	0.3120 (4)	9.6 (6)
C(6)	0.0081 (27)	0.8363 (11)	0.3266 (5)	8.4 (8)
C(7)	0.0222 (30)	0.7776 (12)	0.3168 (5)	10.4 (10)
O(7)	−0.0667 (18)	0.7383 (8)	0.3357 (4)	10.1 (6)
C(8)	0.1086 (24)	0.7539 (10)	0.2875 (4)	6.6 (7)
C(9)	0.1935 (22)	0.7990 (9)	0.2693 (4)	5.9 (6)
C(10)	0.1769 (24)	0.8569 (8)	0.2734 (5)	6.2 (6)
C(11)	0.4515 (20)	0.7775 (7)	0.1897 (4)	4.9 (5)
C(12)	0.4746 (20)	0.7227 (6)	0.1975 (5)	4.2 (5)
C(13)	0.5676 (30)	0.6908 (7)	0.1747 (6)	7.2 (7)
C(14)	0.6308 (23)	0.7127 (7)	0.1441 (4)	4.9 (5)
O(14)	0.7200 (16)	0.6776 (5)	0.1214 (3)	6.3 (4)
C(15)	0.6052 (24)	0.7669 (9)	0.1353 (5)	6.5 (7)
C(16)	0.5143 (23)	0.8044 (8)	0.1560 (5)	5.7 (6)
C(1′)	0.3327 (21)	0.9434 (6)	0.1739 (5)	5.2 (6)
C(2′)	0.4138 (25)	1.0008 (8)	0.1726 (6)	6.4 (6)
O(2′)	0.3900 (22)	1.0265 (6)	0.2089 (5)	10.1 (6)
C(3′)	0.3242 (24)	1.0363 (10)	0.1418 (6)	7.7 (7)
O(3′)	0.4007 (18)	1.0883 (5)	0.1396 (5)	9.2 (6)
C(4′)	0.3254 (21)	1.0052 (7)	0.1079 (6)	5.9 (6)
O(4′)	0.2419 (20)	1.0344 (6)	0.0801 (5)	9.3 (6)
C(5′)	0.2544 (21)	0.9447 (7)	0.1113 (5)	4.8 (5)
C(6′)	0.2696 (23)	0.9108 (8)	0.0760 (6)	6.3 (6)
O(7′)	0.3420 (15)	0.9150 (5)	0.1390 (3)	5.3 (4)
C(1″)	0.2388 (19)	0.8137 (7)	0.0592 (4)	4.3 (5)
O(1″)	0.1916 (14)	0.8580 (4)	0.0831 (3)	5.0 (4)
C(2″)	0.1523 (24)	0.7608 (7)	0.0717 (5)	5.4 (6)
O(2″)	0.2139 (17)	0.7128 (5)	0.0531 (3)	6.7 (4)
C(3″)	−0.0175 (22)	0.7662 (8)	0.0638 (5)	5.6 (6)
O(3″)	−0.0952 (17)	0.7146 (5)	0.0729 (3)	6.9 (4)
C(4″)	−0.0491 (23)	0.7863 (7)	0.0235 (4)	5.2 (5)
O(4″)	−0.2030 (14)	0.8009 (6)	0.0200 (3)	6.4 (4)
C(5″)	0.0595 (26)	0.8382 (8)	0.0138 (5)	6.3 (6)
C(6″)	0.0539 (25)	0.8444 (10)	−0.0301 (6)	7.5 (7)
O(7″)	0.2146 (13)	0.8257 (5)	0.0217 (3)	5.3 (4)
C(1M)	0.8270 (33)	0.9017 (12)	0.8839 (7)	10.5 (10)
O(1M)	0.7038 (24)	0.8840 (8)	0.9038 (5)	12.5 (8)
C(2M)	0.0360 (39)	0.4183 (13)	0.9866 (8)	13.6 (14)
O(2M)	−0.0817 (26)	0.3852 (8)	0.9696 (6)	13.2 (8)
C(3M)	0.7257 (37)	0.4235 (15)	0.4039 (8)	13.5 (13)
O(3M)	0.8188 (29)	0.3933 (11)	0.4287 (7)	17.0 (11)
C(4M)	0.8324 (39)	0.6166 (12)	0.2811 (7)	11.8 (12)
O(4M)	0.9328 (28)	0.6407 (8)	0.3036 (6)	15.0 (10)
C(5M)[c]	0. (0)	0.0472 (8)	0.2500 (0)	14.8 (11)
O(5M)	−0.0918 (62)	0.0945 (14)	0.2432 (14)	15.2 (24)
O(13-I)[b]	0.599 (3)	0.637 (1)	0.182 (6)	7.5 (6)[a]
O(13-II)[b]	0.643 (4)	0.785 (2)	0.103 (1)	7.9 (9)[a]
C(6M)[c]	0.428 (15)	0.489 (6)	0.048 (3)	31.0 (55)[a]
O(6M)[c]	0.461 (7)	0.506 (12)	0.001 (10)	27.4 (33)[a]

$$B_{eq}=4/3\sum_i\sum_j \beta_{ij}\boldsymbol{a}_i\boldsymbol{a}_j$$

a) Isotropic temperature factors. *b*) The occupancy ratio of O(13-I)/O(13-II)=6/4. *c*) The occupancy of each atom is 0.5.

TABLE II. Distances (Å) for Hydrogen Bonds

Intramolecular hydrogen bonds			
O(4)···O(2′)			2.75 (2)
O(4)···O(5)			2.54 (2)
O(7′)···C(16) [O(7′)···H(4)]		3.07 (2)	[2.08 (1)]
Intermolecular hydrogen bonds			
O(14)···O(3′)	($x+1/2$ $y-1/2$ z)		2.71 (2)
O(14)···O(3″)	($x+1$ y z)		2.54 (2)
O(2″)···O(4″)	($x+1/2$ $-y+3/2$ $-z$)		2.75 (2)
Hydrogen bonds for molecules with solvents			
O(1M)···O(2″)	($x+1/2$ $-y+3/2$ $-z+1$)		2.76 (2)
O(1M)···O(3′)	(x $-y+2$ $-z+1$)		3.15 (3)
O(2M)···O(7″)	($x-1/2$ $y-1/2$ $z+1$)		2.94 (2)
O(2M)···O(4′)	($x-1/2$ $-y+3/2$ $-z+1$)		3.03 (3)
O(2M)···O(3″)	(x $-y+1$ $-z+1$)		2.81 (2)
O(3M)···O(4″)	($-x+1/2$ $y-1/2$ $-z+1/2$)		3.03 (3)
O(3M)···O(13-II)	($-x+3/2$ $y-1/2$ $-z+1/2$)		2.82 (4)
O(4M)···O(3′)	($-x+3/2$ $y-1/2$ $-z+1/2$)		2.80 (3)
O(4M)···O(7)	($x+1$ y z)		2.58 (3)
O(5M)···O(13-I)	($x-1/2$ $y-1/2$ z)		2.94 (5)
O(5M)···O(13-I)	($-x+1/2$ $y-1/2$ $-z+1/2$)		2.87 (5)

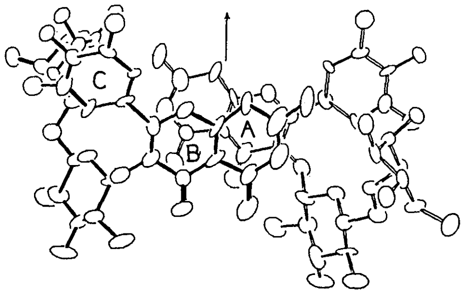

Fig. 2. The Stacking Mode between the A–B Rings of Rutin Molecules Projected to the Lower Fused Ring Plane

The arrow indicates the two-fold axis.

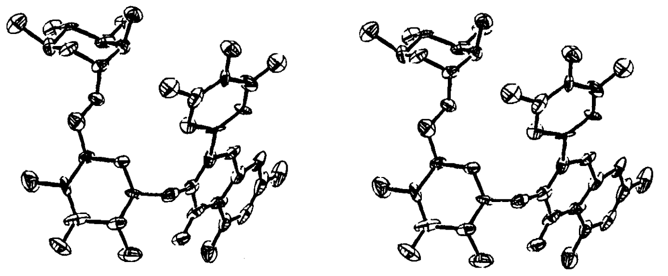

Fig. 3. Stereoview of the Molecular Conformation of Rutin

diagram[10)] in Fig. 1. The methanol molecules as solvents occupy the spaces between the rutin molecules and participate in some hydrogen bondings with the rutin molecules as shown in Table II, except for one methanol molecule situated near the crystal origin. The crystals are labile when exposed to air, probably because the methanol molecule near the origin is so loosely bound that it may be easily liberated from the crystal. All hydroxyl groups of rutin molecules also participate in hydrogen bonds as shown in Table II. There are three intermolecular hydrogen bonds between the rutin molecules. The characteristic feature of the crystal packing is the stacking between the A–B rings of the rutin molecules related by the two-fold symmetry axis with a separation of about 3.5 Å and a dihedral angle of 9.5(3)° as shown in Fig. 2. Such stacking interaction was also found in the crystal structures of some related flavonoids.[11)]

Molecular Conformation The molecular conformation of rutin is shown in a stereographic drawing in Fig. 3. Bond lengths and angles are listed in Tables III and IV, re-

Table III. Bond Lengths (Å) for the Non-hydrogen Atoms

O(1)–C(2)	1.378 (20)	C(15)–C(16)	1.405 (27)
O(1)–C(9)	1.396 (21)	C(1′)–C(2′)	1.527 (27)
C(2)–C(3)	1.355 (24)	C(1′)–O(7′)	1.427 (21)
C(2)–C(11)	1.541 (24)	C(2′)–O(2′)	1.458 (26)
C(3)–O(3)	1.359 (21)	C(2′)–C(3′)	1.596 (30)
C(3)–C(4)	1.467 (27)	C(3′)–O(3′)	1.400 (27)
O(3)–C(1′)	1.469 (21)	C(3′)–C(4′)	1.425 (29)
C(4)–O(4)	1.268 (25)	C(4′)–O(4′)	1.418 (24)
C(4)–C(10)	1.448 (28)	C(4′)–C(5′)	1.561 (25)
C(5)–O(5)	1.386 (25)	C(5′)–C(6′)	1.509 (26)
C(5)–C(6)	1.361 (30)	C(5′)–O(7′)	1.439 (21)
C(5)–C(10)	1.459 (27)	C(6′)–O(1″)	1.443 (23)
C(6)–C(7)	1.432 (34)	C(1″)–O(1″)	1.415 (20)
C(7)–O(7)	1.387 (30)	C(1″)–C(2″)	1.526 (24)
C(7)–C(8)	1.415 (32)	C(2″)–O(2″)	1.419 (22)
C(8)–C(9)	1.453 (27)	C(2″)–C(3″)	1.518 (26)
C(9)–C(10)	1.381 (26)	C(3″)–O(3″)	1.432 (23)
C(11)–C(12)	1.338 (23)	C(3″)–C(4″)	1.551 (25)
C(11)–C(16)	1.476 (25)	C(4″)–O(4″)	1.396 (22)
C(12)–C(13)	1.380 (26)	C(4″)–C(5″)	1.587 (26)
C(13)–O(13-I)	1.332 (31)	C(5″)–C(6″)	1.589 (29)
C(13)–C(14)	1.336 (27)	C(5″)–O(7″)	1.417 (23)
C(14)–O(14)	1.402 (21)	O(7″)–C(1″)	1.396 (20)
C(14)–C(15)	1.334 (26)	C(15)–O(13-II)	1.289 (41)

Table IV. Bond Angles (°) for the Non-hydrogen Atoms

C(2)–O(1)–C(9)	123.1 (13)	C(16)–C(15)–O(13-II)	115.2 (23)
O(1)–C(2)–C(3)	121.0 (15)	C(11)–C(16)–C(15)	112.1 (16)
O(1)–C(2)–C(11)	106.1 (13)	O(3)–C(1′)–C(2′)	104.2 (14)
C(3)–C(2)–C(11)	132.4 (16)	O(3)–C(1′)–O(7′)	102.6 (13)
C(2)–C(3)–O(3)	121.3 (16)	C(2′)–C(1′)–O(7′)	111.3 (14)
C(2)–C(3)–C(4)	119.6 (16)	C(1′)–C(2′)–O(2′)	106.0 (16)
O(3)–C(3)–C(4)	118.7 (16)	C(1′)–C(2′)–C(3′)	104.8 (16)
C(3)–O(3)–C(1′)	111.8 (13)	O(2′)–C(2′)–C(3′)	109.7 (16)
C(3)–C(4)–O(4)	121.3 (18)	C(2′)–C(3′)–O(3′)	105.4 (17)
C(3)–C(4)–C(10)	116.4 (17)	C(2′)–C(3′)–C(4′)	109.0 (17)
O(4)–C(4)–C(10)	122.3 (18)	O(3′)–C(3′)–C(4′)	113.4 (18)
O(5)–C(5)–C(6)	123.4 (18)	C(3′)–C(4′)–O(4′)	110.7 (16)
O(5)–C(5)–C(10)	114.4 (17)	C(3′)–C(4′)–C(5′)	113.5 (16)
C(6)–C(5)–C(10)	122.2 (18)	O(4′)–C(4′)–C(5′)	107.1 (15)
C(5)–C(6)–C(7)	117.0 (20)	C(4′)–C(5′)–C(6′)	112.5 (15)
C(6)–C(7)–O(7)	118.4 (21)	C(4′)–C(5′)–O(7′)	106.7 (13)
C(6)–C(7)–C(8)	127.7 (22)	C(6′)–C(5′)–O(7′)	106.3 (14)
O(7)–C(7)–C(8)	113.7 (20)	C(5′)–C(6′)–O(1″)	105.4 (15)
C(7)–C(8)–C(9)	108.8 (18)	C(1′)–O(7′)–C(5′)	110.7 (12)
O(1)–C(9)–C(8)	112.9 (15)	O(1″)–C(1″)–C(2″)	106.2 (13)
O(1)–C(9)–C(10)	117.3 (16)	O(1″)–C(1″)–O(7″)	113.3 (13)
C(8)–C(9)–C(10)	128.3 (17)	C(2″)–C(1″)–O(7″)	112.1 (13)
C(4)–C(10)–C(5)	122.9 (17)	C(6′)–O(1″)–C(1″)	113.0 (13)
C(4)–C(10)–C(9)	121.7 (17)	C(1″)–C(2″)–O(2″)	108.9 (14)
C(5)–C(10)–C(9)	114.9 (17)	C(1″)–C(2″)–C(3″)	111.2 (15)
C(2)–C(11)–C(12)	121.6 (15)	O(2″)–C(2″)–C(3″)	110.5 (15)
C(2)–C(11)–C(16)	116.3 (14)	C(2″)–C(3″)–O(3″)	110.5 (15)
C(12)–C(11)–C(16)	122.1 (15)	C(2″)–C(3″)–C(4″)	112.0 (15)
C(11)–C(12)–C(13)	119.3 (16)	O(3″)–C(3″)–C(4″)	113.1 (14)
C(12)–C(13)–C(14)	121.7 (18)	C(3″)–C(4″)–O(4″)	109.4 (14)
C(12)–C(13)–O(13-I)	121.6 (20)	C(3″)–C(4″)–C(5″)	109.7 (14)
C(14)–C(13)–O(13-I)	116.7 (20)	O(4″)–C(4″)–C(5″)	111.5 (14)
C(13)–C(14)–O(14)	118.9 (16)	C(4″)–C(5″)–C(6″)	105.9 (15)
C(13)–C(14)–C(15)	119.8 (18)	C(4″)–C(5″)–O(7″)	111.6 (15)
O(14)–C(14)–C(15)	121.3 (16)	C(6″)–C(5″)–O(7″)	104.4 (15)
C(14)–C(15)–C(16)	124.9 (18)	C(1″)–O(7″)–C(5″)	112.4 (13)
C(14)–C(15)–O(13-II)	118.9 (23)		

Table V. Selected Torsional Angles (°)

Jointed portions	
O(1)–C(2)–C(11)–C(12)	−12.9 (91)
O(1)–C(2)–C(11)–C(16)	165.5 (14)
C(3)–C(2)–C(11)–C(16)	−22.7 (27)
C(3)–C(2)–C(11)–C(12)	158.9 (19)
C(2)–C(3)–O(3)–C(1′)	114.1 (18)
C(4)–C(3)–O(3)–C(1′)	−73.6 (19)
C(3)–O(3)–C(1′)–C(2′)	143.1 (15)
C(3)–O(3)–C(1′)–O(7′)	−100.7 (15)
C(5′)–C(6′)–O(1″)–C(1″)	−158.6 (13)
C(4′)–C(5′)–C(6′)–O(1″)	−176.9 (14)
O(7′)–C(5′)–C(6′)–O(1′)	66.8 (16)
C(2″)–C(1″)–O(1″)–C(6′)	177.1 (14)
O(7″)–C(1″)–O(1″)–C(6″)	−59.5 (17)
Glucose moiety	
C(1′)–C(2′)–C(3′)–C(4′)	−56.1 (20)
C(2′)–C(3′)–C(4′)–C(5′)	57.3 (21)
C(3′)–C(4′)–C(5′)–O(7′)	−58.7 (20)
C(4′)–C(5′)–O(7′)–C(1′)	60.7 (16)
C(5′)–O(7′)–C(1′)–C(2′)	−67.6 (17)
O(7′)–C(1′)–C(2′)–C(3′)	61.2 (18)
Average	60.3
Rhamnose moiety	
C(1″)–C(2″)–C(3″)–C(4″)	48.4 (20)
C(2″)–C(3″)–C(4″)–C(5″)	−46.0 (19)
C(3″)–C(4″)–C(5″)–O(7″)	51.4 (19)
C(4″)–C(5″)–O(7″)–C(1″)	−60.7 (18)
C(5″)–O(7″)–C(1″)–C(2″)	63.0 (18)
O(7″)–C(1″)–C(2″)–C(3″)	−56.0 (19)
Average	54.3

spectively. The torsion angles connecting four parts of the rutin molecule, rings A and B, ring C, the glucose moiety and the rhamnose moiety, are listed in Table V.

The A, B and C rings of the quercetin moiety are essentially planar; the maximum deviations from the best A, B and C planes are 0.09(2) Å for the C(10) atom, 0.05(2) Å for the C(10) atom and 0.02(2) Å for the C(11) atom. The dihedral angle between the benzopyran and phenyl rings is 19.0(7)° and that between the A and B rings is 4.8(5)°. The dihedral angles between the A and C rings found in related quercetin compounds[11–13] are within the range of 0° to 45°, and the most frequently observed value is about 20°. This dihedral angle is affected by substituent groups at the C(3) position and stacking interactions tend to produce a smaller dihedral angle between rings A and C, as previously pointed out.[13] Ring C takes a disordered structure, that is, two orientations with the occupancy ratio of O(13-I)/O(13-II) = 6/4 are possible by rotation of the ring around the C(2)–C(11) bond.

The quercetin and glucose moieties are linked by the C(3)–O(3) bond with the torsion angle [C(2)–C(3)–O(3)–C(1′)] of 114.1(18)° and by the O(3)–C(1′) bond with the torsion angle [C(3)–O(3)–C(1′)–C(2′)] of 143.1(15)°, respectively. There are two intramolecular hydrogen bonds between the quercetin and the glucose moieties, one between the carbonyl O(4) at the B ring and hydroxyl group H-O(2′) in the glucose, the other between the hydrogen of the C(16) at the C ring and the oxygen O(7′) in the glucose, which may define and fix the mutual orientations of the quercetin and the glucose moieties. There is also an intramolecular hydrogen bond between the A ring and the B ring, that is, between the carbonyl O(4) at the B ring and the hydroxyl group O(5) at the A ring. These kinds of intramolecular hydrogen bonds [O(4)···O(2′) and O(4)···O(5)] are also found in the reported crystal structure of helichrysoside, a flavonoid glycoside.[14]

The glucose and rhamnose moieties are joined by the C(6′)–O(1′′) bond with nearly trans conformation (torsion angle [C(5)–C(6)–O(1′′)–C(1′′)]: $-158.6(13)^\circ$). The endocyclic torsion angles in the glucose and the rhamnose rings are in good agreement with those previously reported.[15,16)]

From these results, the conformation of rutin appears to be quite rigid because of the two intramolecular hydrogen bonds between O(4) and O(2′) and between C(16) and O(7′) atoms.

Structure–Function Relationship of Rutin Flavonoids including rutin have a striking inhibitory action on lens aldose reductase, the inhibitors of aldose reductase are potentially clinically useful because cataract formation in diabetes is triggered by the accumulation of excessive sorbitol or dulcitol in the lens, synthesized by the action of aldose reductase on glucose and galactose. Varma and Kinoshita[4)] presented extensive studies conducted in search of aldose reductase inhibitors of sufficient potency for the treatment of diabetic cataracts. According to their results, the aglycone of flavonoids, 3-hydroxyflavone (quercetin) has quite a high inhibitory potency. Its molecular structure is nearly flat and the two ring portions are almost coplanar.[13)] Therefore, the mutual orientations of the five hydroxyl groups attached to the 3,5,7,13 and 14-positions of the aglycone and the carbonyl group at the 4-position of the B ring are spatially fixed and probably fit the pocket of the active site in the enzyme. On the other hand, the glycoside portions of the flavonoids are important for strengthening the inhibitory activity. The flavonoids glycosylated at 3-OH of ring B are also potent inhibitors, whereas 7-O-glycosylation of the ring A leads to a decrease of the inhibitory activity. The dihedral angle between the A and C rings in rutin is slightly larger than that of quercetin,[13)] but the overall conformation of the quercetin moiety is flat. Thus rutin and quercetin probably have similar inhibitory activities. The rutin molecule has two intramolecular hydrogen bonds formed between the quercetin and glucose moieties which may fix the orientation of the glycoside portion relative to the aglycone plane. This conformation is somewhat different from that of quercitrin, the most potent inhibitor,[4)] which has L-rhamnose at the 3-O-glycosylation site.

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