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N-(*p*-Tolyl)-amine-1-D-fructose from a Small Crystal

D. Gomez de Anderez,[a]* H. Gil,[a] M. Helliwell[b] and J. Mata Segreda[c]

[a]*Departamento de Quimica, Facultad de Ciencias, Universidad de Los Andes, Merida 5101, Venezuela,* [b]*Department of Chemistry, University of Manchester, Manchester, M13 9PL, England, and* [c]*Departamento de Quimica, Universidad de Costa Rica, 2060 San Jose, Costa Rica*

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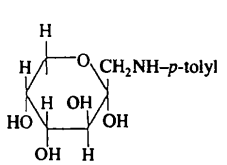
Abstract

Non-enzymatic glycation (reaction of an amino group with a sugar) is the first step in a complex, poorly understood, series of Maillard reactions. The reaction can also serve as a model for the general non-enzymatic processing of proteins. The structure of the title compound, $C_{13}H_{19}NO_5$, is a model for the product in such a process. Despite the small volume of the crystal, the use of a Cu $K\alpha$ rotating-anode source allowed the collection of sufficient data to solve and refine the structure.

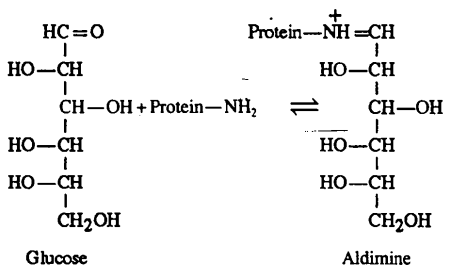
Comment

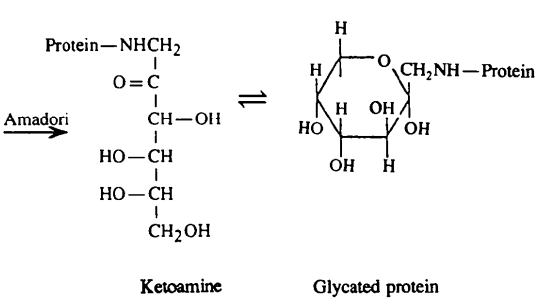
The title compound (1) is formed by a process like that occurring in the reaction of glucose with amino groups in proteins, which occurs non-enzymatically, *in vivo* (Cohen, 1986).



(1)

This intrinisically very slow process appears to be critical in the pathogenesis of various secondary complications associated with diabetes Mellitus (Cohen, 1986; Baynes, Thorpe & Murtiashaw, 1984; Lowrey, Lyness & Soeldner, 1985) and the process of aging (Monnier, Kohn & Cerami, 1984). Glycation is initiated by the condensation of the acyclic form of glucose with protein amino groups to yield a Schiff-base intermediate (aldimine). This aldimine can undergo the practically irreversible Amadori rearrangement to a stable ketoamine derivative, which then cyclizes to the hemiketal structure (Neglia, Cohen, Garber, Thorpe & Baynes, 1985). Although the Schiff-base and Amadori compounds of small organic amines are known to assume cyclic pyranose and furanose conformations in solution (Funcke & Klemer, 1976), relatively little is known about the structures which exist in proteins either *in vivo* or *in vitro*. ^{13}C NMR spectroscopy has been used to characterize Amadori ketoamine adducts formed by the reaction of glucose with amino groups of proteins (Neglia, Cohen, Garber, Thorpe & Baynes, 1985) and with small molecules (Neglia, Cohen, Garber, Ellis, Thorpe & Baynes, 1983). The pyranose form appears to be the predominant structure in solution.





Glycated proteins have been reported to undergo either conformational changes (Shaklai, Garlick & Bunn, 1984) and/or functional changes (Watkins, Thorpe & Baynes, 1987; Cerami, Vlassara & Browlee, 1987). Non-enzymatic glycation of a large polypeptide at a single site can have marked effects on both the conformation as well as the biological properties of the protein. In order to have a much clearer understanding, we have prepared (1) and performed an X-ray crystallographic analysis which can serve as a structural model for the product in the general non-enzymatic processing of proteins. A diagram showing the molecular structure of $C_{13}H_{19}NO_5$ is shown in Fig. 1. Short intermolecular distances between a number of atom pairs indicate hydrogen-bonding interactions between these pairs (Table 2).

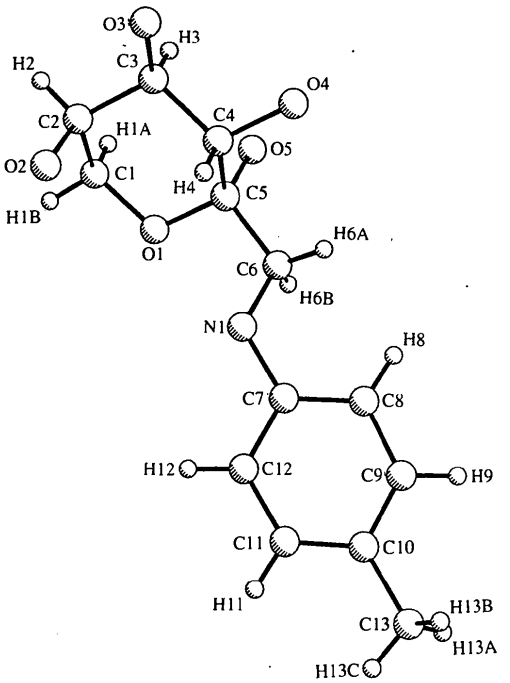


Fig. 1. A perspective view of the molecule showing the labelling of the atoms.

Experimental

(1) was synthesized by mixing 5 g of glucose, 4.2 g of *p*-toluidine and 1.7 g of water. To this was added 35 μl of glacial acetic acid. After heating for 30 min over a water bath, the mixture was cooled to room temperature. Very fine colourless needle crystals (m.p. 426–427 K) were obtained from hot ethanol.

Crystal data

$C_{13}H_{19}NO_5$
$M_r = 269.3$
Orthorhombic
$P2_12_12_1$
$a = 7.121\ (4)$ Å
$b = 35.583\ (7)$ Å
$c = 5.238\ (4)$ Å
$V = 1327\ (1)$ Å^3
$Z = 4$
$D_x = 1.347$ Mg m^{-3}
Cu $K\alpha$ radiation
$\lambda = 1.54178$ Å
Cell parameters from 19 reflections
$\theta = 15.16$–$24.66°$
$\mu = 0.825$ mm^{-1}
$T = 296$ K
Needle
$1.00 \times 0.07 \times 0.005$ mm
Colourless

Data collection

Rigaku AFC-5*R* diffractometer
$\omega/2\theta$ scans
Absorption correction: empirical, ψ scans (*TEXSAN*; Molecular Structure Corporation, 1985)
$T_{min} = 0.97$, $T_{max} = 1.00$
1221 measured reflections
1221 independent reflections
592 observed reflections $[I > 3\sigma(I)]$
$\theta_{max} = 60.05°$
$h = 0 \rightarrow 8$
$k = 0 \rightarrow 40$
$l = 0 \rightarrow 6$
3 standard reflections monitored every 150 reflections
intensity decay: none

Refinement

Refinement on F
$R = 0.091$
$wR = 0.095$
$S = 2.44$
592 reflections
127 parameters
$w = 4F_o^2/\sigma^2(F_o^2)$
$(\Delta/\sigma)_{max} = 0.06$
$\Delta\rho_{max} = 0.40$ e Å^{-3}
$\Delta\rho_{min} = -0.39$ e Å^{-3}
Extinction correction: none
Atomic scattering factors from Cromer & Waber (1974)

Table 1. *Fractional atomic coordinates and equivalent isotropic displacement parameters (Å^2)*

$B_{eq} = (8\pi^2/3)\Sigma_i\Sigma_j U_{ij} a_i^* a_j^* \mathbf{a}_i.\mathbf{a}_j.$

	x	y	z	B_{eq}
O(1)	1.105 (2)	0.1443 (3)	0.369 (2)	2.6 (5)
O(2)	1.367 (2)	0.1914 (3)	0.078 (2)	3.5 (6)
O(3)	1.171 (2)	0.2596 (3)	0.219 (2)	2.8 (5)
O(4)	0.806 (1)	0.2261 (3)	0.244 (2)	2.8 (5)
O(5)	0.883 (2)	0.1762 (3)	0.618 (2)	2.6 (5)
N(1)	0.866 (2)	0.1233 (3)	0.017 (3)	2.6 (3)
C(1)	1.266 (2)	0.1634 (4)	0.467 (3)	2.3 (8)
C(2)	1.312 (2)	0.1998 (4)	0.337 (3)	2.4 (9)
C(3)	1.143 (2)	0.2244 (4)	0.343 (3)	1.9 (7)
C(4)	0.973 (2)	0.2040 (5)	0.228 (4)	2.4 (4)
C(5)	0.940 (2)	0.1668 (4)	0.364 (3)	2.1 (8)
C(6)	0.794 (2)	0.1416 (4)	0.244 (3)	3.0 (8)
C(7)	0.747 (2)	0.0967 (4)	−0.103 (3)	2.2 (3)
C(8)	0.554 (2)	0.1002 (5)	−0.106 (4)	2.9 (4)
C(9)	0.448 (2)	0.0757 (5)	−0.259 (5)	4.2 (5)
C(10)	0.522 (3)	0.0473 (5)	−0.406 (4)	3.6 (4)
C(11)	0.711 (3)	0.0447 (5)	−0.400 (4)	4.9 (5)
C(12)	0.826 (2)	0.0686 (5)	−0.252 (4)	3.8 (4)
C(13)	0.402 (3)	0.0241 (5)	−0.580 (4)	6.5 (6)

Table 2. *Selected geometric parameters (Å, °)*

O(1)—C(5)	1.42 (2)	C(1)—C(2)	1.50 (2)
O(1)—C(1)	1.43 (2)	C(2)—C(3)	1.49 (2)
O(2)—C(2)	1.44 (2)	C(3)—C(4)	1.53 (2)
O(3)—C(3)	1.43 (1)	C(7)—C(8)	1.39 (2)
O(4)—C(4)	1.43 (2)	C(7)—C(12)	1.39 (2)
O(5)—C(5)	1.43 (2)	C(8)—C(9)	1.40 (2)
N(1)—C(6)	1.45 (2)	C(9)—C(10)	1.37 (3)
N(1)—C(7)	1.42 (2)	C(10)—C(11)	1.35 (2)
C(6)—C(5)	1.51 (2)	C(10)—C(13)	1.50 (3)
C(5)—C(4)	1.52 (2)	C(11)—C(12)	1.41 (2)
C(5)—O(1)—C(1)	114 (1)	C(2)—C(3)—C(4)	111 (1)
C(6)—N(1)—C(7)	117 (1)	O(4)—C(4)—C(5)	109 (1)
N(1)—C(6)—C(5)	111 (1)	O(4)—C(4)—C(3)	112 (1)
O(1)—C(5)—O(5)	110 (1)	C(5)—C(4)—C(3)	111 (1)
O(1)—C(5)—C(6)	104 (1)	N(1)—C(7)—C(8)	123 (2)
O(1)—C(5)—C(4)	112 (1)	N(1)—C(7)—C(12)	119 (1)
O(5)—C(5)—C(6)	109 (1)	C(8)—C(7)—C(12)	117 (2)
O(5)—C(5)—C(4)	106 (1)	C(7)—C(8)—C(9)	119 (2)
C(6)—C(5)—C(4)	115 (1)	C(8)—C(9)—C(10)	125 (2)
O(1)—C(1)—C(2)	115 (1)	C(9)—C(10)—C(11)	115 (2)
O(2)—C(2)—C(1)	108 (1)	C(9)—C(10)—C(13)	122 (2)
O(2)—C(2)—C(3)	111 (1)	C(11)—C(10)—C(13)	123 (2)
C(1)—C(2)—C(3)	109 (1)	C(10)—C(11)—C(12)	123 (2)
O(3)—C(3)—C(2)	113 (1)	C(7)—C(12)—C(11)	121 (2)
O(3)—C(3)—C(4)	110 (1)		

Table 3. *Contact distances (Å)*

O(2)···O(3^i)	3.18 (2)	O(3)···O(4^{ii})	3.01 (2)
O(3)···O(4^i)	2.66 (2)	O(5)···N(1^{iii})	2.81 (2)
O(3)···O(5^{ii})	2.87 (1)		

Symmetry codes: (i) $\frac{1}{2}+x, \frac{1}{2}-y, -z$; (ii) $\frac{1}{2}+x, \frac{1}{2}-y, 1-z$; (iii) $x, y, 1+z$.

The crystals were very fine, weakly scattering needles. The one selected for data analysis had a scattering efficiency of 194

$\times 10^{12}$ e^2 Å^{-3}. This is comparable with the study of a very small crystal of piperazine silicate whose scattering efficiency was 200 $\times 10^{12}$ e^2 Å^{-3} and which required a focused synchrotron radiation beam and electronic area detector for the data collection (Andrews *et al.*, 1988). However, in the piperazine silicate case the crystal mosaic spread was also very broad (approx 3°) compared with 0.6° here. Hence, the advantages of the high intensity and Cu $K\alpha$ wavelength of a laboratory rotating-anode diffractometer were adequate, compared with a laboratory sealed tube Mo $K\alpha$ diffractometer (Helliwell, Gallois, Kariuki, Kaucic & Helliwell, 1993), to obtain a data set sufficient to solve and refine the structure of this fructose deriviative. Obviously a much more intense synchrotron beam could be utilized to further improve the data-to-parameter ratio and will be the subject of a future study.

The structure was solved by direct methods. Due to the small crystal volume and rather poor quality, only the O atoms and five C atoms were refined anisotropically, the remaining non-H atoms being refined isotropically. H atoms attached to C atoms were placed in calculated positions which were updated after each refinement and assigned isotropic displacement parameters 20% greater than the B_{eq} value of the bonded atom. Those attached to the N and O atoms were not included. Full-matrix least-squares refinement of 127 parameters minimized the function $\Sigma w(|F_o| - |F_c|)^2$.

Data collection: *TEXSAN* (Molecular Structure Corporation, 1985). Cell refinement: *TEXSAN*. Data reduction: *TEXSAN*. Program(s) used to solve structure: *MITHRIL* (Gilmore, 1984); *DIRDIF* (Beurskens, 1984). Program(s) used to refine structure: *TEXSAN*. Molecular graphics: *PLUTO* (Motherwelll & Clegg, 1978). Software used to prepare material for publication: *TEXSAN*.

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Lists of structure factors, anisotropic displacement parameters, H-atom coordinates and complete geometry have been deposited with the IUCr (Reference: SZ1005). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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6-[1,2-(*Z*)-Bis(methoxycarbonyl)vinyl]-amino-5-dimethylamino-2-methoxy-3-methyl-4(3*H*)-pyrimidinone

JOHN N. LOW,[a] GEORGE FERGUSON,[b] JUSTO COBO,[c] MANUEL NOGUERAS[c] AND ADOLFO SÁNCHEZ[c]

[a]*Department of Applied Physics and Electronic & Mechanical Engineering, University of Dundee, Dundee DD1 4HN, Scotland,* [b]*Department of Chemistry and Biochemistry, University of Guelph, Guelph, Ontario, Canada N1G 2W1, and* [c]*Departamento de Química Inorgánica y Orgánica, Facultad de Ciencias Experimentales, Universidad de Jaén, 23071 Jaén, Spain*

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Abstract

The molecular conformation of the title compound, dimethyl (*Z*)-1-[5-dimethylamino-2-methoxy-3-methyl-4(3*H*)-oxo-6-pyrimidinylamino]ethylene-1,2-dicarboxylate, $C_{14}H_{20}N_4O_6$, in the solid state is determined by an intramolecular bifurcated hydrogen-bond system involving the H atom on the amino N6 atom and adjacent dimethylamino N5 and carbonyl O61 atoms [N6···N5 2.722 (2) and N6···O61 2.767 (2) Å].