ELSEVIER

Carbohydrate Research 264 (1994) 319–325

CARBOHYDRATE
RESEARCH

Note

Structure and taste of 4,4′,6,6′-tetrachloro-4,4′,6,6′-tetradeoxy-*α,α-galacto*-trehalose ☆

C.-Kuan Lee [a,*], Anthony Linden [b]

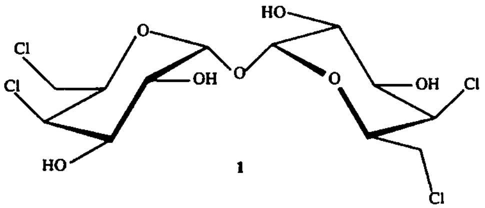
[a] *Department of Chemistry, National University of Singapore, Kent Ridge, Singapore 0511*
[b] *Organisch-Chemisches Institut, Universität Zürich, Winterthurerstrasse 190, CH-8057 Zürich, Switzerland*

Received 21 February 1994; accepted in final form 10 June 1994

Keywords: 4,4′,6,6′-Tetrachloro-4,4′,6,6′-tetradeoxy-*α,α-galacto*-trehalose; Chlorodeoxy sugars; Structure–taste relationship; Bitterness; Hydrophobicity

The discovery that selective halogenation of certain hydroxyl groups in sucrose could cause a dramatic increase in the sweetness of the sugar [1,2] was most remarkable. Until then, all of the halogenated analogues of carbohydrates that had been tested, including those of methyl α-D-hexopyranoside, maltose, lactose, and α,α-trehalose, not only failed to show any enhancement of sweetness, but they were all extremely bitter [3]. In order to understand this phenomenon, we were, therefore, interested in the X-ray structure of 4,4′,6,6′-tetrachloro-4,4′,6,6′-tetradeoxy-*α,α-galacto*-trehalose [4] (4,6-dichloro-4,6-dideoxy-α-D-galactopyranosyl 4,6-dichloro-4,6-dideoxy-α-D-galactopyranoside, **1**).

The structure of **1**, its atomic numbering, and crystal packing are shown in Figs. 1 and 2, respectively. These figures also depict the correct absolute configuration of the molecule as established by its synthesis. The atomic coordinates of the non-H atoms are given in Table 1. Bond lengths, bond angles, and selected torsion angles are given in Table 2.



1

☆ Crystal Structure of Trehalose Derivatives, Part 6. For Part 5, see Ref [1].

* Corresponding author.

SSDI 0008-6215(94)00204-S

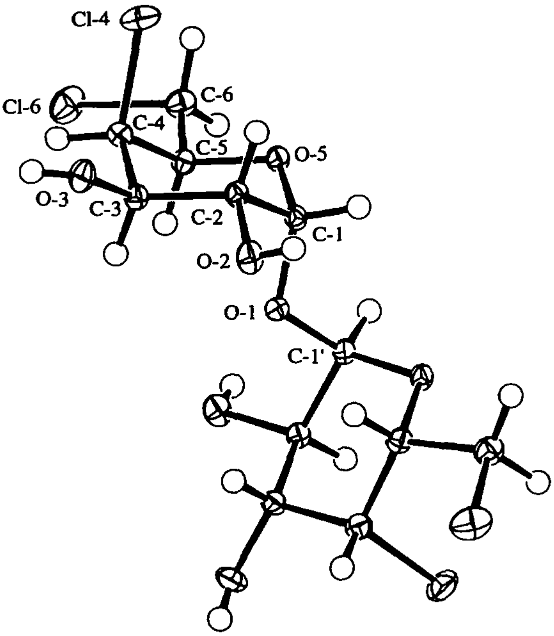


Fig. 1. ORTEP drawing of **1**.

The bond lengths and angles are normal, and generally agree with the corresponding values in other sugars. The C–O bond lengths associated with the anomeric carbon atoms and ring oxygen atoms also show similar systematic trends.

The two hexopyranosyl residues are exactly related by a two-fold axis through the O-1 atom. As is usually found for crystalline α-pyranosides [5] and α,α-trehalose [6], the conformation about the C-1–O-1 bond corresponds to the $A1$ conformer, in which the O-1–C-1′ bond is +*synclinal* to C-1–O-5 [77.3(1)°] and *antiperiplanar* to C-1–C-2 [161.0(1)°] (Table 2). In this conformation there is no interaction between the lone-pair electrons of the glycosidic oxygen and those of the ring oxygen [7] (exo-anomeric effect). The pyranose rings have very slightly distorted $^4C_1$ conformations, with puckering parameters [8], $Q=0.58$, $\theta=2.55°$, $\phi_2=228°$, $q_2=0.026$ Å, $q_3=0.580$ Å. The distortion is towards the ^4E conformation as indicated by the ϕ_2 value. The flattening of the oxygen apex allows the ring C–O–C angle to widen to 113.1(2)°, as observed in 4,4′-dideoxy-α,α-*xylo*-trehalose [9].

The conformation of the C-5 chloromethyl substituent is *trans–gauche*. This conformation is also reported [10] for methyl 4,6-dichloro-4,6-dideoxy-α-D-galactopyranoside, and is unlike that of the hydroxymethyl group of the 4-chlorodeoxygalactopyranosyl ring of the intensely sweet 4,1′,6′-trichloro-4,1′,6′-trideoxy-*galacto*-sucrose [2] and the majority of galactopyranosides, which is *gauche–trans* [11]. In α,α-trehalose dihydrate, the conformation of the C-5 substituent is *gauche–gauche* in one ring and *gauche–trans* in the other [6]. Both the *trans–gauche* and *gauche–trans* conformations for a galactosidic C-5–C-6 bond should be preferred over the *gauche–gauche* conformation, since, with the former, there will be no unfavorable 1–3 *peri* interaction, as in glucopyranosides, but a short C-6–X···C-4–Y contact would occur with the latter.

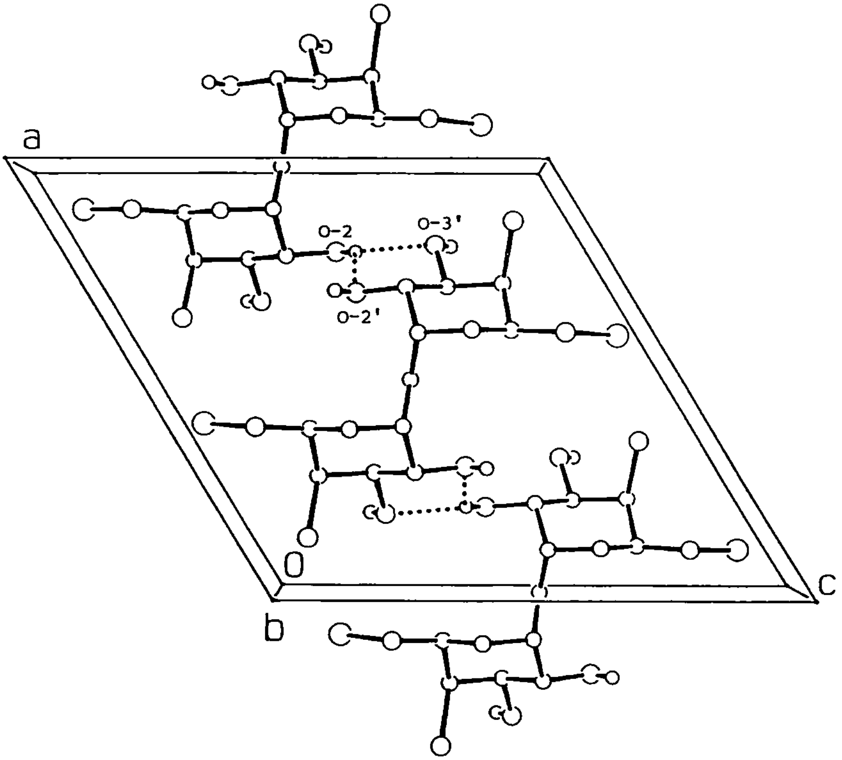


Fig. 2. Molecular packing of the crystal of 4,4',6,6'-tetrachloro-4,4',6,6'-tetradeoxy-α,α-*galacto*-trehalose viewed down the *b*-axis

Table 1
Fractional atomic coordinates and equivalent isotropic temperature factors (Å^2) with standard deviations in parentheses

Atom	x	y	z	U_{eq} [a]
Cl-4	0.14264(4)	0.0 [b]	0.13470(4)	0.0241(2)
Cl-6	0.39915(5)	−0.0709(2)	0.06852(4)	0.0283(2)
O-1	0.5	−0.0457(4)	0.5	0.0138(7)
O-2	0.3018(1)	−0.1863(3)	0.5041(1)	0.0191(6)
O-3	0.1874(1)	−0.4377(3)	0.2991(1)	0.0201(6)
O-5	0.3890(1)	0.1914(3)	0.3342(1)	0.0143(5)
C-1	0.3952(2)	0.0949(4)	0.4345(2)	0.0130(6)
C-2	0.2901(2)	−0.0765(4)	0.4043(1)	0.0137(6)
C-3	0.2861(2)	−0.2808(4)	0.3261(2)	0.0147(7)
C-4	0.2805(2)	−0.1681(4)	0.2203(2)	0.0156(7)
C-5	0.3881(2)	0.0014(4)	0.2596(1)	0.0145(6)
C-6	0.3935(2)	0.1420(5)	0.1657(2)	0.0186(8)

[a] U_{eq} is defined as one third of the trace of the orthogonalized U_{ij} tensor.
[b] Origin defined by fixing the y coordinate of Cl-4.

Table 2
Bond lengths (Å), bond angles (deg), and selected torsion angles (deg) with standard deviations in parentheses

Bond lengths (Å)			
Cl-6–C-6	1.785(2)	C-1–C-2	1.528(3)
O-1–C-1	1.411(2)	C-2–C-3	1.517(3)
O-2–C-2	1.418(2)	C-3–C-4	1.532(3)
O-3–C-3	1.427(2)	C-4–C-5	1.528(3)
O-5–C-1	1.427(2)	C-5–C-6	1.521(3)
Bond angles (deg)			
C-1–O-1–C-1′	114.8(2)	O-3–C-3–C-4	113.4(2)
C-1–O-5–C-5	113.1(2)	C-2–C-3–C-4	109.8(2)
O-1–C-1–O-5	110.9(1)	Cl-4–C-4–C-3	110.7(1)
O-1–C-1–C-2	106.8(2)	Cl-4–C-4–C-5	110.9(1)
O-5–C-1–C-2	111.5(1)	C-3–C-4–C-5	108.8(1)
O–2-C-2–C-1	111.1(1)	O-5–C-5–C-4	110.1(1)
O-2–C-2–C-3	108.4(2)	O-5–C-5–C-6	104.5(2)
C-1–C-2–C-3	109.3(1)	C-4–C-5–C-6	116.2(1)
O-3–C-3–C-2	108.2(2)	Cl-6–C-6–C-5	109.9(2)
Selected torsion angles (deg) Within the pyranose ring		Outside the pyranose ring	
O-5–C-1–C-2–C-3	55.9(2)	O-1–C-1–O-5–C-5	60.2(2)
C-1–C-2–C-3–C-4	−55.6(2)	O-1–C-1–C-2–C-31	−65.5(2)
C-2–C-3–C-4–C-5	57.2(2)	O-2–C-2–C-3–O-3	58.8(2)
C-3–C-4–C-5–O-5	−58.0(2)	O-3–C-3–C-4–Cl-4	56.2(2)
C-4–C-5–O-5–C-1	59.8(2)	O-5–C-5–C-6–Cl-6	177.7(1)
C-5–O-5–C-1–C-2	−58.8(2)	C-1–O-1–C-1′–O-5′	77.3(1)
		C-1–O-1–C-1′–C-2′	161.0(1)
		C-1–O-5–C-5–C-6	−174.7(1)
		C-2–C-3–C-4–Cl-4	−65.0(2)
		C-3–C-4–C-5–C-6	−176.5(2)
		C-4–C-5–C-6–Cl-6	−60.8(2)
		Cl-4–C-4–C-5–C-6	−54.6(2)
		Cl-4–C-4–C-5–O-5	63.9(2)

The molecules are held together by a simple network of very weak hydrogen bonds (Fig. 2), with the H···O distances all being rather long (Table 3). The hydrogen bonds link the molecules into infinite two-dimensional networks which lie parallel to the *xy*-plane. Each

Table 3
Hydrogen bonding in 4,4′,6,6′-tetrachloro-4,4′6,6′-tetradeoxy-α,α-*galacto*-trehalose (**1**)

Hydrogen bond	Symmetry operator[a]	Distance (Å)			Angle (deg)
		O–H	O···O	H···O	O–H···O
O-2–H···O-2′	[2,001]	0.78	3.001(2)	2.41	133
O-2–H···O-3′	[2,001]	0.78	2.938(2)	2.23	152
O-3′···H-12···O-2′					72.6

[a] Symmetry operators: (1) x, y, z; (2) $1/2-x$, $1/2+y$, $-z$

molecule is involved in 4 donor and 4 acceptor interactions. Each hydroxyl O-atom is an acceptor, while only the hydroxyl group at O-2 acts as a donor, the H-atom forming bifurcated hydrogen bonds.

The Shallenberger and Acree AH,B theory of sweetness [12] proposes that the sweet taste of a compound results from the interaction of an A–H···B moiety with a complementary glucophore at the receptor site. A third hydrophobic binding *γ* site [13], if present, determines the intensity of sweetness [14]. Unlike 4,6,1′,6′-tetrachloro-4,6,1′,6′-tetradeoxy-*galacto*-sucrose [2], which has a sweetness ca. 200 times that of sucrose [15], 4,4′,6,6′-tetrachloro-4,4′,6,6′-tetradeoxy-*α,α-galacto*-trehalose (**1**) is extremely bitter [3,16], even though it also possesses a 4,6-dichloro-4,6-dideoxy-*α*-D-galactopyranosyl moiety. The X-ray data of **1** shows that the only interatomic distances that can constitute an AH,B,*γ* glucophore are O-2···O-3, O-2···Cl-4, and O-3···Cl-4 (2.75, 4.46, and 3.10 Å, respectively). However, this will require OH-3 to function as AH of the tripartite glucophore. But O-3 has been shown [17,18] to function as B in $^4C_1$ pyranoid structures. There is, therefore, no sweet AH,B,*γ* glucophore present in **1**, and thus the absence of a sweet taste.

Taste studies of sugars and other organic compounds [3,14,16–19] have established that the sweet and bitter tastes are intimately associated, and chemical modification of sugars may alter the taste of sweet compounds so that the product is bitter-sweet or bitter. Kubota and Kubo [20] suggested that a very short A···B distance (<1.5 Å) (compared with ~3 Å for sweetness) is a requirement for bitterness. There is very little evidence to support this, and in bitter tasting sugar analogues [3,16–18], even in 3,6-anhydro-*α*-D-hexopyranose derivatives [21] with 1,3-diaxial hydroxyl groups, O···O distances shorter than 2.5 Å are not commonly encountered. Temussi et al. [22] recently suggested that, since simple amino acids and peptides can taste sweet only if their asymmetric *α*-carbon adjacent to the AH,B system has the D configuration, and change their taste quantitatively from sweet to bitter when the chirality of this carbon is changed (L), the change in taste may possibly be accounted for by simply inverting the AH,B entities of the receptors for sweet and bitter tastes via a binary operation. Based on this proposal, there is, therefore, a bitter glucophore in **1** which has the conformation that allows it to superposition on the receptor tripartite unit for bitterness, thus accounting for the bitterness. It is relevant to note that 4,6,1′,6′-tetrachloro-4,6,1′,6′-tetradeoxy-*galacto*-sucrose, while being considerably less sweet than 4,1′-dichloro-4,1′-dideoxy-*galacto*-sucrose (600 × sucrose) and 4,1′,6′-trichloro-4,1′,6′-trideoxy-*galacto*-sucrose (650 × sucrose) [15], also has a strong bitter aftertaste [23]. Furthermore, 6-chloro-6-deoxysucrose [15] and 6-chloro derivatives of D-glucose, D-galactose, and D-mannose [24], like **1**, are all also very bitter, therefore, implicating the importance of the C-6 substituent. Although these molecules possess a perfect AH,B entity (2-OH, 3-O), the increase in the hydrophobic character at C-6 and C-4 probably exerts a strong enough influence for the molecule to fit only the mirror-image bitter active site, as has been proposed [22] for 5,6-benzosaccharin. The dimensions for such a bitter AH,B,g glucophoric triangle in these sugars are O-2···O-3 (A···B) = ~2.75 Å and O-2···C-6, or Cl-6 (A···*γ*) = ~4.9–5.5 Å and O-3···C-6, or Cl-6 (B···*γ*) = ~5.6–6.7 Å. A 6-deoxy group probably functions likewise but the effect of the methyl group may be only such that 6-deoxy sugars can fit both receptor sites, resulting in these sugars having a sweet-bitter taste [17]. We are currently studying the taste of 4-halodeoxy pyranosides.

Table 4
Crystal data collection and refinement data for 4,4′,6,6′-tetrachloro-4,4′,6,6′-tetradeoxy-α,α-*galacto*-trehalose

Crystal data
$C_{12}H_{18}Cl_4O_7$; M_r 416.08; mp 229–230°C; monoclinic; space group C2 5); $Z = 2$
Cell dimensions at −100°C: $a = 13.102(4)$ Å, $b = 5.407(2)$ Å, $c = 13.631(1)$ Å, $\beta = 121.16°$
$V = 826.4\ (5)$ Å^3; D_{calcd} 1.672 g cm^{-3}; $\mu = 0.749$ mm^{-1}; $F(000) = 428$ e.
Crystal dimensions: 0.14 × 0.28 × 0.33 mm
Radiation: Mo$K\alpha$ ($\lambda = 0.71069$) graphite monochromator
Cell dimensions based on 23 carefully centred reflections in the range $39° < 2\theta < 40°$
Data collection
Rigaku AFC5R diffractometer
1373 reflections with $2\theta < 60°$ were measured by $\omega/2\theta$ scan technique of which 1321 were unique and 1286 were observed, $I > 3\sigma(I)$
Scan rate: 16° min^{-1} with up to 4 scans/reflection; scan width = $(1.37 + 0.35\tan\theta)°$
Standard reflections: 3 measured every 150 reflections, no decay
Corrections: Lorentz-polarisation, no absorption correction
Refinement
Function minimised, $\Sigma w(|F_o| - |F_c|)^2$, using TEXSAN [26] where $w^{-1} = \sigma^2(F_o) + (0.005F_o)^2$
Full matrix least-squares refinement using 1286 observed reflection and 134 variable parameters
Final agreement factors: $R = 0.023$, $R_w = 0.026$; goodness-of-fit = 1.928
$(\Delta/\sigma)_{max} = 0.004$; $\Delta\rho_{max} = 0.28$ e Å^{-3}
Atomic scattering factors and dispersion terms from [27]

1. Experimental

4,4′,6,6′-Tetrachloro-4,4′,6,6′-tetradeoxy-α,α-*galacto*-trehalose (**1**) was prepared by the method of Birch et al. [4]. Colourless prisms of **1** were grown by slow evaporation of an aqueous acetone solution at room temperature. The crystal data collection and refinement data are given in Table 4 [1].

The structure was solved by Patterson methods [25], which revealed the positions of the C-l atoms. All remaining non-hydrogen atoms were located in a Fourier expansion of the Patterson solution. The molecule possesses crystallographic C_2 symmetry through the bridging O-atom. The non-hydrogen atoms were refined anisotropically. All of the hydrogen atoms were placed in the positions indicated by a difference electron density map and, except for those of the hydroxyl groups, their positions were allowed to refine. Attempts to refine the positions of the hydroxyl H-atoms led to unreasonably short O–H distances. Individual isotropic temperature factors were refined for all of the hydrogen atoms. All calculations were performed using the TEXSAN [26] crystallographic package.

Acknowledgements

We thank the National University of Singapore for financial support and Miss I. Klingenfuss for technical assistance.

---

[1] Atomic coordinates and equivalent isotropic temperature factors, non-hydrogen atoms anisotropic temperature factors, eventual additional interatomic distances, bond angles, torsion angles, and observed and calculated structure factors for this structure have been deposited with the Cambridge Crystallographic Data Centre. The deposited materials may be obtained on request from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

References

[1] A. Linden and C.K. Lee, *Acta Crystallogr. Sect. C*, 50 (1994) 1108–1112.

[2] L. Hough and S.P. Phadnis, *Nature*, 263 (1976) 800.

[3] C.K. Lee, Ph.D. Thesis, University of Reading, UK, 1973; *Adv. Carbohydr. Chem. Biochem.*, 45 (1987) 199–351.

[4] G.G. Birch, C.K. Lee, and A.C. Richardson, *Carbohydr. Res.*, 36 (1974) 97–109.

[5] E.L. Eliel, *Svensk. Kem. Tidskr.*, 81 (1969) 22–27; A.J. de Hoog, H.R. Bus, C. Altona, and E. Havinga, *Tetrahedron*, 25 (1969) 3365–3375.

[6] G.M. Brown, D.C. Rohrer, B. Berking, C.A. Beevers, R.O. Gould, and R. Simpson, *Acta Crystallogr., Sect. B*, 28 (1972) 3145–3158; T. Taga, M. Senma, and K. Osaki, *ibid.*, 28 (1972) 3258–3263; G.A. Jeffrey and R. Nanni, *Carbohydr. Res.*, 137 (1985) 21–30.

[7] R.U. Lemieux, *Pure Appl. Chem.*, 25 (1971) 527–548; S. Perez and R.H. Marchessault, *Carbohydr. Res.*, 65 (1978) 114–120.

[8] D. Cremer and J.A. Pople, *J. Am. Chem. Soc.*, 97 (1975) 1354–1358.

[9] C.K. Lee and A. Linden, *J. Carbohydr. Chem.*, 13 (1994) 619–629.

[10] M. Mathlouthi, C. Maciejewski, S. Serghat, R.W.W. Hooft, J.A. Kanters, and J. Kroon, *J. Mol. Struct.*, 291 (1993) 173–182.

[11] J.A. Kanters, R.L. Scherrenberg, B.R. Leeflang, J. Kroon, and M. Mathlouthi, *Carbohydr. Res.*, 180 (1988) 175–182; F. Longchambon, J. Ohanessian, D. Avenel, and A. Neuman, *Acta Crystallogr., Sect. B*, 31 (1975) 2623–2627.

[12] R.S. Shallenberger and T.E. Acree, *Nature (London)*, 216 (1967) 480–482.

[13] E.W. Deutsch, and C. Hansch, *Nature (London)*, 211 (1966) 75.

[14] B. Kier, *J. Pharm. Sci.*, 61 (1972) 1394–1397; R.S. Shallenberger, and M.G. Lindley, *Food Chem.*, 2 (1977) 145–153.

[15] L. Hough and R. Khan, *Trends Biol. Sci.*, 3 (1978) 61–63.

[16] C.K. Lee, *Stärke*, 29 (1977) 204–209; G.G. Birch and C.K. Lee, *J. Food Sci.*, 41 (1976) 1403–1407.

[17] G.G. Birch and C.K. Lee, *J. Food Sci.*, 39 (1974) 947–949.

[18] G.G. Birch and M.G. Lindley, *J. Food Sci.*, 38 (1973) 1179–1181.

[19] R.S. Shallenberger, T.E. Acree, and C.Y. Lee, *Nature (London)*, 221 (1969) 555–556; J. Solms, *J. Agric. Food Chem.*, 17 (1969) 686–688; A. Petrischeck, F. Lynen, and H.D. Belitz, *Dtsch. Forsch. Lebensmittelchem.*, 5 (1972) 47–55.

[20] T. Kubota and I. Kubo, *Nature (London)*, 223 (1969) 97–99.

[21] G.G. Birch and C.K. Lee, *J. Food Sci.*, 41 (1976) 1043–1047; C.K. Lee, L.L. Koh, and Y. Xu, *Acta Crystallogr., Sect. C*, 50 (1994) 597–601; C.K. Lee, L.L. Koh, and Y. Xu, *Food Chem.*, in press.

[22] P.A. Temussi, F. Lelj, and T. Tancredi, *ACS Symp. Ser.*, 450 (1991) 143–161.

[23] C.K. Lee, unpublished results.

[24] S.Z. Dziedzic and G.G. Birch, *J. Sci. Food Agric.*, 32 (1981) 283–287.

[25] G.M. Sheldrick, *Acta Crystallogr., Sect. A*, 46 (1970) 467–473.

[26] TEXSAN-TEXRAY, Single Crystal Structure Analysis Package, Version 5.0, Molecular Structure Corporation, The Woodlands, TX, 1989.

[27] International Tables for X-ray Crystallography, Vol. IV, Kynoch Press, Birmingham, UK, 1974, pp 71–98 and 149–150 (distributed by Kluwer Academic Press, Dordrecht, Netherlands).