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Synthesis and Stereochemistry of 3,7-Diazatricyclo[4.2.2.$2^{2,5}$]dodeca-9,11-dienes Derived by [4+4] Cyclodimerization of 2,3-Dihydroisoquinoline Derivatives

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2-Acyl(or sulfonyl)-*c*-4-bromo-*r*-1-cyano-*t*-3-methoxy-1,2,3,4-tetrahydroisoquinolines 2b—g when treated with triethylamine or K_2CO_3 gave cyclodimers 5b—g of 2-acyl(or sulfonyl)-1-cyano-3-methoxy-2,3-dihydroisoquinolines in high yields. The dimers are composed of two tetrahydroisoquinoline units fused at the 1,1′- and 4,4′-positions to form a triheterocyclic 3,7-diazatricyclo[4.2.2.$2^{2,5}$]dodeca-9,11-diene ring. 2,3-Dihydroisoquinoline type compounds 3 are the key intermediate for this unusual [4+4] cyclodimerization. The structures of the dimers with an *exo*-type configuration have been determined by X-ray crystallography. The reaction mechanism of the cyclodimerization is discussed in conjunction with the stereochemistry of the products.

Key words diazatricyclododecadiene; cyclodimerization; dihydroisoquinoline; tetrahydroisoquinoline; X-ray crystallography; stereochemistry

We previously postulated the existence of 2,3-dihydroisoquinoline type compound **3** from NMR evidence[1] as a metastable intermediate in the amine-induced conversion reactions from the 4-bromo-3-methoxy-1,2,3,4-tetrahydroisoquinoline derivatives **2**, which have been derived[2,3] from the isoquinoline Reissert compounds **1**, to the 4-amino derivatives **4** (see Chart 1). The highly stereoselective conversion of **2a**—**e** into **4a**—**e** also requires the involvement of **3a**—**e** in the course of the reaction. Kirby *et al.* proposed for the first time the involvement of a similar intermediate in base-induced rearrangements of halogenohydrins to form isochromene as the final product.[4] Simig and Schlosser have also briefly reported the spontaneous cyclodimerization of 2,3-dihydroisoquinolines to form 3,7-diazatricyclo[4.2.2.$2^{2,5}$]-dodeca-9,11-dienes *via* a similar intermediate promoted by methanol elimination.[5] We report herein that the key intermediate **3** undergoes a facile [4+4] cyclodimerization to give a diazatricyclo[4.2.2.$2^{2,5}$]dodecadiene ring under mild basic conditions in a highly stereoselective manner.

Results and Discussion

Synthesis When diethylamine was used for the reaction with 2-acetyl derivative **2b** ($R=COCH_3$), the expected 4-diethylamino derivative **4b** was obtained in 40% yield together with an unknown by-product **5b** in 45% yield. Compound **5b**, on treatment with BF_3–Et_2O in methanol at room temperature,[2] gave compound **6b** in 80% yield. The structure of the product **6b** was determined by a series of IR, NMR, and MS spectroscopies, and ultimately by X-ray crystallography (Fig. 1). As seen in the structure of **6b**, two isoquinoline rings are bonded at C_4 to each other. Routine analysis of **5b** indicated it to be a dimer ($C_{26}H_{24}N_4O_4$) and the melting point was 285—287 °C. At this early stage of analysis, therefore, the structure of **5b** was considered to be a simple dimer possessing two tetrahydroisoquinoline rings bonded at positions 4 and 4′ (tail to tail) despite some doubts about the NMR spectrum (see the data for **5b** in Table 1). In order to examine the

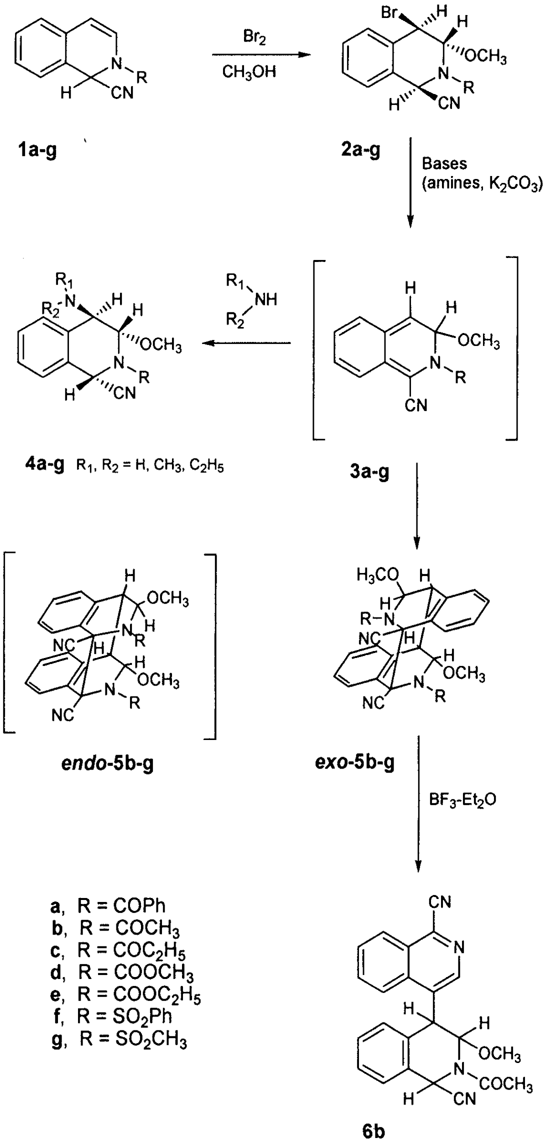

Chart 1

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more detailed structure of **5b**, X-ray crystallography was carried out and the result is shown in Fig. 2.

It is of great interest that two **3b** molecules are combined to make a triheterocyclic dimer bonded together at the 1,1′-(head to head) and 4,4′-positions (tail to tail). This structure agreed with the NMR and other spectral data. It is confirmed that the cyclodimerization of **2** occurs even under mild basic conditions using simple amines without elimination of substituents.

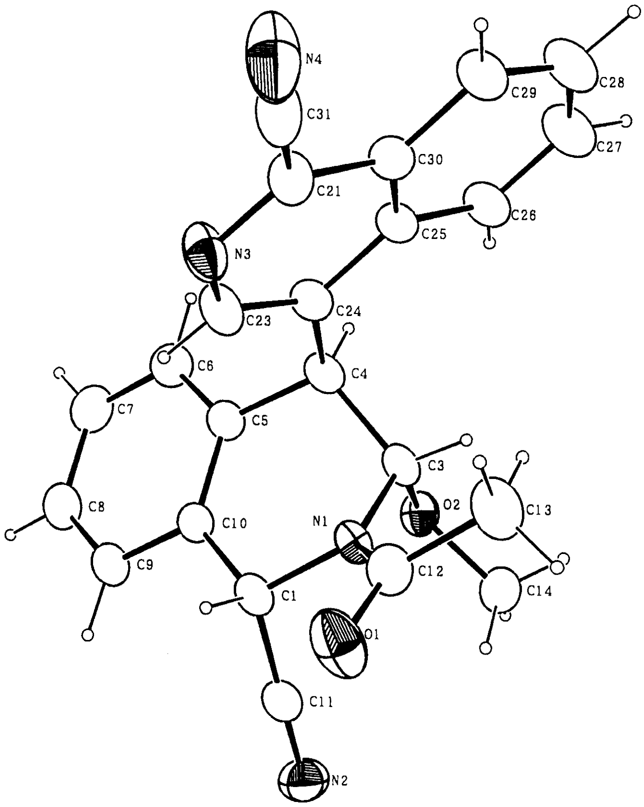

Fig. 1. ORTEP Drawing of **6b** with 30% Probability Ellipsoids for Non-hydrogen Atoms

Octant shaded ellipsoids indicate hetero atoms.

The yield of **5** from compound **2** seems to depend on the bulkiness of the amine constituent used.[1)] It is expected that triethylamine, a tertiary amine, would not produce the adduct **4**. In fact, the reaction of **2b** with triethylamine in methanol at room temperature for 0.5 h afforded only **5b** in a yield of 92%. Furthermore, when K_2CO_3 was used instead of triethylamine, **5b** was exclusively formed in high yield.

To examine the generality of this cyclic dimerization under simple basic conditions, **2c**—**g** were allowed to react with K_2CO_3 in methanol, and the corresponding **5c**—**g** were obtained in high yields (Chart 1 and Table 1). The structure of dimer **5e** has also been confirmed by X-ray crystallography (see Experimental and Table 2).

With respect to **2a** (R=COPh), the reaction with diethylamine gave the corresponding 4-diethylamino derivative **4a** in 45% yield with accompanying resin formation (*ca.* 50%). The reaction of **2a** with K_2CO_3 in methanol afforded only the resin product, presumably due to the fact that polymeric reaction would be favored by the steric effects of the phenyl substituent. The cyclodimerization of **3** is competitive with polymer formation through the steric or electronic effects of the *N*-substituents.

Description of Molecular Structure and Stereochemistry of Dimers In the view of all of the molecular structures of dimers determined crystallographically, two tetrahydropyridine rings with boat conformation are fused in bow-to-bow and stern-to-stern fashion. Abnormally long distances

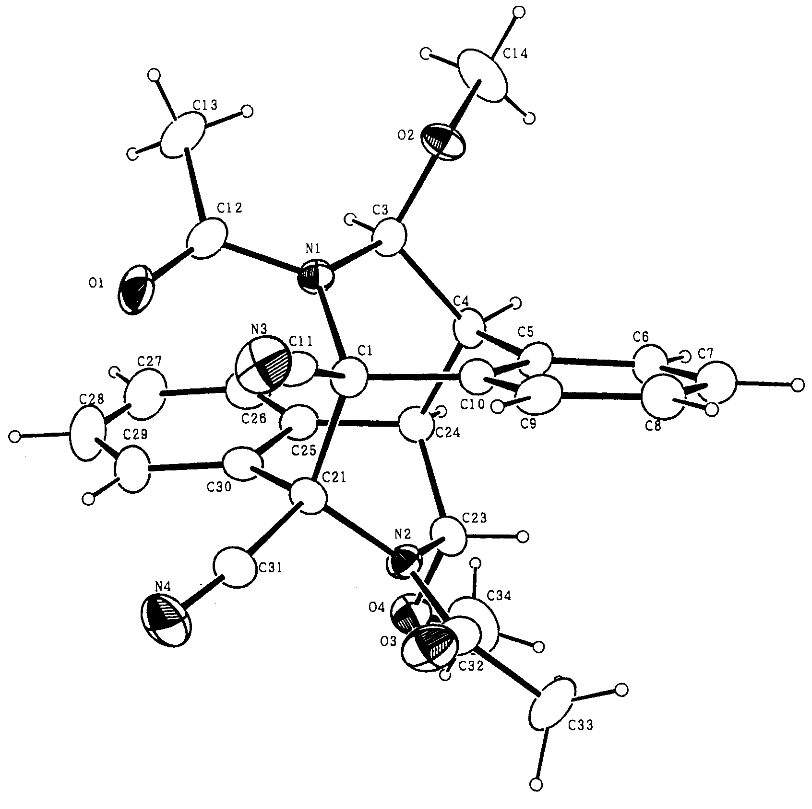

Fig. 2. ORTEP Drawing of **5b** with 30% Probability Ellipsoids for Non-hydrogen Atoms

Octant shaded ellipsoids indicate hetero atoms.

Table 1. Yields and Physical Properties of **5b**—**g**

Entry	R	Yield (%)	mp (°C)	IR ν cm^{-1} (KBr)	MS (FAB$^+$) m/z (MH$^+$)	NMR (in DMSO-d_6)			Formula	Elemental analysis (%): Found (required)		
						3-H(s)	4-H(s)	3-OCH$_3$(s)		C	H	N
5b	COCH$_3$	83.0	285—287	1675 (C=O)	457	4.52	4.18	3.09	$C_{26}H_{24}N_4O_4$	68.24 (68.41)	5.51 (5.30)	12.41 (12.27)
5c	COC$_2$H$_5$	85.4	>300	1674 (C=O)	465	4.53	4.17	3.08	$C_{28}H_{28}N_4O_4$	69.62 (69.41)	6.01 (5.82)	11.74 (11.56)
5d	COOCH$_3$	79.3	240—243	1728 (C=O)	489	4.74$^{a)}$	3.94$^{a)}$	3.03$^{a)}$	$C_{26}H_{24}N_4O_6$	63.88 (63.93)	4.71 (4.95)	11.55 (11.47)
5e	COOC$_2$H$_5$	80.3	249—252	1716 (C=O)	517	4.74$^{a)}$	3.92$^{a)}$	3.08$^{a)}$	$C_{28}H_{28}N_4O_6$	65.03 (65.11)	5.72 (5.46)	10.69 (10.85)
5f	SO$_2$Ph	83.2	165—167	1357, 1179 (SO$_2$)	652$^{b)}$	4.81	4.21	3.06	$C_{34}H_{28}N_4O_6S_2$	62.39 (62.56)	4.09 (4.32)	8.27 (8.58)
5g	SO$_2$CH$_3$	73.4	196—197	1345, 1162 (SO$_2$)	528$^{b)}$	4.78	3.86	3.21	$C_{24}H_{24}N_4O_6S_2$	54.62 (54.53)	4.69 (4.58)	10.72 (10.60)

a) 100 °C; *b)* M$^+$.

Table 2. Summary of Crystal Data and Intensity Collection Parameters for **5b**, **5e** and **6b**

	5b	**5e**	**6b**
Formula	$C_{26}H_{24}N_4O_4 \cdot 1/2CH_2Cl_2 \cdot 1/2C_6H_6$	$C_{28}H_{28}N_4O_6$	$C_{23}H_{18}N_4O_2$
M	538.03	516.6	382.4
Crystal size/mm	0.63×0.48×0.12	0.09×0.21×0.36	0.12×0.15×0.36
Crystal system	Monoclinic	Monoclinic	Monoclinic
Space group	$P2_1/c$	$P2_1/c$	$P2_1/c$
T/K	293	293	293
a/Å	19.183(3)	14.494(3)	8.410(2)
b/Å	10.311(1)	15.664(3)	8.430(1)
c/Å	13.368(2)	23.325(3)	27.254(5)
β/°	95.2 (1)	103.20(2)	95.48(2)
V/Å^3	2632.8(11)	5155.3(32)	1923.1(11)
Z	4	8$^{a)}$	4
F(000)	1128	2176	800
Dx/g cm^{-3}	1.357	1.331	1.321
μ/cm^{-1}	2.83	0.89	0.81
Diffractometer		Enraf–Nonius CAD4	
Radiation		Graphite monochromated Mo-K_α	
2θ range/°	4—50	4—50	4—50
Scan technique	$\omega-2\theta$	$\omega-2\theta$	$\omega-2\theta$
Scan range (ω)/°	$0.85+1.20\tan\theta$	$0.60+1.00\tan\theta$	$0.68+0.96\tan\theta$
No. of measured data	5118	9800	3680
No. of unique obsd. data [$F_O>3.0\sigma(F_O)$]	2722	3116	2250
$R^{b)}$	0.093	0.083	0.063
$R_w$$^{c)}$	0.090	0.087	0.061
No. of variables	377	685	262

a) Two independent dimers in an symmetric unit; *b)* $R=\Sigma| |F_O|-|F_C||/\Sigma|F_O|$; *c)* $Rw=[\Sigma w(|F_O|-|F_C|)^2/\Sigma wF_O{}^2]^{1/2}$ where $w=1$.

for the C1–C1′ bond (1.67(1) Å for **5b** and 1.70(1) Å and 1.69(2) Å for **5e**$^{6)}$) and also significantly long distance of the C4–C4′ bond (an average 1.58(2) Å for **5b** and **5e**$^{6)}$) are observed. The former bond distances portend facile cleavage. A similar unusually long C–C bond distance has been found in a related compound.$^{7)}$ The X-ray structures of **5b** and **5e** show the *exo*-type compound carrying the methoxy groups oriented outward relative to each other. The ^{1}H-NMR spectra of all dimer products (Table 1) show singlet 3-H and 3′-H protons around 4.5—4.8 ppm which are significantly shifted upfield compared with those of the 3-H proton of compound **6b**: 5.46 ppm. Such ring current effects$^{8)}$ support the belief that all dimers are of the *exo*-type and of the same conformations.$^{9)}$ It is important to point out in the stereochemistry of dimers that the dimer coupling is allowed only for the 3*S*-3′*S* or 3*R*-3′*R* pair even though compound **2** is racemic. Indeed the 3*S*-3′*S* pair in Fig. 2 is related to the other undepicted 3*R*-3′*R* enantiomer by the crystallographic symmetry, *i.e.*, no 3*R*-3′*S* or 3*S*-3′*R* pair was observed in the crystal at all. The same stereochemical circumstances are also adopted for **5e**.

Reaction Mechanism Such a cyclodimerization forming a triheterocyclic compound has been hitherto known mainly for the photochemical dimerization of some pyridones and pyridines$^{10-14)}$ and in one case for treatment of 4-methoxy-1,2,3,4-tetrahydroisoquinolines with lithium diisopropylamide.$^{5)}$ Although the key intermediate **3** possesses a diene moiety, this unusual non-photochemical cyclodimerization of halogenohydrins **2** cannot be categorized into simple cyclization of the Diels–Alder type but rather into the quasi-photodimer formation[10—14] or catalytic cyclooctadiene formation from dienes.[15—18] For both categories, the stepwise bond formation mechanism[19] may conform to the requirements for the symmetry conservation.[20] The true reason for, or exception to, the exclusive bond formation at the same positions 1,1′ and 4,4′ of the dihydroquinoline precursor is yet unknown, but it may be due to the electronic effects of substituents, *e.g.*, CN of the intermediate. If this bond formation mechanism is accepted *a priori*, the stereoselectivity for the *exo*-type adduct formation can be explained easily by steric hindrance of the substituent bulk with the use of Dreiding models: the formation of *endo*-type **5b** appears impossible because of the bulkiness of the substituents at positions 2 and 3, and the mutual repulsion of the phenyl parts. Thus the cyclic dimerization proceeds in a highly stereoselective manner. The stereochemical restrictions on the cyclodimer formation mentioned above imply that the dimer coupling is forbidden for the 3*R*-3′*S* or 3*S*-3′*R* pair. This means that **3** is able to recognize the partner's chirality in the cyclodimerization, *i.e.*, the chiral molecular recognition occurs spontaneously. Even though the stepwise bond formation mechanism circumvents the symmetry requirement, the recognition mechanism should involve subtle environmental effects such as diastereomeric molecular complex formation[21] recognizing mutual chirality.

Further studies to examine these steric/electronic effects on the reactions will be required for complete elucidation of the reaction mechanism–stereochemistry relationships.

Experimental

Melting points were measured using a Yanagimoto micromelting point apparatus and are reported without correction. The ^{1}H-NMR spectra were recorded on JEOL JNM A-400 (400 MHz) and JEOL JNM A-600 (600 MHz) spectrometers with tetramethylsilane as an internal standard. Chemical shifts are given in ppm (δ) and signals are expressed as s (singlet), d (doublet), m (multiplet) and br (broad). Mass spectra (MS) were taken with JEOL HX-110 and Hitachi M-80B-GC-MS spectrometers. The aluminum oxide used for the column chromatography was Merck Alminiumoxid 90 active, neutral (70—230 mesh).

Preparation of 2-Acetyl-*r*-1-cyano-*t*-4-diethylamino-*c*-3-methoxy-1,2,3,4-tetrahydroisoquinoline (4b) and Cyclodimer (5b) of 2-Acyl-1-cyano-3-methoxy-2,3-dihydroisoquinoline Methanol (20 ml), CH_2Cl_2 (20 ml), and diethylamine (0.025 mol) were added slowly at 0—20 °C to a stirred solution of 2-acetyl-*c*-4-bromo-*r*-1-cyano-*t*-3-methoxy-1,2,3,4-tetrahydroisoquinoline (**2b**) (0.01 mol) in CH_2Cl_2 (25 ml) and the mixture was kept at room temperature for 0.5 h. The reaction mixture was then poured into ice water and extracted with CH_2Cl_2. The CH_2Cl_2 solution was washed with 5% $NaHCO_3$. The CH_2Cl_2 solution was dried over $MgSO_4$, filtered, and concentrated. The residue was chromatographed on a silica gel column with benzene to give **4b** and **5b**.

4b: Yield 40% as an oil. ^{1}H-NMR ($CDCl_3$) δ: 6.40 (1-$\underline{H}$, 1H, s), 5.14 (3-$\underline{H}$, 1H, d, J=1.8 Hz), 4.09 (4-$\underline{H}$, 1H, d, J=1.8 Hz), 3.44 (3-$OC\underline{H}_3$, 3H, s). ^{13}C-NMR ($CDCl_3$) δ: 117.83 (1-$\underline{C}N$), 86.51 (3-$\underline{C}$), 60.64 (4-$\underline{C}$), 40.35 (1-$\underline{C}$). IR cm^{-1}: $\nu_{C=O}$ 1655; ν_{CN} 2240. *Anal.* Calcd for $C_{17}H_{23}N_3O_2$: C, 67.75; H, 7.69; N, 13.94. Found: C, 67.44; H, 7.41; N, 13.86. MS (FAB$^+$) *m/z*: 302 (MH$^+$).

5b: Yield 45.0%. Physical properties of **5b** are shown in Table 1.

Reaction of 5b with BF_3–Et_2O To a solution of **5b** (0.002 mol) in CH_3OH (50 ml) was added BF_3–Et_2O (5 ml), and the mixture was stirred at room temperature for 48 h. The reaction mixture was then poured into water and extracted with CH_2Cl_2. The CH_2Cl_2 solution was washed with 5% $NaHCO_3$. The CH_2Cl_2 solution was dried over $MgSO_4$, filtered, and concentrated. The residue was chromatographed on a silica gel column with benzene to give **6b**. Yield 80%. mp 244—246 °C. ^{1}H-NMR (70 °C, DMSO-d_6) δ: 3.11 ($COC\underline{H}_3$, 3H, s), 3.45 ($OC\underline{H}_3$, 3H, s), 5.46 (CH_3OC-$\underline{H}$, 1H, s), 6.74 (CN–C–$\underline{H}$, 1H, s), 7.58 (C=N–C$\underline{H}$=C, 1H, s). IR cm^{-1}: $\nu_{C=O}$ 1655; ν_{CN} 2230. *Anal.* Calcd for $C_{23}H_{18}N_4O_2$: C, 72.24; H, 4.74; N, 14.65. Found: C, 74.02; H, 4.51; N, 14.55. MS (EI) *m/z*: 382 (M$^+$).

Dimerization of 2-Acyl(or sulfonyl)-*c*-4-bromo-*r*-1-cyano-*t*-3-methoxy-1,2,3,4-tetrahydroisoquinolines (2a—g) K_2CO_3 (0.025 mol), CH_3OH (20 ml), and CH_2Cl_2 (20 ml) were added slowly to a stirred solution of **2a—g** (0.01 mol) in CH_2Cl_2 (50 ml) at 0—20 °C, and the mixture was kept at room temperature for 0.5 h. The reaction mixture was then poured into ice water and extracted with CH_2Cl_2. The CH_2Cl_2 solution was washed with 5% $NaHCO_3$. The CH_2Cl_2 solution was dried over $MgSO_4$, filtered, and concentrated. The crystalline residue was recrystallized from benzene–CH_2Cl_2 (1:1) to give **5b—g** (Table 1).

X-Ray Crystallography Crystals suitable for X-ray analysis were obtained by slow evaporation of the CH_2Cl_2–benzene solution. The crystal data[22] and data collection parameters for **5b**, **5e** and **6b** are given in Table 2. For all three crystals, the net intensities were reduced to a set of relative structure factors by the application of standard Lorentz and polarization factors. No absorption correction was done. Almost the same techniques were applied to all three structural analyses, described representatively here for **5b**. The structure was solved by the direct method,[23] then refined by the difference Fourier (DF) and least-squares techniques.[23] Most non-hydrogen atoms of the main dimeric molecule in the asymmetric unit were found in the initial E-map. Subsequent DF syntheses revealed not only all non-hydrogen atomic positions of the main molecule but also badly disordered solvent atoms. The solvents seemed to be approximately two dichloromethanes and two benzenes per unit cell, but the disorders and overlapping of solvents were too severe to locate the chemically significant positions. Thus several chlorine and carbon atoms with appropriate occupancy factors were disposed in the Fourier maps. The non-hydrogen atoms of the main molecule were refined with anisotropic thermal parameters, and hydrogen atoms bound to carbons except for the disordered solvents were included in calculated positions as fixed parameters. Final cycles of full-matrix least-squares refinement were carried to convergence at R=0.093. The final DF map showed some residual peaks at the 0.34 e/Å^3 level, but these were judged to be essentially featureless.

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