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The Structures of Different Diastereomers of Bicyclo[2.2.1]hept-5-en-2-yl Phenyl Sulfoxide

BY X. JI AND D. VAN DER HELM

Chemistry Department, University of Oklahoma, Norman, OK 73019, *USA*

AND R. V. WILLIAMS AND W. J. EBEY

Chemistry Department, Memphis State University, Memphis, Tennessee 38152, *USA*

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Abstract

Three diastereomers of bicyclo[2.2.1]hept-5-en-2-yl phenyl sulfoxide were prepared by Diels–Alder [4 + 2] cycloadditions between phenyl vinyl sulfoxide and cyclopentadiene. The isomers were separated by column chromatography on silica gel and repeated recrystallizations gave the pure racemates of three of the four possible diastereomers. It proved to be impossible to assign the stereochemistry of the products from low-resolution NMR spectra. The X-ray diffraction studies of the three diastereomers showed the relative configuration at the two chiral centers and these stereochemical assignments were, subsequently, correlated with the two-dimensional NMR spectroscopic results. Compound (I), *exo*-(2*R**,8*S**)-bicyclo[2.2.1]-hept-5-en-2-yl phenyl sulfoxide [or the *exo*-(2*S**,8*R**)-isomer], $C_{13}H_{14}OS$, $M_r = 218{\cdot}31$, orthorhombic, $P2_12_12_1$, $a = 10{\cdot}517\ (2)$, $b = 10{\cdot}914\ (2)$, $c = 9{\cdot}642\ (3)$ Å, $V = 1106{\cdot}7$ Å^3, $Z = 4$, $D_x = 1{\cdot}31$ g cm^{-3}, Cu $K\alpha$, $\lambda = 1{\cdot}54178$ Å, $\mu = 22{\cdot}14$ cm^{-1}, $F(000) = 464$, $T = 138\ (2)$ K, $R = 0{\cdot}042$ for 1151 data. Compound (II), *exo*-(2*RS*,8*RS*)-bicyclo[2.2.1]hept-5-en-2-yl phenyl sulfoxide, $C_{13}H_{14}OS$, $M_r = 218{\cdot}31$, triclinic, $P\bar{1}$, $a = 8{\cdot}775\ (4)$, $b = 16{\cdot}353\ (8)$, $c = 7{\cdot}804\ (3)$ Å, $\alpha = 90{\cdot}67\ (3)$, $\beta = 101{\cdot}08\ (4)$, $\gamma = 85{\cdot}64\ (5)°$, $V = 1095{\cdot}8$ Å^3, $Z = 4$, $D_x = 1{\cdot}32$ g cm^{-3}, Mo $K\alpha$, $\lambda = 0{\cdot}71069$ Å, $\mu = 2{\cdot}18$ cm^{-1}, $F(000) = 464$, $T = 138\ (2)$ K, $R = 0{\cdot}062$ for 3264 data. The two molecules in the asymmetric unit are crystallographically independent, but their conformations are similar. Compound (III), *endo*-(2*SR*,8*SR*)-bicyclo[2.2.1]hept-5-en-2-yl phenyl sulfoxide, $C_{13}H_{14}OS$, $M_r = 218{\cdot}31$, orthorhombic, $P2_12_12_1$, $a = 14{\cdot}454\ (2)$, $b = 14{\cdot}800\ (2)$, $c = 10{\cdot}388\ (1)$ Å, $V = 2222{\cdot}2$ Å^3, $Z = 8$, $D_x = 1{\cdot}31$ g cm^{-3}, Mo $K\alpha$, $\lambda = 0{\cdot}71069$ Å, $\mu = 2{\cdot}15$ cm^{-1}, $F(000) = 928$, $T = 138\ (2)$ K, $R = 0{\cdot}029$ for 2385 data. The two molecules in the asymmetric unit are enantiomeric with respect to both chiral atoms C(2) and S(8) and their conformations show small differences. For both the *exo*-(2*RS*,8*RS*) and *endo*-(2*SR*,8*SR*) conformers, the two molecules in the asymmetric unit have closely similar molecular dimensions. The results show an appreciable distortion from mirror symmetry for the norbornene ring system. The distortion is similar in size for the compounds but in opposite directions for the 2-*exo*- and the 2-*endo*-substituted norbornene systems.

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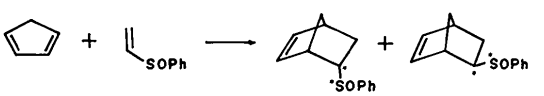
Introduction

Reaction of racemic phenyl vinyl sulfoxide with cyclopentadiene in benzene at 323 K gave the expected (Maignan & Raphael, 1983; Paquette, Moerck, Harirchian & Magnus, 1978) Diels–Alder addition to yield four diastereomers, each as a racemic mixture (Fig. 1).



Repeated column chromatography and recrystallization gave pure samples of three of the four racemic pairs, (I), (II) and (III). The ratio of the isomers could be controlled to some extent by selection of conditions favoring kinetic or thermodynamic control. From the initial low-resolution ^{1}H NMR spectra it was impossible to assign the stereochemistry of these compounds with confidence. Usually *endo* or *exo* stereochemistry can be reliably assigned to a substituent on a norbornyl nucleus by means of the characteristic spin–spin coupling patterns (see, for example, Jackman & Sternhell, 1969, and references cited therein). However, in this case X-ray analysis revealed that even this initial tentative assignment was made incorrectly. Specifically, compound (II) was assigned as having the sulfoxide group in an *endo*, rather than *exo*, position owing to the clear doublet of doublets of doublets observed in the low-field NMR spectrum for the proton α to this sulfoxide group. Similarly the stereochemistry of the sulfoxide group in compound (III) was misassigned on the basis of the poorly resolved NMR signal for the proton adjacent to the sulfoxide group. A norbornene substituted in the *exo* position with a phenyl sulfoxide group has been isolated by trapping benzene sulfenic

acid with norbornadiene (Barrett, Barton & Nagubandi, 1980). This procedure would be expected to yield a mixture of the *exo*-substituted diastereomers as racemic pairs. The subsequent purification (distillation and recrystallization) of this reaction mixture gives, however, a single product. The NMR data reported for this compound most closely agree with our data for compound (I). However, there are several discrepancies. The most obvious is that we observe a complex multiplet (400 mHz) in the aromatic region for compound (I) compared with the singlet reported for Barrett's compound (Barrett, Barton & Nagubandi, 1980). Differences in resolution could obviously account for these discrepancies. Therefore in order to elucidate rigorously the stereochemistry of all the adducts, recourse was made to X-ray crystallography. Three of the four racemic pairs appeared to be available as 'good' crystals. With the use of X-ray crystallography, the configuration of these diastereomers has been determined and, as a result, the assignment of their stereochemistry has been successfully accomplished. Compound (I) is *exo*-(*RS*)-$C_7H_9SOC_6H_5$, compound (II) is *exo*-(*RR,SS*)-$C_7H_9SOC_6H_5$, and compound (III) is *endo*-(*SS,RR*)-$C_7H_9SOC_6H_5$. Owing to the ambiguous low-resolution ^1H NMR spectral data, high-field (400 mHz) spectra were obtained. By means of two-dimensional NMR spectroscopy (*COSY*: Aue, Bartholdi & Ernst, 1976), the high-field data could be correlated with the stereochemistry established by X-ray crystallography.

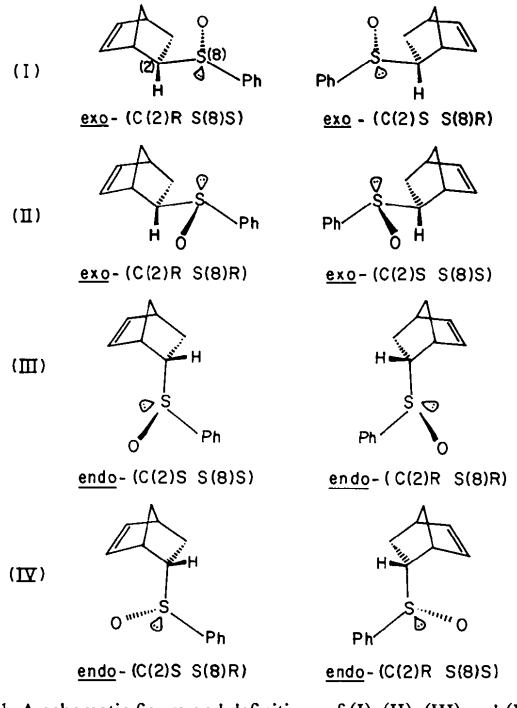


Fig. 1. A schematic figure and definitions of (I), (II), (III) and (IV).

Experimental

(*a*) *NMR studies*

^1H NMR spectra were recorded on a Varian T60 and a Bruker AM400 spectrometer and mass spectra on a Hewlett Packard GC/mass selective detector (5970A). Melting points were determined in open capillaries and are uncorrected. Microanalyses were performed by Galbraith Laboratories Inc.

A stirred solution of freshly cracked cyclopentadiene (6·51 g, 0·099 mol) and phenyl vinyl sulfoxide (5 g, 0·033 mol) in benzene (15 ml) was warmed to 323 K under a nitrogen atmosphere. Every 20 h freshly cracked cyclopentadiene (2 ml) was added to the mixture which was kept for 1 week. The solvent was removed by evaporation *in vacuo* and the excess cyclopentadiene and its dimer were removed by filtration column chromatography (silica, petroleum ether gradually increasing eluent polarity to 50% ethyl acetate in petroleum ether). The resulting mixture of diastereomers (5·96 g, 83%) was further purified by repeated column chromatographies (silica, petroleum ether increasing polarity to 15% ethyl acetate in petroleum ether) and repeated recrystallizations (ethyl acetate and petroleum ether) to give pure samples of each diastereomer as a racemic pair.

Eluting first upon column chromatography was compound (I), white needles, m.p. 343–344 K (ethyl acetate and petroleum ether). ^1H NMR ($CDCl_3$, Me_4Si) $\delta = 7{\cdot}45$ (5H, *m*, Ph), 6·1 (2H, *m*, olefinic), 3·0 and 2·9 (1H each, broad *s*, bridgehead protons), 2·5 (1H, *m*, H—CSOPh), 2·1 (1H, *m*, H3*x*), 1·8 (1H, *m*, H7*s*), 1·4 (1H, *m*, H7*a*) and 1·15 (1H, *m*, H3*n*). ^{13}C NMR ($CDCl_3$) 139·9, 138·0, 135·2, 130·7, 128·0, 124·2, 64·8, 45·7, 41·3 and 25·5. Mass spectrum, *m/Z* (%), 218 (1), 136 (22), 93 (100), 91 (99), 77 (88) and 51 (26). Analysis: calculated for $C_{13}H_{14}OS$, C 71·52, H 6·46%; found C 71·24, H 6·49%.

Eluting second was compound (II), white plates, m.p. 347–348 K (ethyl acetate and petroleum ether). ^1H NMR ($CDCl_3$, Me_4Si) $\delta = 7{\cdot}3$–$7{\cdot}7$ (5H, *m*, Ph), 6·15 and 6·05 (1H each, *m*, olefinic), 3·5 and 3·0 (1H each, broad *s*, bridgehead protons), 2·65 (1H, *ddd*, H—CSOPh), 1·75 (1H, *d*, H7*s*), 1·5 (2H, *m*, H7*a* and H3*x*), and 1·05 (1H, *m*, H3*n*). ^{13}C NMR ($CDCl_3$) 143·6, 139·1, 134·8, 131·1, 129·1, 124·9, 66·0, 45·4, 43·4, 42·0 and 28·0. Mass spectrum *m/Z* (%), 218 (1), 136 (26), 93 (98), 91 (100), 77 (89) and 51 (25). Analysis: calculated for $C_{13}H_{14}OS$, C 71·52, H 6·46%; found C 71·64, H 6·68%.

Eluting next was compound (III), white prisms, m.p. 352–353 K (ethyl acetate and petroleum ether). ^1H NMR ($CDCl_3$, Me_4Si) $\delta = 7{\cdot}3$–$7{\cdot}7$ (5H, *m*, Ph), 6·35 and 6·25 (2H, *m*, olefinic), 3·45 (1H, broad *s*, bridgehead proton), 3·35 (1H, *m*, H—CSOPh), 2·85 (1H, broad *s*, bridgehead proton), 1·65 (1H, *m*, H7*s*), 1·5 (1H, *m*, H3*x*), 1·25 (1H, *d*, H7*a*) and 0·85 (1H, *m*,

H3*n*). ^{13}C NMR ($CDCl_3$) 143·7, 138·4, 132·8, 131·1, 129·1, 124·9, 67·8, 48·5, 44·4, 42·0 and 27·3. Mass spectrum, *m/Z* (%) 218(1), 136(41), 135(32), 93(86), 91 (100), 77 (84) and 51 (26). Analysis: calculated for $C_{13}H_{14}OS$, C 71·52, H 6·46%; found C 71·39, H 6·36%.

(*b*) *Single-crystal X-ray analysis*

Most of the crystallographic data are listed in Table 1. Data collection for all three compounds was carried out on an Enraf–Nonius CAD-4, using θ–2θ scan techniques. The maximum scan time was 60 s with 40 s used for scanning the peak and 10 s used for scanning each of the left and right backgrounds. The receiving aperture, located 173 mm from the data crystal, had a constant height at 6 mm. Three intensity-control monitors were measured every 2 h of X-ray exposure time. Lorentz–polarization corrections were applied. No absorption correction was made. The structures were solved using the heavy-atom method and refined with *SHELX*76 (Sheldrick, 1976). Anisotropic temperature factors were used for non-H atoms. The locations of H atoms were determined from successive difference Fourier syntheses and refined isotropically except for one fixed temperature factor for H(5) of (I). $\sum w(|F_o| - |kF_c|)^2$ was minimized in the full-matrix least-squares refinement, in which $w = 1/\sigma^2(F)$.* Atomic scattering factors taken from *SHELX*.

Discussion

(*a*) *X-ray*

The final coordinates of the non-H atoms are given in Table 2 for (I), Table 3 for (II) and Table 4 for (III). The atom-numbering schemes are shown in Fig. 2 for (I), Fig. 3 for (II) and Fig. 4 for (III) (Johnson, 1965). Bond distances, angles and selected torsion angles are given in Table 5.

The configurations at C(2) and S can be ascertained from the figures. There is, however, free rotation about both C(2)–S and S–C(10) bonds and the particular configurations can also be recognized by differences in conformational angles for these bonds. An *R* configuration for C(2) can be recognized by the fact that the torsion angle C(10)–S(8)–C(2)–C(3) is approximately 110° larger than the angle C(10)–S(8)–C(2)–C(1), while for the *S* configuration this angle is 110° smaller. Similarly the *S* configuration for S(8) is recognized by the fact that the C(15)–C(10)–S(8)–C(2) angle is approximately 110° larger than the C(15)–C(10)–S(8)–O(9) torsion angle.

* Lists of structure factors, anisotropic thermal parameters and H-atom parameters have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 51294 (41 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 1. *Crystallographic data*

	(I)	(II)	(III)
Crystal(s) used	1	3	1
Crystal size (mm)	0·10 × 0·10 × 0·48	0·03 × 0·05 × 0·25	0·35 × 0·40 × 0·25
Reflections for lattice constants	72 ($23 > \theta > 13°$)	46 ($18 > \theta > 9°$)	48 ($14 > \theta > 11°$)
Systematic absences	*h*00 (*h* = 2*n* + 1)	None	*h*00 (*h* = 2*n* + 1)
	0*k*0 (*k* = 2*n* + 1)		0*k*0 (*k* = 2*n* + 1)
	00*l* (*l* = 2*n* + 1)		00*l* (*l* = 2*n* + 1)
Range of 2θ (°)	1·0–150·0	1·0–53·0	1·0–53·0
Range of *hkl*	$0 \le h \le 13$	$-11 \le h \le 11$	$0 \le h \le 18$
	$0 \le k \le 13$	$0 \le k \le 20$	$0 \le k \le 18$
	$0 < l < 12$	$-9 < l \le 9$	$0 \le l \le 13$
Scan width (°)	1·10 + 0·20 tanθ	0·80 + 0·20 tanθ	0·80 + 0·20 tanθ
Width of receiving aperture (mm)	4·00 + 0·86 tanθ	3·00 + 0·86 tanθ	4·00 + 0·86 tanθ
Max. difference of intensity control monitors (e.s.d.)	0·010 (0·003)	(NA)	0·024 (0·007)
Total data	1385	4790	2687
Unique data	1343	4497	2615
Observed data $[I \ge 2\sigma(I)]$	1151	3264	2385
Final *R*	0·042	0·062	0·029
wR	0·047	0·071	0·035
Max. Δ/σ			
Non-H atoms	0·049	0·015	0·030
H atoms	0·014	0·033	0·032
Final Fourier map (e Å^{-3})			
Largest peak	0·22	0·14	0·23
Smallest peak	−0·27	−0·24	−0·22
E.o.f.*	1·5	2·0	1·3
Number of reflections used (*N*)	1151	3264	2385
Number of LS parameters (*NP*)	191	383	383

* E.o.f. = $[\sum w(F_o - F_c)^2/(N-NP)]^{1/2}$, where $w = 1/\sigma^2(F)$.

Table 2. *Final coordinates of the non-*H *atoms with e.s.d.'s in parentheses for* (I), *exo-*(2*R**,8*S**)*-bicyclo-*[2.2.1]*hept-5-en-2-yl phenyl sulfoxide*

	x	*y*	*z*	U_{eq}† (Å^2)
C(1)	0·1378 (4)	−0·1794 (4)	0·0080 (4)	0·037 (1)
C(2)	0·1545 (4)	−0·0429 (4)	−0·0353 (4)	0·030 (1)
C(3)	0·0225 (4)	−0·0070 (4)	−0·0938 (4)	0·032 (1)
C(4)	−0·0509 (4)	−0·1310 (4)	−0·0861 (4)	0·037 (1)
C(5)	0·0159 (5)	−0·2165 (4)	−0·1858 (4)	0·041 (1)
C(6)	0·1282 (5)	−0·2454 (4)	−0·1291 (5)	0·040 (1)
C(7)	−0·0020 (5)	−0·1810 (4)	0·0537 (4)	0·039 (1)
S(8)	0·20971 (9)	0·04801 (9)	0·11153 (9)	0·0308 (2)
O(9)	0·1056 (3)	0·0543 (3)	0·2188 (2)	0·0388 (9)
C(10)	0·2110 (4)	0·1946 (3)	0·0270 (4)	0·033 (1)
C(11)	0·1329 (4)	0·2865 (4)	0·0788 (4)	0·039 (1)
C(12)	0·1377 (5)	0·4004 (4)	0·0201 (5)	0·046 (2)
C(13)	0·2200 (5)	0·4247 (4)	−0·0893 (5)	0·049 (2)
C(14)	0·2984 (5)	0·3325 (4)	−0·1392 (4)	0·039 (1)
C(15)	0·2934 (4)	0·2182 (4)	−0·0820 (4)	0·037 (1)

† $U_{eq} = \frac{1}{3}\sum_i\sum_j U_{ij}a_i^*a_j^*\mathbf{a}_i.\mathbf{a}_j$ for Tables 2, 3 and 4.

The crystal for (I) contains only molecules with the 2*R**,8*S** configuration or the opposite (the absolute configuration for the data crystal was not determined). Both the (II) and (III) crystals, however, contain a racemic mixture. For (II) this is dictated by the symmetry of the space group while for (III) this occurs because the two enantiomers co-crystallize in a chiral space group. From the results it is clear that molecule *A* for (II) is 2*R*,8*R* and that molecule *A* for (III) is 2*S*,8*S* and molecules *B* have the opposite configuration. The conformation about the C(2)–S bonds is quite different for the two *exo* derivatives. In (I) the S–O bond is *trans* to C(2)–H(2*n*) while in (II) [and also in (III)] this bond is *trans* to C(2)–C(3). The conformation around the

Table 3. *Final coordinates of the non-*H *atoms with e.s.d.'s in parentheses for* (II), *exo-*(2*RS*,8*RS*)*-bicyclo-*[2.2.1]*hept-5-en-2-yl phenyl sulfoxide*

	x	*y*	*z*	U_{eq}(Å²)
C(1)*A*	0·2106 (5)	0·0666 (3)	0·6473 (6)	0·025 (1)
C(2)*A*	0·3853 (5)	0·0857 (2)	0·6922 (5)	0·022 (1)
C(3)*A*	0·4095 (5)	0·1295 (3)	0·5245 (6)	0·029 (1)
C(4)*A*	0·2474 (5)	0·1249 (3)	0·4016 (6)	0·032 (1)
C(5)*A*	0·2284 (5)	0·0349 (3)	0·3649 (7)	0·040 (2)
C(6)*A*	0·2063 (5)	0·0004 (3)	0·5098 (6)	0·033 (1)
C(7)*A*	0·1396 (5)	0·1418 (3)	0·5332 (6)	0·029 (1)
S(8)*A*	0·4140 (1)	0·15561 (6)	0·8777 (1)	0·0252 (3)
O(9)*A*	0·3803 (4)	0·1106 (2)	1·0297 (4)	0·039 (1)
C(10)*A*	0·6234 (5)	0·1564 (2)	0·9061 (5)	0·022 (1)
C(11)*A*	0·7150 (5)	0·1012 (2)	1·0231 (5)	0·026 (1)
C(12)*A*	0·8771 (5)	0·1015 (3)	1·0483 (6)	0·031 (1)
C(13)*A*	0·9436 (5)	0·1571 (3)	0·9584 (6)	0·033 (1)
C(14)*A*	0·8499 (5)	0·2128 (3)	0·8419 (6)	0·033 (1)
C(15)*A*	0·6899 (5)	0·2133 (3)	0·8183 (6)	0·028 (1)
C(1)*B*	0·2309 (4)	0·4220 (2)	0·1362 (5)	0·021 (1)
C(2)*B*	0·4123 (4)	0·4098 (2)	0·1826 (5)	0·018 (1)
C(3)*B*	0·4556 (5)	0·3765 (2)	0·0091 (5)	0·021 (1)
C(4)*B*	0·2937 (5)	0·3784 (2)	−0·1166 (5)	0·024 (1)
C(5)*B*	0·2359 (5)	0·4679 (3)	−0·1385 (6)	0·026 (1)
C(6)*B*	0·1986 (5)	0·4935 (3)	0·0110 (6)	0·027 (1)
C(7)*B*	0·1936 (5)	0·3518 (3)	0·0088 (5)	0·025 (1)
S(8)*B*	0·4709 (1)	0·33152 (6)	0·3529 (1)	0·0251 (3)
O(9)*B*	0·4089 (4)	0·3637 (2)	0·5085 (4)	0·042 (1)
C(10)*B*	0·6766 (4)	0·3448 (2)	0·3985 (5)	0·021 (1)
C(11)*B*	0·7342 (5)	0·3985 (3)	0·5293 (5)	0·027 (1)
C(12)*B*	0·8933 (5)	0·4089 (3)	0·5672 (5)	0·027 (1)
C(13)*B*	0·9920 (5)	0·3659 (3)	0·4724 (5)	0·027 (1)
C(14)*B*	0·9333 (5)	0·3126 (3)	0·3408 (6)	0·031 (1)
C(15)*B*	0·7750 (5)	0·3013 (2)	0·3035 (5)	0·027 (1)

Table 4. *Final coordinates of the non-*H *atoms with e.s.d.'s in parentheses for* (III) *endo-*(2*SR*,8*SR*)*-bicyclo-*[2.2.1]*hept-5-en-2-yl phenyl sulfoxide*

	x	*y*	*z*	U_{eq}(Å²)
C(1)*A*	0·3746 (2)	0·5998 (2)	0·3252 (3)	0·0232 (7)
C(2)*A*	0·3108 (2)	0·6195 (1)	0·4431 (2)	0·0212 (6)
C(3)*A*	0·2194 (2)	0·5717 (2)	0·4071 (3)	0·0265 (7)
C(4)*A*	0·2434 (2)	0·5266 (2)	0·2759 (3)	0·0285 (7)
C(5)*A*	0·2538 (2)	0·6038 (2)	0·1818 (3)	0·0352 (9)
C(6)*A*	0·3310 (2)	0·6470 (2)	0·2110 (3)	0·0301 (8)
C(7)*A*	0·3453 (2)	0·5020 (2)	0·2983 (3)	0·0261 (8)
S(8)*A*	0·29961 (4)	0·74039 (4)	0·46845 (6)	0·0265 (2)
O(9)*A*	0·3938 (1)	0·7714 (1)	0·5098 (2)	0·0433 (7)
C(10)*A*	0·2288 (2)	0·7358 (2)	0·6104 (2)	0·0249 (7)
C(11)*A*	0·2708 (2)	0·7354 (2)	0·7302 (3)	0·0311 (8)
C(12)*A*	0·2157 (2)	0·7320 (2)	0·8395 (3)	0·0390 (9)
C(13)*A*	0·1199 (2)	0·7294 (2)	0·8297 (3)	0·040 (1)
C(14)*A*	0·0786 (2)	0·7316 (2)	0·7091 (3)	0·0358 (9)
C(15)*A*	0·1325 (2)	0·7355 (2)	0·5990 (3)	0·0286 (7)
C(1)*B*	0·1493 (2)	0·1071 (2)	0·5637 (3)	0·0255 (7)
C(2)*B*	0·1309 (1)	0·0525 (2)	0·4387 (2)	0·0207 (7)
C(3)*B*	0·1832 (2)	−0·0373 (2)	0·4617 (3)	0·0254 (7)
C(4)*B*	0·2299 (2)	−0·0206 (2)	0·5953 (3)	0·0286 (8)
C(5)*B*	0·1522 (2)	−0·0190 (2)	0·6921 (3)	0·0322 (9)
C(6)*B*	0·1042 (2)	0·0561 (2)	0·6738 (2)	0·0307 (8)
C(7)*B*	0·2512 (2)	0·0808 (2)	0·5850 (3)	0·0321 (8)
S(8)*B*	0·00759 (4)	0·03846 (4)	0·41540 (6)	0·0228 (2)
O(9)*B*	−0·0296 (1)	0·1325 (1)	0·4027 (2)	0·0352 (6)
C(10)*B*	0·0104 (2)	−0·0094 (2)	0·2568 (2)	0·0220 (6)
C(11)*B*	0·0204 (2)	0·0465 (2)	0·1515 (2)	0·0243 (7)
C(12)*B*	0·0189 (2)	0·0102 (2)	0·0287 (3)	0·0316 (8)
C(13)*B*	0·0078 (2)	−0·0819 (2)	0·0129 (3)	0·0332 (8)
C(14)*B*	−0·0019 (2)	−0·1385 (2)	0·1190 (3)	0·0329 (8)
C(15)*B*	−0·0011 (2)	−0·1018 (2)	0·2422 (3)	0·0276 (7)

S—C(10) bond is similar in all three diastereomers, involving five independent molecules, with the S—O bond approximately coplanar with the phenyl ring (6·4–27·9°). Both molecules *A* and *B* in (II) have similar conformations. The largest difference is observed for C(3)—C(2)—S(8)—C(10): 4·4°. The differences in conformation are large for molecules *A* and *B* in (III)

Table 5. *Bond distances* (Å), *angles* (°) *and selected conformational angles* (°) *with e.s.d.'s in parentheses*

A and *B* refer to the two independent molecules in the asymmetric unit for (II) and (III).

		(II)		(III)	
	(I)	*A*	*B*	*A*	*B*
C(1)—C(2)	1·557 (6)	1·561 (6)	1·561 (5)	1·561 (4)	1·553 (4)
C(1)—C(6)	1·508 (6)	1·512 (6)	1·507 (6)	1·513 (4)	1·518 (4)
C(1)—C(7)	1·535 (7)	1·547 (6)	1·523 (6)	1·535 (4)	1·540 (4)
C(2)—C(3)	1·549 (6)	1·556 (5)	1·556 (5)	1·544 (3)	1·547 (3)
C(2)—S(8)	1·823 (4)	1·825 (4)	1·830 (4)	1·816 (2)	1·811 (2)
C(3)—C(4)	1·560 (6)	1·561 (6)	1·562 (5)	1·558 (4)	1·564 (4)
C(4)—C(5)	1·513 (6)	1·513 (8)	1·514 (6)	1·511 (4)	1·508 (4)
C(4)—C(7)	1·542 (6)	1·534 (6)	1·522 (5)	1·536 (4)	1·536 (4)
C(5)—C(6)	1·339 (7)	1·323 (6)	1·325 (5)	1·322 (4)	1·325 (4)
S(8)—O(9)	1·508 (3)	1·492 (3)	1·498 (3)	1·500 (2)	1·498 (2)
S(8)—C(10)	1·796 (4)	1·809 (4)	1·801 (4)	1·796 (3)	1·794 (3)
C(10)—C(11)	1·389 (6)	1·387 (6)	1·384 (6)	1·384 (4)	1·379 (4)
C(10)—C(15)	1·387 (6)	1·388 (6)	1·393 (5)	1·397 (4)	1·386 (4)
C(11)—C(12)	1·366 (6)	1·399 (6)	1·393 (6)	1·388 (4)	1·385 (4)
C(12)—C(13)	1·390 (7)	1·383 (6)	1·391 (6)	1·388 (5)	1·382 (4)
C(13)—C(14)	1·388 (6)	1·398 (6)	1·387 (6)	1·388 (5)	1·391 (4)
C(14)—C(15)	1·365 (6)	1·380 (7)	1·390 (6)	1·386 (4)	1·390 (4)
C(1)—C(2)—C(3)	103·8 (3)	103·1 (3)	102·8 (3)	103·3 (2)	103·6 (2)
C(1)—C(2)—S(8)	110·4 (3)	109·2 (2)	109·6 (2)	110·5 (2)	109·9 (2)
C(1)—C(6)—C(5)	107·7 (4)	107·6 (4)	107·7 (4)	107·9 (2)	107·5 (2)
C(1)—C(7)—C(4)	93·7 (3)	93·3 (3)	94·9 (3)	93·9 (2)	93·7 (2)
C(2)—C(3)—C(4)	102·0 (3)	102·1 (3)	102·5 (3)	102·6 (2)	102·2 (2)
C(2)—C(1)—C(6)	103·3 (3)	104·0 (3)	104·3 (3)	106·5 (2)	107·4 (2)
C(2)—C(1)—C(7)	101·3 (3)	100·8 (3)	101·1 (3)	99·0 (2)	98·8 (2)
C(2)—S(8)—O(9)	109·0 (2)	106·7 (2)	106·2 (2)	105·2 (1)	105·0 (1)
C(2)—S(8)—C(10)	97·7 (2)	97·6 (2)	98·0 (2)	97·6 (1)	98·4 (1)
C(3)—C(2)—S(8)	115·5 (3)	110·2 (3)	109·3 (3)	114·2 (2)	113·7 (2)
C(3)—C(4)—C(5)	105·9 (3)	106·1 (4)	105·9 (3)	105·3 (2)	105·8 (2)
C(3)—C(4)—C(7)	100·6 (3)	100·2 (3)	100·1 (3)	100·5 (2)	100·4 (2)
C(4)—C(5)—C(6)	107·2 (4)	107·7 (4)	107·7 (3)	107·6 (2)	107·9 (2)
C(5)—C(4)—C(7)	100·5 (3)	101·0 (4)	99·7 (3)	100·5 (2)	100·4 (2)
C(6)—C(1)—C(7)	100·5 (4)	100·7 (3)	100·0 (3)	100·2 (2)	100·2 (2)
S(8)—C(10)—C(11)	118·4 (3)	118·2 (3)	118·8 (3)	119·2 (2)	119·5 (2)
S(8)—C(10)—C(15)	120·9 (3)	120·6 (3)	120·1 (3)	119·8 (2)	119·2 (2)
O(9)—S(8)—C(10)	106·0 (2)	107·2 (2)	106·4 (2)	107·1 (1)	107·1 (1)
C(10)—C(11)—C(12)	119·1 (4)	119·1 (4)	119·5 (4)	118·9 (3)	119·7 (3)
C(10)—C(15)—C(14)	120·0 (4)	119·6 (4)	119·1 (4)	119·3 (3)	119·2 (3)
C(11)—C(10)—C(15)	120·5 (4)	121·1 (4)	121·1 (4)	120·9 (2)	121·2 (2)
C(11)—C(12)—C(13)	120·7 (4)	119·8 (4)	119·7 (4)	120·9 (3)	119·6 (3)
C(12)—C(13)—C(14)	119·7 (4)	120·5 (4)	120·5 (4)	119·7 (3)	120·8 (3)
C(13)—C(14)—C(15)	120·0 (4)	119·8 (4)	120·1 (4)	120·3 (3)	119·5 (3)
C(1)—C(2)—S(8)—O(9)	−67·8 (3)	64·3 (3)	−61·4 (3)	−67·5 (2)	61·3 (2)
C(1)—C(2)—S(8)—C(10)	−177·7 (3)	174·9 (3)	−171·2 (2)	−177·6 (2)	171·6 (2)
C(2)—S(8)—C(10)—C(11)	118·8 (3)	−93·1 (3)	92·1 (3)	91·4 (2)	−80·7 (2)
C(2)—S(8)—C(10)—C(15)	−65·1 (4)	89·5 (3)	−88·2 (3)	−90·5 (2)	101·6 (2)
C(3)—C(2)—S(8)—O(9)	49·6 (3)	176·9 (3)	−173·4 (3)	176·6 (2)	176·8 (2)
C(3)—C(2)—S(8)—C(10)	−60·4 (3)	−72·5 (3)	76·9 (3)	66·5 (2)	−72·8 (2)
O(9)—S(8)—C(10)—C(11)	6·4 (4)	17·0 (4)	−17·5 (4)	−17·1 (2)	27·9 (2)
O(9)—S(8)—C(10)—C(15)	−177·5 (3)	−160·3 (3)	162·2 (3)	161·0 (2)	−149·8 (2)
O(9)—S(8)—C(2)—H(2*n*)	175 (3)	−61 (2)	63 (2)	—	—
O(9)—S(8)—C(2)—H(2*x*)	—	—	—	50 (2)	−60 (2)

with several angles differing by more than 10° (Table 5).

In both (II) and (III), the two independent molecules in the asymmetric unit have nearly identical bond distances and angles. In all five independent molecules of the three compounds, the two C—S bonds are unequal, S—C(10) being shorter than S—C(2), because of the different hybridization of C(10) (sp^2) and C(2) (sp^3). This has been widely observed in related structures (see, for example, Soriano-Garcia, Toscano, Garcia, Larraza & Sanchez, 1984; Kimura, Ward, Watson & Venier, 1979; Beckhaus, Kimura, Watson, Venier & Kojic-Prodic, 1979). The C(4)—C(5) and C(1)—C(6) bond distances are shorter than the other C—C single bonds in the norbornene ring because they are C(sp^3)—C(sp^2) rather than C(sp^3)—C(sp^3) bonds.

The contraction of the C(2)–S–C(10) angle which was described previously (Day, Kingsburg & Day, 1981; Hoyos Guerrero, Martínez-Carrera & García-Blanco, 1983) is also observed for all five independent molecules. The O(9)–S–C(10) angle is slightly larger than the O(9)–S–C(2) angle in (II) and (III), while it is the opposite in (I). In (I), a short intramolecular contact exists between O(9) and H(7*a*) of 2·46 Å. This is the reason for the enlargement of the bond angle O(9)–S–C(2).

In all three compounds there is only an approximate mirror plane through C(7) and the midpoints of the C(2)–C(3) and C(5)–C(6) bonds. In other words, substitution with the phenylsulfinyl group at position 2 destroys the mirror symmetry of the norbornene system. The torsion angles in the norbornene ring systems of the five independent molecules of $C_7H_9SOC_6H_5$ and of another 2-*endo*-substituted norbornene molecule (Glass, Reineke & Shanklin, 1984) are given in Table 6. Previously it was predicted that 2-*exo*-substituted 5,6-norbornenes would show an appreciable distortion and that 2-*endo* derivatives would display only a small one, if any at all (Altona & Sundaralingam, 1970). However, appreciable distortion occurs in both the 2-*exo*- and the 2-*endo*-substituted norbornenes, and the distortion is found in only one half of the norbornene skeletons [C(1), C(2), C(3), C(4) and C(7)] as indicated by the torsion angles: $a \neq c$, $d \neq e$, $f \neq g$ and $b \neq 0$. The other half is almost not influenced at all by the 2-substitution as shown by the torsion angles: $a' = c'$, $d' = e'$, $f' = g'$ and $b' = 0$ within experimental error. The determining factor for these observations might be the rigidity of the C(5)=C(6) double bond. Furthermore, it can be seen that, for 2-*exo*-substituted norbornenes, $a < c$, by 5–6°, $d > e$ by 2–3° and $f > g$ by 5–6°, while, for the 2-*endo* derivatives, $a > c$ by 4–8°, $d < e$ by 1–3°, and $f < g$ by 5–9°. There is therefore a noticeable and opposite distortion in torsion angles for 2-*endo*- and 2-*exo*-substituted norbornene ring systems.

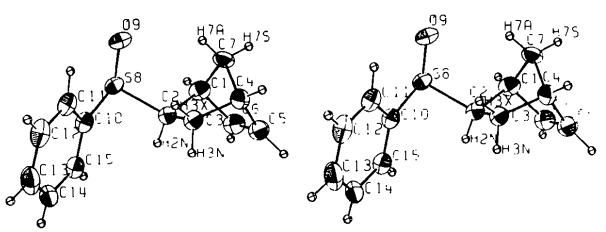


Fig. 2. A stereoview of the molecule and atom-numbering scheme for (I), *exo*-(2*R**,8*S**)-bicyclo[2.2.1]hept-5-en-2-yl phenyl sulfoxide.

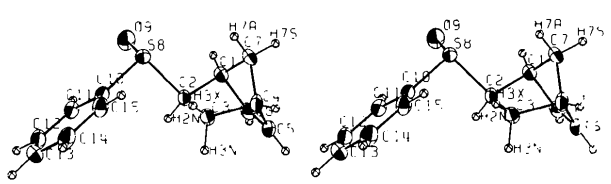


Fig. 3. A stereoview of molecule *A* and atom-numbering scheme for (II), *exo*-(2*R*,8*R*)-bicyclo[2.2.1]hept-5-en-2-yl phenyl sulfoxide.

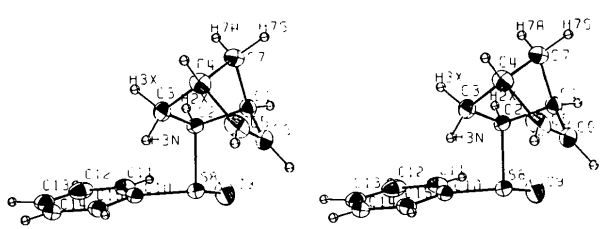
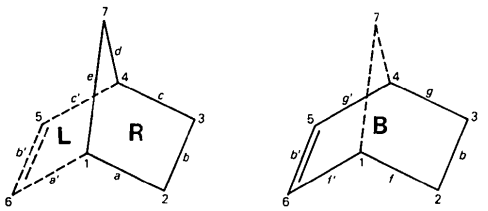


Fig. 4. A stereoview of molecule *A* and atom-numbering scheme for (III), *endo*-(2*S*,8*S*)-bicyclo[2.2.1]hept-5-en-2-yl phenyl sulfoxide.

Table 6. *Torsion angles* (°) *in 2-substituted norbornene systems*

E.s.d.'s are in parentheses.



Torsion angles in the norbornene system: *a*–*e* in 5-membered ring *R*(1–2–3–4–7); *a'*–*e'* in 5-membered ring *L*(1–7–4–5–6); *f*, *g*, *f'*, *g'* in 6-membered ring *B*(1–2–3–4–5–6).

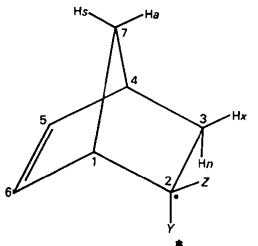
	2-*exo*-substituted			2-*endo*-substituted		
	(I)	(II) *A*	(II) *B*	(III) *A*	(III) *B*	CIKMUE*
Ring *R*						
a	33·1 (4)	34·0 (4)	33·5 (4)	38·9 (2)	39·5 (2)	41·2
b	3·8 (4)	3·2 (4)	2·8 (4)	2·6 (2)	3·0 (2)	5·1
c	39·2 (4)	39·7 (4)	38·2 (4)	34·7 (2)	34·7 (2)	33·5
d	58·7 (4)	59·7 (4)	58·5 (3)	58·3 (2)	58·5 (2)	58·8
e	56·0 (3)	57·4 (3)	56·9 (3)	59·3 (2)	59·9 (2)	61·7
Ring *L*						
a'	33·6 (4)	33·1 (4)	33·0 (4)	32·9 (3)	33·0 (3)	34·0
b'	0·3 (6)	0·3 (8)	0·2 (6)	0·1 (5)	0·2 (5)	0·9
c'	32·9 (4)	33·0 (4)	32·7 (4)	33·1 (3)	33·5 (3)	33·5
d'	49·9 (4)	49·1 (4)	49·7 (3)	49·6 (2)	49·9 (2)	51·0
e'	50·0 (4)	49·3 (4)	50·0 (3)	49·3 (2)	49·7 (2)	50·9
Ring *B*						
f	70·6 (4)	70·0 (4)	69·9 (4)	64·6 (2)	64·2 (2)	61·9
g	65·0 (4)	65·0 (4)	65·0 (3)	69·3 (2)	69·4 (2)	71·2
f'	70·8 (4)	71·0 (4)	71·2 (4)	69·7 (3)	69·6 (3)	68·7
g'	71·3 (4)	71·2 (4)	70·8 (4)	70·9 (3)	70·5 (3)	71·4

* (I) is *exo*-(2*R*,8*S*)-$C_7H_9SOC_6H_5$ (present work); (II) is *exo*-(2*RS*,8*RS*)-$C_7H_9SOC_6H_5$ (present work); (III) is *endo*-(2*SR*,8*SR*)-$C_7H_9SOC_6H_5$ (present work); CIKMUE is (±)-(2*S*,*R*)-*S*-(*endo*-bicyclo[2.2.1]hept-5-en-2-yl)-*N*-(phthalimido)-*p*-toluenesulfinamide (Glass *et al.*, 1984).

(*b*) *NMR*

The salient features usually observed in the ^{1}H NMR spectra of bicyclo[2.2.1]heptenes are: (1) The protons in the *endo* positions [H(2*n*) and H(3*n*)] resonate at higher field than the corresponding *exo* protons [H(2*x*) and H(3*x*)]. (2) In addition to the appreciable vicinal and geminal spin–spin couplings between the *endo* and *exo* protons bound to C(2) and C(3), there is also a

Table 7. *NMR assignments showing only major spin–spin couplings between saturated sites*



(I) $Y = H, Z = -\overset{*}{S}OPh$
(II) $Y = H, Z = -\overset{*}{S}OPh$
(III) $Y = -\overset{*}{S}OPh, Z = H$

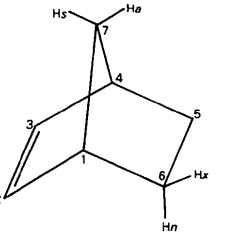
Compound	Chemical shift (p.p.m. downfield from Me_4Si)	Assignment	Coupled to
(I)	7·45	Ph	
	6·20 + 6·05	Olefinics	
	3·0	H(4)	H(3*x*)
	2·9	H(1)	H(3*x*)
	2·5	H(2*n*)	H(3*x*), H(3*n*)
	2·1	H(3*x*)	H(4), H(1), H(2*n*), H(3*n*)
	1·8	H(7*s*)	H(7*a*)
	1·4	H(7*a*)	H(7*s*)
	1·15	H(3*n*)	H(2*n*), H(3*x*)
(II)	7·3–7·7	Ph	
	6·15 + 6·05	Olefinics	
	3·5	H(1) or H(4)	H(3*x*) or H(7*a*), H(7*s*)
	3·0	H(1) or H(4)	H(3*x*) or H(7*a*)
	2·65	H(2*n*)	H(3*x*), H(3*n*)
	1·75	H(7*s*)	H(1) or H(4), H(7*a*), H(3*n*)
	1·50	H(7*a*) + H(3*x*)	H(1), H(4), H(2*n*), H(7*s*), H(3*n*)
	1·05	H(3*n*)	H(2*n*), H(7*s*), H(3*x*)
(III)	7·3–7·7	Ph	
	6·35 + 6·25	Olefinics	
	3·45	H(1)	No major couplings
	3·35	H(2*x*)	H(3*x*), H(3*n*)
	2·85	H(4)	H(3*x*), H(3*n*)
	1·65	H(7*s*)	H(7*a*)
	1·50	H(3*x*)	H(2*x*), H(4), H(3*n*)
	1·25	H(7*a*)	H(7*s*)
	0·85	H(3*n*)	H(2*x*), H(4), H(3*x*)

The largest coupling is underlined.

diagnostically useful coupling between the bridgehead proton and the corresponding *exo* proton [*i.e.* H(4) and H(3*x*), and in the *endo*-substituted isomers only H(1) and H(2*x*)]. A smaller coupling is found between H(7*s*) and H(3*n*), and H(7*s*) and H(2*n*) if this *endo* proton is present (see the drawing in Table 7).

In this study 400 mHz NMR spectra were obtained for each diastereomer and the spectra were interpreted with the aid of two-dimensional NMR techniques (*COSY*). The two *exo* isomers [(I), (II)] gave high-field spectra entirely consistent with expectations. However, the *endo* sulfoxide exhibited a much smaller than expected coupling between H(2*x*) and H(1). A simple Karplus relationship would predict a slight reduction in this coupling constant as the H(2*x*)–C(2)–C(1)–H(1) dihedral angle is only 42° (X-ray data, this paper). However, it is well known that factors such as torsional effects, long-range electronic interactions and the electronegativity of a substituent also exert a profound influence upon vicinal couplings (see, for example, Marchand, 1982).

Table 8. *NMR assignments showing only major* (2Hz) *spin–spin couplings between saturated sites (Abraham & Fisher,* 1985)



Chemical shift (p.p.m. downfield from Me_4Si)	Assignment	Coupled to
5·99	H(2) + H(3)	
2·84	H(1)	H(6*x*)
	H(4)	H(5*x*)
1·60	H(5*x*)	H(4), H(6*x*), H(6*n*), H(5*n*)
	H(6*x*)	H(1), H(5*x*), H(5*n*), H(6*n*)
1·31	H(7*s*)	H(7*a*), H(5*n*), H(6*n*)
1·07	H(7*a*)	H(7*s*)
0·95	H(5*n*)	H(7*s*), H(6*x*), H(5*x*), H(6*n*)
	H(6*n*)	H(7*s*), H(5*x*), H(6*x*), H(5*n*)

The largest coupling is underlined.

The chemical shifts and major couplings between saturated positions (from the *COSY* experiments) for every proton is shown in Table 7. Each signal exhibited extensive long-range couplings. However, only the dominant couplings are considered in Table 7. For comparison the corresponding data are shown for the parent hydrocarbon norbornene (Abraham & Fisher, 1985) in Table 8.

In the present study both *exo* and *endo* isomers are studied and it is therefore possible to observe the relative difference in chemical shift for both configurations of the proton at the 2-position. As can be seen in Table 7, the *exo* proton H(2*x*) resonates approximately 1 p.p.m. lower field than the *endo* proton H(2*n*) which is in complete agreement with previous work (Abraham & Fisher, 1985; Marchand, 1982). Although individual coupling constants cannot be extracted directly from our data, the *COSY* spectra allow for the identification of the major spin–spin couplings. This additional information aids the assignments of stereochemistry. The X-ray data not only confirm the *endo* or *exo* disposition of the sulfoxide group but also establish the relative configuration at each chiral center. Clearly this could not easily be accomplished by NMR spectroscopy. The X-ray structure for the *endo* sulfoxide, (III), provides a rationalization for the smaller than expected spin–spin coupling observed between H(2*x*) and H(1). (III) was initially incorrectly identified from the 60 mHz NMR spectrum as having the sulfoxide in the *exo* position. This misassignment is a direct consequence of the reduced coupling observed between H(2*x*) and H(1).

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Structure of Insulin: Results of Joint Neutron and X-ray Refinement

BY ALEXANDER WLODAWER* AND HUGH SAVAGE†

Center for Chemical Physics, National Bureau of Standards, Gaithersburg, MD 20899, *USA, and Laboratory of Molecular Biology, National Institute of Diabetes, and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD* 20892, *USA*

AND GUY DODSON

Department of Chemistry, University of York, York, England

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Abstract

Neutron diffraction data for porcine 2Zn insulin were collected to 2·2 Å resolution from a single crystal deuterated by slow exchange of mother liquor. A joint neutron/X-ray restrained-least-squares refinement was undertaken using the neutron data, as well as the 1·5 Å resolution X-ray data collected previously. The final R factors were 0·182 for the X-ray data and 0·191 for the neutron data. Resulting atomic coordinates were compared with the initial X-ray model, showing a total r.m.s. shift of 0·36 Å for the protein and 0·6 Å for the solvent. Protonation of a number of individual amino acids was investigated by analysis of the neutron maps. No D atoms were found between the carboxylates of Glu *B*13 which make an intermolecular contact, suggesting nonbonded interaction rather than the predicted hydrogen bond. Amide hydrogen exchange was investigated in a refinement of their atomic occupancies. Regions of unexchanged amide groups were found in the center of the *B* helices. The results of this study emphasize the limited amount of information available in neutron diffraction studies of proteins at resolution lower than 2 Å.

Introduction

Insulin was one of the first polypeptide hormones to be crystallized (Abel, 1926) and characterized by X-ray diffraction (Crowfoot, 1935). The first report of its structure based on multiple isomorphous replacement methods was published by Adams *et al.* (1969). The principal difficulty in determining the crystal structure was in finding and solving heavy-atom derivatives. At one stage it was suggested by S. Ramaseshan (unpublished) that neutron diffraction and the use of a strong anomalous scatterer such as ^{157}Gd, ^{149}Sm or ^{113}Cd might alleviate the problems (also see Schoenborn,

* Current address: National Cancer Institute, Crystallography Laboratory, BRI-FCRF, PO Box B, Frederick, MD 21701, USA.

† Current address: Department of Chemistry, University of York, York, England.

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