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Structural Studies of Mitomycins. I. Absolute Configurations of Mitomycins A and B

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Abstract

The absolute configurations of mitomycins A and B were determined by the Bijvoet difference method. (*A*) 1-*N*-(*p*-Bromobenzoyl)mitomycin A, $C_{23}H_{22}BrN_3O_7$, $M_r = 520{\cdot}35$, orthorhombic, $P2_12_12$, $a = 20{\cdot}277\ (1)$, $b = 27{\cdot}320\ (4)$, $c = 8{\cdot}348\ (4)$ Å, $V = 4624{\cdot}5\ (6)$ Å^3, $Z = 8$, $D_x = 1{\cdot}493$ g cm^{-3}, Cu $K\alpha$ radiation (graphite-monochromated), $\lambda = 1{\cdot}54184$ Å, $\mu = 28{\cdot}34$ cm^{-1}, $F(000) = 2176$, $T = 295$ K. (*B*) 7-*p*-Bromoanilino-7-demethoxymitomycin B, $C_{21}H_{21}BrN_4O_5$, $M_r = 507{\cdot}4$, orthorhombic, $P2_12_12_1$, $a = 29{\cdot}183\ (2)$, $b = 9{\cdot}251\ (1)$, $c = 7{\cdot}9324\ (5)$ Å, $V = 2141{\cdot}0\ (3)$ Å^3, $Z = 4$, $D_x = 1{\cdot}518$ g cm^{-3}, Cu $K\alpha$ radiation (graphite-monochromated), $\lambda = 1{\cdot}54184$ Å, $\mu = 29{\cdot}68$ cm^{-1}, $F(000) = 1000$, $T = 297$ K. The final R values are 0·047 and 0·057 for 4179 and 2102 reflections, respectively. The results indicate that the currently employed absolute configurations of mitomycins A and B are incorrect and should be revised. The configurations at C1, C2, and C9a are *S*, *S* and *R* in these two compounds, and the configurations at C9 are *S* and *R* in mitomycins A and B, respectively.

Introduction

Mitomycins are very effective antitumor compounds and mitomycin C, a prominent member of the mitomycins, is clinically used extensively and successfully today. The absolute configurations of mitomycins A (Tulinsky & van den Hende, 1967) and B (Yahashi & Matsubara, 1976, 1978), which are essential members of the mitomycin family, were determined by X-ray analysis using heavy-atom derivatives.

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Studies of the biosynthesis of mitomycins have been carried out by Hornemann and co-workers (Hornemann, Kehrer, Nunez & Ranieri, 1974; Hornemann & Aikman, 1973). Their results are not necessarily consistent with the configurations determined by X-ray analysis. D-Glucosamine is incorporated into mitomycins efficiently (incorporation rate of 2·3%) by *Streptomyces verticillatus* and provides its C6 unit of C1, C2, C3, C9a, C9 and C10 and the N atom of the aziridine ring without any cleavage of C–C and C–N bonds of the amino sugar during biosynthesis (Hornemann *et al.*, 1974). On the other hand, incorporation rates of L-glucosamine and D-mannosamine, both with the same configuration at C2 as determined by X-rays, are 0·6% and less than 0·01%, respectively. The rates reveal that these molecules cannot be incorporated as precursors of the C6 unit (Fig. 1) (Hornemann & Aikman, 1973). If both independent experiments, X-ray analyses and biosynthesis studies, are correct, the epimerization must occur during or after incorporation of D-glucosamine in the biosynthetic process. Such an epimerization might be possible, but it seems to be less probable. These results have prompted us to reinvestigate the absolute configurations of mitomycins.

As mitomycin C had been chemically derived from mitomycin A (Uzu, Harada & Wakaki, 1964), their absolute configurations were believed to be identical with that proposed by Tulinsky & van den Hende (1967), although their optical rotations had not been determined because of their strong UV and visible absorption. The molecular structures of mitomycin C (Arora, 1979) and its hydrate (Ogawa, Nomura, Fujiwara & Tomita, 1979) were determined by X-ray analysis, but the absolute configurations were not determined. Therefore we have determined the

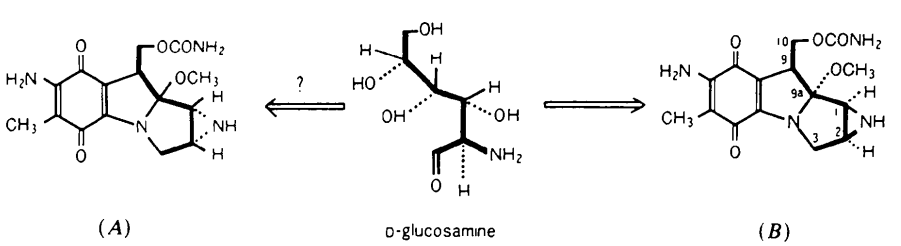

Fig. 1. Biosynthesis of mitomycins.

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Table 1. *Experimental details*

	(*A*)	(*B*)
Crystal size (mm)	0·3 × 0·3 × 0·2	0·3 × 0·3 × 0·2
Range of θ (°)	$2 \le \theta \le 75$	$2 \le \theta \le 75$
Scan width (°)	0·90 + 0·14 tan θ	0·85 + 0·14 tan θ
Aperture width (mm)	2·75 + 0·50 tan θ	2·75 + 0·50 tan θ
Scan mode	$\omega/2\theta$	$\omega/2\theta$
SIGPRE*	0·333	0·333
NPIPRE†	4	4
Maximum scan time (s)	60	60
hkl *h*	0–25	0–36
k	0–34	0–11
l	0–10	0–9

* Prescan acceptance parameter; if $\sigma(I)/I$ of the prescan data is greater than SIGPRE, the reflection is considered observed.

† Prescan speed parameter. Scan speed is defined by 20/NPIPRE (° min^{-1}).

Table 2. *Comparison of R and S values*

	(*A*)	(*B*)
R	0·0474	0·0566
wR	0·0675	0·0685
S	2·2551	2·3771
R^{E*}	0·0546	0·0635
wR^{E*}	0·0781	0·0788
S^{E*}	2·6120	2·7326
wR^E/wR	1·157	1·150
H atoms	Not refined	Refined
Final $(\Delta/\sigma)_{max}$	0·15	0·21
$\Delta\rho$ values (e Å^{-3})	+0·33 to −0·25	+0·35 to −0·30

* R^E, wR^E and S^E denote *R*, *wR* and *S* values of the antipode.

absolute configurations of mitomycin C by the Bijvoet method using its heavy-atom derivative (Shirahata & Hirayama, 1983). The configuration is compatible with the results of biosynthesis studies and indicates that the absolute configurations of mitomycins A and B determined by X-ray analysis were suspicious. As the optical rotation is useless in this case, the chemical results on the interconversion between mitomycins cannot be confirmed to specify the absolute configurations. Accordingly, to determine the absolute configurations of mitomycins *A* and *B* unequivocally they must be redetermined by X-ray analysis. In this paper we will report the redetermination of the absolute configurations of the two main mitomycins A and B using their heavy-atom derivatives *N*-(*p*-bromobenzoyl)mitomycin *A* (*A*) and 7-*p*-bromoanilino-7-demethoxymitomycin B (*B*). Preliminary results have already been published (Hirayama & Shirahata, 1984).

Experimental

After initial measurements from oscillation and Weissenberg photographs, the final cell dimensions and intensity data were measured with an Enraf–Nonius CAD-4 diffractometer. Experimental details are shown in Table 1. Lattice parameters were calculated from 25 reflections with $35 < \theta < 55°$. Intensities were converted into structure amplitudes in the usual way. No absorption correction was applied to the data. Three standard reflections, no intensity variation. 5377 and 2562 independent reflections were collected for (*A*) and (*B*), respectively. Of these 4179 and 2102 having intensities $I > 3{\cdot}0\sigma(I)$ for (*A*) and (*B*) were considered observed and were used in the structure analysis.

Both structures were solved by direct methods. The structure of (*B*) was solved by *MULTAN*11/82 (Main, Fiske, Hull, Lessinger, Germain, Declercq & Woolfson, 1982), but the structure of (*A*) was solved by *RANTAN* (Yao Jia-xing, 1981) incorporated in *MULTAN*11/82. An *E* map calculated using the best set of phases gave only fragments of the two crystallographically independent molecules. Successive difference Fourier synthesis revealed the locations of the remaining non-H atoms and completed the skeletons of the molecules. The structural parameters were refined on *F* by full-matrix least squares. The details of the results of the refinement are listed in Table 2. The weighting scheme used in the final refinement is $w = 4F_o^2/[\sigma^2(I_o) + (0{\cdot}05F_o^2)^2]$. The programs used throughout the analysis were provided by Enraf–Nonius, *i.e.* CAD-4 *SDP-Plus*, version 1.0 (Frenz, 1982) and version 1.1 (Frenz, 1983). Atomic scattering factors were taken from *International Tables for X-ray Crystallography* (1974). Atomic parameters are listed in Tables 3 and 4.* The atomic notation used in the tables is shown in Fig. 2.

Results and discussion

The absolute configurations were determined by the Bijvoet difference method. Each structure was independently determined with atoms in both enantiomorphic configurations. The f' and f'' values of C, N, O and Br were taken from *International Tables for X-ray Crystallography* (1974). The *R* factors and *S* values of the antipodes of the correct absolute configurations, R^E, wR^E and S^E, are also listed in Table 2. At the end of each refinement, reflections with F_c differing significantly were chosen. Of these, the reflections with good agreement between F_o and F_c were screened. The contributions of the anomalous-dispersion terms to these reflections must be rather large. The reflections used to determine the absolute configurations are listed in Table 5. The intensities of these reflections were remeasured by the diffractometer with great care. The scan speed employed in the remeasuring was 0·44–2·0° (2θ) min^{-1}, which is more than two times slower than that employed during the normal data collection. For (*A*) and (*B*), all eight reflections equivalent to *hkl* in the centrosymmetric group were collected.

* Lists of structure factors, anisotropic thermal parameters and H-atom coordinates have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 44184 (36 pp). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 3. *Positional parameters of* (*A*) ($\times 10^5$ *for* Br, $\times 10^4$ *for other non-*H *atoms*) *and equivalent isotropic temperature factors* (Å^2) *for non-*H *atoms*

$B_{eq} = \frac{4}{3}\sum_i \sum_j \beta_{ij}\mathbf{a}_i.\mathbf{a}_j$

	x	y	z	B_{eq}
Molecule *A*				
Br	78409 (3)	82546 (3)	37440 (10)	7·59 (2)
O5	11410 (2)	7776 (1)	−1876 (5)	5·64 (9)
O7	13152 (2)	7472 (2)	1536 (9)	9·6 (1)
O8	12766 (2)	6484 (1)	1578 (6)	6·26 (9)
O9a	10808 (2)	5941 (1)	−2544 (4)	4·18 (6)
O10	11177 (2)	5388 (1)	782 (4)	4·30 (6)
O10a	10816 (2)	5221 (1)	3273 (4)	5·37 (8)
O11	9799 (2)	6236 (1)	2871 (5)	6·06 (9)
N1	10158 (2)	6669 (1)	699 (5)	3·98 (7)
N4	10997 (2)	6769 (1)	−1745 (5)	3·59 (7)
N10	10771 (2)	4656 (1)	1283 (6)	5·05 (9)
C1	10258 (2)	6255 (2)	−406 (6)	3·91 (9)
C2	9905 (2)	6702 (2)	−942 (6)	4·28 (9)
C3	10346 (2)	6988 (21)	−2013 (7)	4·4 (1)
C4a	11495 (2)	6971 (2)	−883 (6)	3·48 (8)
C5	11700 (2)	7498 (2)	−1023 (6)	4·04 (9)
C6	12281 (3)	7641 (2)	−92 (8)	5·1 (1)
C6a	12464 (3)	8178 (2)	−160 (10)	6·8 (2)
C7a	13577 (4)	7274 (4)	2290 (1)	11·8 (2)
C7	12627 (2)	7313 (2)	752 (7)	4·9 (2)
C8a	11832 (2)	6648 (1)	2 (6)	3·56 (8)
C8	12428 (2)	6775 (2)	826 (6)	4·27 (9)
C9a	10921 (2)	6251 (2)	−1227 (6)	3·59 (8)
C9	11548 (2)	6139 (2)	−243 (6)	3·66 (8)
C9b	11298 (2)	5932 (2)	−3763 (8)	5·7 (1)
C10a	10918 (2)	5094 (2)	1911 (6)	4·11 (9)
C10	11409 (2)	5857 (2)	1305 (6)	4·33 (9)
C11	9766 (2)	6601 (2)	2048 (6)	4·28 (9)
C12	9322 (2)	7018 (2)	2450 (6)	4·26 (9)
C13	8800 (3)	6930 (2)	3510 (10)	6·6 (1)
C14	8362 (3)	7289 (2)	3890 (10)	7·3 (2)
C15	8438 (2)	7745 (2)	3196 (7)	5·1 (1)
C16	8950 (3)	7847 (2)	2200 (7)	5·5 (1)
C17	9390 (3)	7477 (2)	1807 (7)	4·9 (1)
Molecule *B*				
Br	5788 (4)	63736 (3)	99810 (10)	9·17 (2)
O5	4865 (1)	4266 (1)	3436 (5)	5·37 (8)
O7	4234 (2)	2793 (2)	5719 (7)	7·4 (1)
O8	2930 (2)	3165 (1)	5807 (6)	6·16 (9)
O9a	2416 (2)	4783 (1)	2259 (4)	4·43 (6)
O10	1598 (1)	4414 (1)	5607 (4)	4·80 (7)
O10a	1197 (2)	4175 (2)	8000 (5)	5·92 (9)
O11	2732 (2)	5352 (2)	7936 (5)	5·61 (8)
N1	3331 (2)	5104 (1)	5780 (5)	3·92 (7)
N4	3495 (2)	4576 (1)	3173 (5)	3·43 (6)
N10	559 (2)	4561 (2)	6189 (6)	5·9 (1)
C1	2796 (2)	5101 (2)	4593 (6)	3·92 (9)
C2	3439 (2)	5351 (2)	4262 (6)	4·40 (9)
C3	3836 (2)	5049 (2)	3101 (6)	4·42 (9)
C4a	3721 (2)	4160 (2)	3900 (5)	3·33 (7)
C5	4425 (2)	3995 (2)	3931 (6)	4·02 (9)
C6	4557 (2)	3517 (2)	4523 (7)	4·7 (1)
C6a	5256 (3)	3333 (3)	4465 (9)	7·1 (2)
C7a	3818 (3)	2412 (2)	6030 (10)	8·1 (2)
C7	4066 (2)	3237 (2)	5131 (7)	4·41 (9)
C8	3363 (2)	3411 (2)	5205 (7)	4·15 (9)
C8a	3242 (2)	3887 (2)	4565 (6)	3·51 (8)
C9	2592 (2)	4145 (2)	4418 (6)	3·60 (8)
C9a	2792 (2)	4641 (2)	3603 (5)	3·50 (8)
C9b	2451 (3)	4477 (2)	890 (7)	5·7 (1)
C10a	1116 (2)	4365 (2)	6714 (6)	4·18 (9)
C10	2224 (2)	4198 (2)	5997 (6)	4·09 (9)
C11	3252 (2)	5347 (2)	7234 (6)	4·22 (9)
C12	3870 (2)	5568 (2)	7903 (6)	4·26 (9)
C13	3818 (3)	5823 (2)	9310 (7)	5·0 (1)
C14	4382 (3)	6046 (2)	9941 (8)	6·0 (1)
C15	4957 (3)	6017 (2)	9180 (7)	5·7 (1)
C16	5021 (3)	5748 (3)	7815 (8)	6·5 (1)
C17	4472 (3)	5527 (3)	7152 (8)	6·0 (1)

Table 4. *Positional parameters of* (*B*) ($\times 10^5$ *for* Br, $\times 10^4$ *for other non-*H *atoms*) *and equivalent isotropic temperature factors* (Å^2) *for non-*H *atoms*

O*W* denotes the O atom of the water molecule.
$B_{eq} = \frac{4}{3}\sum_i \sum_j \beta_{ij}\mathbf{a}_i.\mathbf{a}_j$.

	x	y	z	B_{eq}
Br	9007 (2)	109060 (10)	12290 (10)	7·18 (2)
O5	3012 (1)	4103 (4)	−1030 (5)	3·67 (7)
O8	3719 (1)	9191 (4)	818 (6)	4·03 (8)
O9a	4713 (1)	4112 (3)	824 (4)	2·80 (5)
O10	4707 (1)	6416 (3)	−1381 (4)	2·84 (5)
O10a	5126 (1)	8263 (4)	−2434 (5)	3·66 (7)
N1	3796 (1)	4522 (5)	3872 (5)	3·03 (7)
N4	3896 (1)	4244 (4)	550 (5)	2·46 (6)
N7	2871 (1)	9208 (5)	−160 (7)	3·75 (9)
N10	5008 (2)	6190 (5)	−3911 (5)	3·86 (9)
C1	4250 (2)	4222 (5)	3208 (6)	2·81 (8)
C1a	3779 (2)	4586 (7)	5720 (7)	4·3 (1)
C2	3895 (2)	3089 (6)	3175 (7)	3·27 (9)
C3	3730 (2)	2912 (5)	1379 (7)	3·24 (9)
C4a	3625 (1)	5397 (5)	203 (6)	2·51 (7)
C5	3154 (1)	5282 (5)	−564 (6)	2·74 (8)
C6	2893 (1)	6606 (6)	−760 (6)	3·07 (8)
C6a	2451 (2)	6467 (7)	−1711 (8)	4·3 (1)
C7	3079 (1)	7880 (5)	−198 (6)	2·92 (8)
C8	3573 (1)	8000 (5)	399 (6)	2·82 (8)
C8a	3825 (1)	6690 (5)	510 (6)	2·45 (7)
C9a	4314 (1)	4784 (5)	1439 (6)	2·46 (7)
C9	4297 (1)	6462 (5)	1250 (6)	2·44 (7)
C10	4688 (1)	7121 (5)	244 (6)	2·54 (7)
C10a	4967 (1)	7049 (5)	−2568 (7)	2·63 (7)
C11	2409 (2)	9539 (6)	149 (7)	3·38 (9)
C12	2257 (2)	10935 (6)	−318 (8)	4·2 (1)
C13	1808 (2)	11333 (7)	12 (9)	4·8 (1)
C14	1521 (2)	10396 (7)	797 (8)	4·7 (1)
C15	1666 (2)	9066 (7)	1341 (8)	4·3 (1)
C16	2115 (2)	8627 (6)	999 (7)	3·8 (1)
O*W*	4558 (1)	338 (5)	2110 (6)	4·98 (9)

$F_o(hkl)$ was taken as the mean value of $F_o(hkl)$, $F_o(\bar{h}\bar{k}l)$, $F_o(\bar{h}k\bar{l})$, $F_o(h\bar{k}\bar{l})$, and $F_o(\bar{h}\bar{k}\bar{l})$ as the mean value of the other four reflections. The ΔF_o's in Table 5 represent the differences between the averaged $F_o(hkl)$ and $F_o(\bar{h}\bar{k}\bar{l})$. The ΔF_o and ΔF_c values of (*A*) and (*B*) are compared in Table 5. The standard deviations determined from the distribution of the equivalent reflections from the mean were compared with the standard deviations expected from counting statistics. The larger values are shown in Table 5. The signs of ΔF_o and ΔF_c of (*A*) listed in Table 5 are the same for the 39 Bijvoet pairs. The magnitudes of ΔF_o and ΔF_c are similar. This result indicates unambiguously the correct absolute configuration as shown

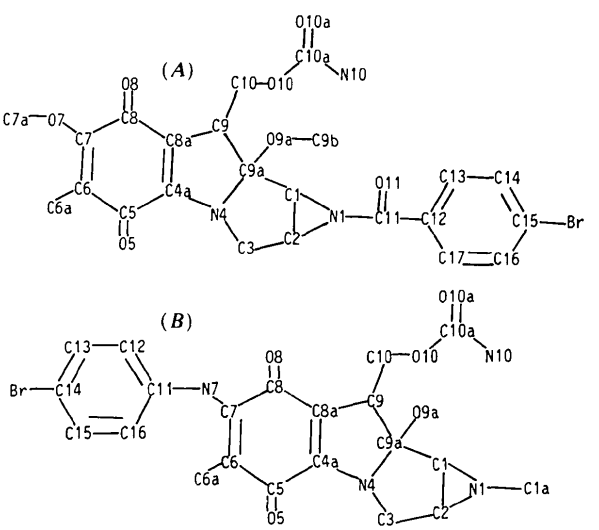


Fig. 2. Atomic notation of mitomycins A and B.

Table 5. *Comparison of ΔF_o and ΔF_c values* (×10)

Index			ΔF_c	ΔF_o	σ	Index			ΔF_c	ΔF_o	σ
(*A*)											
5	26	1	+16	+12	3	8	2	4	+14	+14	1
8	22	1	+24	+19	2	8	7	4	−13	−13	2
11	17	1	+24	+29	2	14	11	4	+13	+11	2
3	14	1	−37	−31	2	10	12	4	+20	+21	2
7	12	1	−25	−37	1	12	6	4	+13	+9	3
15	11	1	−22	−11	2	10	17	4	−15	−13	3
12	7	1	−20	−21	2	10	14	5	+15	+15	3
10	4	1	−28	−25	2	18	9	5	−10	−8	3
14	4	2	−24	−22	2	5	7	5	+21	+19	2
10	6	2	−20	−20	3	3	4	5	+27	+35	2
14	9	2	−23	−21	2	2	3	5	+26	+21	2
13	19	2	−18	−21	2	14	3	6	+34	+19	2
3	20	2	+27	+34	2	2	4	6	−16	−18	2
11	22	2	−19	−14	2	3	10	6	+19	+20	2
2	15	3	−20	−17	1	6	14	6	+16	+18	3
10	9	3	+24	+14	2	4	15	6	+20	+17	3
6	6	3	−24	−24	1	3	6	7	−14	−16	3
3	5	3	−40	−32	1	11	4	7	+14	+14	3
15	2	3	−15	−11	3	3	2	7	+20	+15	2
3	2	4	−22	−14	1						
(*B*)											
1	6	1	+10	+19	1	23	2	3	+12	+14	2
5	5	1	−16	−20	2	9	2	3	+18	+18	2
11	3	1	−9	−9	1	1	1	3	−13	−21	1
23	3	1	−12	−14	2	8	1	3	−11	−19	1
25	1	1	−13	−15	1	12	1	3	−22	−27	2
17	1	2	+25	+31	2	20	1	3	−22	−26	2
9	2	2	−14	−24	2	24	1	3	+14	+14	2
26	2	2	−13	−13	2	1	1	4	−22	−24	2
15	4	2	−18	−18	2	28	4	4	+10	+10	1
19	4	2	−19	−25	2	15	5	4	+12	+16	1
16	5	2	+16	+25	2	2	6	4	−13	−16	2
11	5	2	−13	−10	1	1	4	5	+16	+6	2
5	5	2	−12	−13	1	19	2	5	+13	+11	1
21	6	3	+9	+9	2	1	2	5	−15	−18	2
18	3	3	−19	−22	2	21	1	5	+12	+7	2
26	2	3	−14	−18	1	12	1	6	−14	−16	1
25	2	3	+14	+15	2						

in Fig. 3, in which one of the two crystallographically independent molecules, molecule *A*, is depicted. The 33 Bijvoet pairs of (*B*) are also listed in Table 5. The signs of ΔF_o and ΔF_c are the same and the magnitudes are very similar. They clearly determine the absolute configuration as shown in Fig. 4. Figs. 3 and 4 were drawn by *ORTEP*II (Johnson, 1976).

The absolute configurations of mitomycins A and B disclosed by the present analysis are summarized in Fig. 5. The correct absolute configuration of mitomycin C (Shirahata & Hirayama, 1983) is also shown in the figure. The configurations at C1, C2 and C9a are *S*, *S* and *R*, and the configurations at C9 are *S* and *R* for (*A*) and (*B*), respectively. These results indicate that the absolute configurations derived from biosynthesis studies are correct and the previously employed configurations based on X-ray analysis should be revised.

We want to discuss briefly the reasons which led to the wrong results in the analysis by Tulinsky & van den Hende (1967) and Yahashi & Matsubara (1978). The former employed the *R*-factor-ratio test at a rather high *R*-factor level, *i.e.* 0·094 and 0·087. The *R*-factor ratio in this case is 1·08. It is significantly smaller than those listed in Table 2. Even if there are some heavy atoms in a molecule, the *R*-factor-ratio test at high *R* factor would possibly mislead the assignment of the correct absolute configurations. Although the latter authors used the Bijvoet method, they also determined the absolute configuration at a rather high *R* factor of 0·119. We cannot exclude other possible reasons for the wrong assignments, but these two examples seem to warn that the determina-

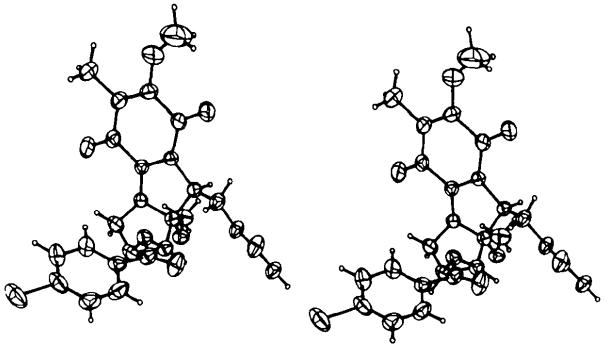


Fig. 3. Absolute configuration of (*A*) with thermal ellipsoids at 30% probability. One of the two crystallographically independent molecules (molecule *A*) is shown.

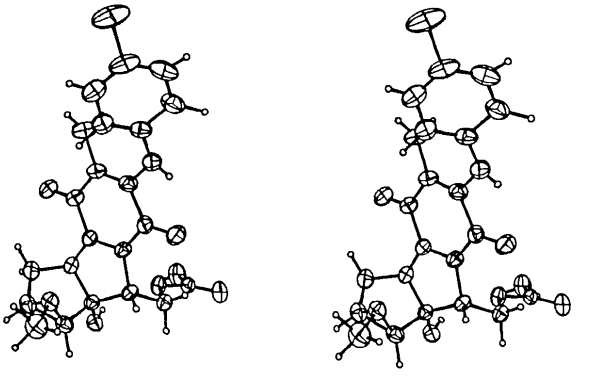
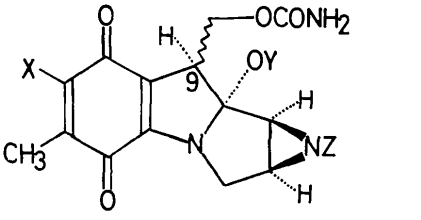


Fig. 4. Absolute configuration of (*B*) with thermal ellipsoids at 30% probability.



	X	Y	Z	9
mitomycin A	OCH_3	CH_3	H	β
mitomycin B	OCH_3	H	CH_3	α
mitomycin C	NH_2	CH_3	H	β

Fig. 5. Revised absolute configurations of (*A*), (*B*) and mitomycin C.

tion of the absolute configurations at high R is quite risky in some cases even though the structure contains heavy atoms.

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Theoretical Studies of Solid-State Reactivity by Packing Density and Potential-Energy Maps: Hydrogen Transfer in 5-Nitro-3-thiophenecarboxaldehyde Crystals

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Abstract

Packing-density maps and potential-energy maps for hydrogen migration in the title crystal are described. The two kinds of information are similar and complementary to one another. This resemblance could be exploited to trace non-van der Waals interactions in crystals. It is proposed that the packing-density–potential-energy methodology offers a sound and systematic basis for the discussion of intermolecular effects in solid-state reactivity.

Introduction and purpose

It is well known that irradiation by X-rays causes damage in organic crystals, usually by formation of radicals, that can also diffuse in the crystalline matrix, leading to a variety of products. These reactions can have very low conversion factors, so that the photolytic guest is unnoticed in ordinary X-ray diffraction analyses [but see Wei & Einstein (1981), who detected the presence of such a compound during the usual refinement procedures]. Spin resonance spectroscopies are, however, sensitive enough to give considerable structural and chemical information on these systems, whose theoretical importance lies in the fact that they provide models for the first stages of reaction, where the products are trace impurities and the crystal matrix is largely unperturbed. Such cases provide unique insight on the crystal-lattice constraints on the path of solid-state organic reactions.

We have previously undertaken the packing analysis of photochemical reactions in crystals (Gavezzotti & Bianchi, 1986; Gavezzotti, 1987). We present in this paper some calculations for the hydrogen transfer after radicalization in 5-nitro-3-thiophenecarboxaldehyde (NTCA) crystals, a reaction that has been studied by ESR and ENDOR as a function of temperature (Geoffroy, Celalyan-Berthier, Reddy, Bernardinelli & Papadopoulos, 1985). This is one of the few, but rapidly increasing in number, cases in which a full X-ray structure determination was carried out. Our results confirm (or, at least, do not contradict) the conclusions drawn from the spectroscopic study, and illustrate the potential applications of a simultaneous use of packing-density and packing-energy methods in mapping the most favourable reaction paths in organic crystals.

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