solche Untergruppen von $G_1$ berücksichtigt zu werden, die Obergruppen von $G_7 = P312$ sind. Die Raumgruppe $G_2 = P\bar{3}2/m1$, deren Elementarzelle noch nicht auf die *H*-Zelle vergrößert ist, kann nicht weggelassen werden, obwohl man sich nur für die *H*-Zelle interessiert; $G_2$ bietet nämlich gegenüber $G_1$ eine neue Möglichkeit zur Verteilung von Atomen auf die Oktaederlücken. Wird $G_2$ im Stammbaum von Fig. 8 weggelassen, so ergeben sich für $G_6$ und $G_7$ falsche Zahlen. Andererseits kann die Raumgruppe $P\bar{6}m2$ als maximale Untergruppe von $G_1$ weggelassen werden; sie ergibt gegenüber $G_1$ keine neue Möglichkeit zur Besetzung der Oktaederlücken (beide Oktaederlücken bleiben symmetrieäquivalent), und sie wird auch nicht als Zwischenglied zwischen $G_1$ und einer der Raumgruppen der *H*-Zelle benötigt.

Ich danke dem Fonds der Chemischen Industrie für die Unterstützung dieser Arbeit.

### Literatur

BÄRNIGHAUSEN, H. (1980). *Commun. Math. Chem.* **9**, 139–175.
BECK, P. A. (1967). *Z. Kristallogr.* **124**, 101–114.
DEBLIECK, R., TENDELOO, G. V. & LANDUYT, J. V. (1985). *Acta Cryst.* **B41**, 319–329.
HÄGG, G. (1943). *Arch. Kem. Mineral. Geol.* **16B**, 1–6.
HAUCK, J., HENKEL, D. & MIKA, K. (1988). *Z. Kristallogr.* **182**, 217–306.
HAWTHORNE, F. C. (1983). *Acta Cryst.* **A39**, 724–736.
HELLNER, E. (1979). *Struct. Bonding (Berlin)*, **37**, 61–140.
HELLNER, E. (1986). *Z. Kristallogr.* **175**, 227–248.
KOCH, E. (1984). *Acta Cryst.* **A40**, 593–600.
KOCH, E. & FISCHER, W. (1987). *International Tables for Crystallography*, Bd. A, 2. Aufl., Tabelle 15.3.2., S. 856–864. Dordrecht: Kluwer.
KOCH, E. & MÜLLER, U. (1990). *Acta Cryst.* **A46**, 826–831.
LIMA-DE-FARIA, J. (1965). *Z. Kristallogr.* **122**, 359–374.
LIMA-DE-FARIA, J. & FIGUEIREDO, M. O. (1969*a*). *Z. Kristallogr.* **130**, 41–53.
LIMA-DE-FARIA, J. & FIGUEIREDO, M. O. (1969*b*). *Z. Kristallogr.* **130**, 54–67.
MCLARNAN, T. J. (1978). *J. Solid State Chem.* **26**, 235–244.
MCLARNAN, T. J. (1981*a*). *Z. Kristallogr.* **155**, 227–245.
MCLARNAN, T. J. (1981*b*). *Z. Kristallogr.* **155**, 247–268.
MCLARNAN, T. J. (1981*c*). *Z. Kristallogr.* **155**, 269–291.
MCLARNAN, T. J. & BAUR, W. H. (1982). *J. Solid State Chem.* **42**, 283–299.
MÜLLER, U. (1978). *Acta Cryst.* **A34**, 256–267.
MÜLLER, U. (1979). *Acta Cryst.* **A35**, 188–193.
MÜLLER, U. (1981). *Acta Cryst.* **B37**, 532–545.
MÜLLER, U. (1986). *Acta Cryst.* **B42**, 557–564.
MÜLLER, U. (1988). *Z. Kristallogr.* **182**, 189–190.
MÜLLER, U. & CONRADI, E. (1986). *Z. Kristallogr.* **172**, 154–156.
PÓLYA, G. (1937). *Acta Math.* **68**, 145–254.
SMIRNOVA, N. L. (1956). *Kristallografiya*, **1**, 165–171; *Sov. Phys. Crystallogr.* **1**, 128.
WELLS, A. F. (1984). *Structural Inorganic Chemistry*, 5. Aufl., S. 161–186. Oxford: Clarendon Press.
WHITE, D. (1974). *Proc. Am. Math. Soc.* **47**, 41.
WHITE, D. (1975). *Discret. Math.* **13**, 277–295.
WONDRATSCHEK, H. (1987*a*). *International Tables for Crystallography*, Bd. A, 2 Aufl., S. 724. Dordrecht: Kluwer.
WONDRATSCHEK, H. (1987*b*). *International Tables for Crystallography*, Bd. A, 2. Aufl., S. 730–732. Dordrecht: Kluwer.

---

*Acta Cryst.* (1992). **B48**, 178–185

# Synthesis and Structure of New Bronchospasmolytic Agents. I

BY S. IANELLI AND M. NARDELLI*

*Istituto di Chimica Generale, Università degli Studi di Parma,*
*Centro di Studio CNR per la Strutturistica Diffrattometrica, Viale delle Scienze, I-*43100 *Parma, Italy*

D. BELLETTI

*Istituto di Strutturistica Chimica, Università degli Studi di Parma,*
*Centro di Studio CNR per la Strutturistica Diffrattometrica, Viale delle Scienze, I-*43100 *Parma, Italy*

AND B. JAMART-GREGOIRE, A. MOUADDIB AND P. CAUBERE

*Laboratoire de Chimie Organique* I, *UA CNRS n°* 457, *Université de Nancy* I, *BP* 239,
54506 *Vandoeuvre-Les-Nancy CEDEX, France*

(*Received* 15 *July* 1991; *accepted* 8 *October* 1991)

## Abstract

The crystal structures of two phenylethanolamines showing bronchospasmolytic activity have been determined at room temperature [293 (2) K]. Crystal data are as follows: 11-morpholinotricyclo[6.3.0.0$^{2,7}$]undeca-2,4,6-trien-1-ol (3), $C_{15}H_{19}NO_2$, $M_r = 245.3$, triclinic, $P\bar{1}$, $a = 10.360$ (5), $b = 12.169$ (5), $c = 12.488$ (4) Å, $\alpha = 95.14$ (10), $\beta = 108.49$ (12), $\gamma =$

---

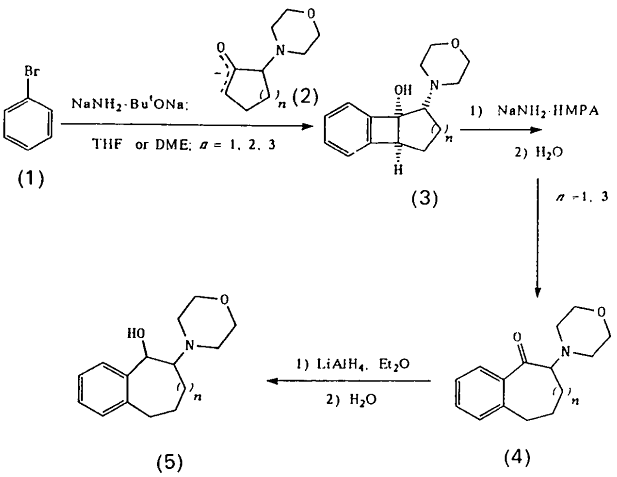
* To whom all correspondence should be addressed.

0108-7681/92/020178-08$03.00

114.69 (5)°, $V = 1311$ (2) Å$^3$, $Z = 4$, $D_x = 1.243$ Mg m$^{-3}$, Cu $K\alpha_1$ radiation, $\lambda = 1.540562$ Å, $\mu = 0.618$ mm$^{-1}$, $F(000) = 528$, $R = 0.0537$ for 3009 observed reflections; 4-morpholino-1,2-benzocyclononen-3-ol monohydrate (5), $C_{17}H_{25}NO_2.H_2O$, $M_r = 293.4$, monoclinic, $P2_1/c$, $a = 10.063$ (9), $b = 19.398$ (5), $c = 8.670$ (5) Å, $\beta = 110.56$ (1)°, $V = 1585$ (2) Å$^3$, $Z = 4$, $D_x = 1.230$ Mg m$^{-3}$, Mo $K\alpha_1$ radiation, $\lambda = 0.709300$ Å, $\mu = 0.0778$ mm$^{-1}$, $F(000) = 640$, $R = 0.0376$ for 1407 observed reflections. The stereochemistry of compound (3) is found to be 'all *cis*', which allows the mechanism of formation of these compounds to be interpreted. The various aspects of the conformations of these molecules are discussed.

## Introduction

Among biomolecules with adrenergic properties, phenylethanolamines are of paramount interest (Goodman & Gilman, 1980). As part of our program aimed at the synthesis of new structures bearing this interesting pharmacophore, and at finding new ways of obtaining these important substrates, we carried out the reactions shown in the scheme below (THF = tetrahydrofuran; DME = dimethoxyethane; HMPA = hexamethylphosphoramide).



A pharmacological study showed interesting bronchospasmolytic properties for compounds (3) and (5) (Aatif, Mouaddib, Carré, Jamart-Grégoire, Geoffroy, Zouaoui, Caubère, Blanc, Gnassounou & Advenier, 1990), and the stereochemistry of these compounds was found to be important. Although classical spectroscopic methods allow correlation among derivatives belonging to the same family, they cannot provide a direct picture of the molecular structure, so that an X-ray crystal structure determination of two representative substrates of the above reactions, *i.e.* (3) $n = 1$ and (5) $n = 3$, was necessary. In addition, this study gives information on the conformational properties of these molecules and on the deformations that occur in these polycyclic systems.

Table 1. *Experimental data for the crystallographic analyses*

| | Compound (3) | | Compound (5) |
|---|---|---|---|
| Radiation | Mo $K\alpha$ | Cu $K\alpha$ | Mo $K\alpha$ |
| Diffractometer | CAD-4 | Siemens AED | CAD-4 |
| Lattice parameters | | | |
| No. of reflections | 25 | 25 | 25 |
| $\theta$ range (°) | 9/16 | 17/37 | 10/17 |
| Crystal size (mm) | 0.23 × 0.26 × 0.43 | | 0.19 × 0.26 × 0.37 |
| Extinction parameter $g$ | – | 0.46 (23) × $10^{-7}$ | 0.11 (1) × $10^{-7}$ |
| Scan speed (° min$^{-1}$) | 1.5/3.3 | 3/12 | 1.65/3.3 |
| Scan width (°) | 0.8 + 0.35tan$\theta$ | 1.2 + 0.35tan$\theta$ | 1.2 + 0.35tan$\theta$ |
| $\theta$ range for intensity collection (°) | 3/22 | 3/70 | 3/25 |
| $h$ | – 10/10 | – 10/10 | – 11/11 |
| $k$ | – 12/12 | – 14/14 | 0/22 |
| $l$ | 0/13 | 0/15 | 0/10 |
| Standard reflection | $\bar{3}63$ | 332 | $\bar{1}$,12,4 |
| No. of measured reflections | 3189 | 4992 | 1498 |
| No. of observed reflections | 1371 | 3009 | 1407 |
| Condition for observed reflections | $I > 2\sigma(I)$ | | $I > 2\sigma(I)$ |
| $R_{int}$ | – | – | 0.0155 |
| Max. LS shift to e.s.d. ratio | 0.02 | 0.04 | 0.04 |
| Min./max. heights in final $\Delta\rho$ map (e Å$^{-3}$) | – 0.08/0.13 | – 0.13/0.26 | – 0.09/0.06 |
| No. of refined parameters | 441 | 441 | 271 |
| $R$ | 0.0357 | 0.0575 | 0.0376 |
| $w$ | Unit | Unit | Unit |

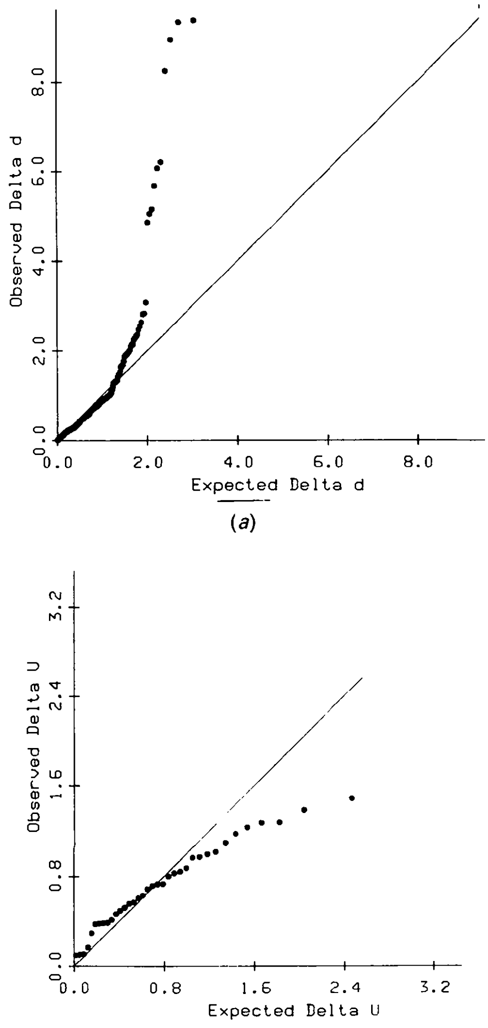
## Experimental

Table 1 summarizes the relevant data of the crystal structure analyses. For compound (3) two series of intensity data were collected with the same crystal, the first using Mo $K\alpha$ the second Cu $K\alpha$ radiation, because with the Mo data the ratio of the number of observations to the number of refined parameters was too low (3.1).* The molecular geometries derived from the two sets of data were compared by means of probability plot analysis (Abrahams & Keve, 1971), using all interatomic distances not involving hydrogens to a limit of 4.65 Å (De Camp, 1973). From the half-normal probability plot of Fig. 1(*a*) it appears that the coordinate e.s.d.'s are underestimated by a factor of two and that there is also some systematic error (possibly uncorrected absorption and extinction effects), the slope and intercept of the least-squares line being 2.12 (9) and −0.68 (9), respectively ($r = 0.855$). Fig. 1(*b*) gives the same plot for $U_{eq}$'s [slope 0.61 (2), intercept 0.23 (2), $r = 0.978$]. A comparison of single geometrical parameters (bond distances, angles, torsions, *etc.*) from the two data sets shows no significant differences. In the following discussion only data from the Cu $K\alpha$ analysis are considered.

---

* The lattice parameters determined with Mo $K\alpha_1$ radiation ($\lambda = 0.709300$ Å) are: $a = 10.377$ (8), $b = 12.155$ (7), $c = 12.500$ (8) Å, $\alpha = 94.99$ (5), $\beta = 108.73$ (5), $\gamma = 114.75$ (5)°, $V = 1310$ (2) Å$^3$, $\mu = 0.0767$ mm$^{-1}$.

The integrated intensities were measured using a modified version (Belletti, Ugozzoli, Cantoni & Pasquinelli, 1979) of the Lehmann & Larsen (1974) peak-profile analysis procedure. The data were corrected for Lorentz and polarization effects, but not for absorption; extinction was considered according to Zachariasen (1963). The structures were solved by direct methods with *SHELX*86 (Sheldrick, 1986) and refined by anisotropic full-matrix least squares on *F*, using *SHELX*76 (Sheldrick, 1976). The H atoms were placed in calculated positions riding on the attached carbon atoms, except for the OH hydrogens of both compounds and the water hydrogens of compound (5), which were found from a difference Fourier synthesis and refined isotropically. There are no significant differences between the two crystallographically independent molecules in compound (3). From the *PLUTO* (Motherwell & Clegg, 1976) drawing of the cell contents, shown in Fig. 6, and from the non-bonded contacts calculated by *PARST* (Nardelli, 1983*a*), it appears that the two independent molecules occupy different environments. The correctness of the space-group choice was checked using the *TRACER* (Lawton & Jacobson, 1965), *NEWLAT* (Mugnoli, 1985), *LEPAGE* (Spek, 1988) and *MISSYM* (Le Page, 1987) programs.



(*a*)

(*b*)

Fig. 1. Half-normal probability plots comparing the results of the analyses carried out on compound (3) with Mo and Cu data: (*a*) comparison of all interatomic distances $d < 4.65$ Å; (*b*) comparison of $U_{eq}$ values (Å$^2$).

Table 2. *Atomic coordinates* ($\times 10^4$) *and equivalent isotropic atomic displacement parameters* (Å$^2 \times 10^4$) *with e.s.d.'s in parentheses*

$U_{eq} = 1/3$ (trace of the orthogonalized $U_{ij}$ tensor).

| | *x* | *y* | *z* | $U_{eq}$ |
|---|---|---|---|---|
| Compound (3) | | | | |
| N1*A* | 8764 (4) | 2625 (3) | 1959 (3) | 449 (16) |
| O1*A* | 7211 (4) | 3426 (3) | 368 (3) | 534 (16) |
| O2*A* | 8828 (5) | 2255 (4) | 4196 (3) | 800 (23) |
| C1*A* | 8075 (5) | 2936 (4) | − 1156 (3) | 468 (21) |
| C2*A* | 9074 (5) | 3844 (4) | − 1522 (4) | 570 (24) |
| C3*A* | 8867 (6) | 3505 (5) | − 2678 (4) | 678 (30) |
| C4*A* | 7757 (6) | 2316 (6) | − 3415 (4) | 727 (33) |
| C5*A* | 6773 (6) | 1401 (5) | − 3033 (4) | 663 (28) |
| C6*A* | 6976 (5) | 1771 (4) | − 1884 (3) | 508 (22) |
| C7*A* | 6391 (5) | 1300 (4) | − 950 (3) | 493 (20) |
| C8*A* | 7690 (4) | 2641 (3) | − 102 (3) | 429 (19) |
| C9*A* | 8886 (5) | 2422 (4) | 824 (3) | 440 (19) |
| C10*A* | 8594 (5) | 1103 (4) | 276 (4) | 526 (23) |
| C11*A* | 6856 (5) | 341 (4) | − 487 (4) | 533 (22) |
| C12*A* | 10209 (5) | 2952 (5) | 2952 (4) | 635 (25) |
| C13*A* | 10073 (7) | 3285 (5) | 4084 (4) | 822 (33) |
| C14*A* | 7419 (6) | 1963 (5) | 3257 (4) | 717 (31) |
| C15*A* | 7479 (5) | 1589 (4) | 2088 (3) | 523 (22) |
| N1*B* | 2674 (4) | 2936 (3) | − 2878 (3) | 462 (16) |
| O1*B* | 2415 (3) | 5005 (3) | − 2816 (3) | 528 (16) |
| O2*B* | 1101 (4) | 725 (3) | − 2232 (3) | 720 (18) |
| C1*B* | 4586 (5) | 6161 (4) | − 3377 (3) | 453 (20) |
| C2*B* | 4334 (5) | 6469 (4) | − 4440 (4) | 570 (25) |
| C3*B* | 5571 (7) | 7624 (5) | − 4401 (5) | 700 (31) |
| C4*B* | 6871 (6) | 8315 (4) | − 3416 (5) | 729 (31) |
| C5*B* | 7102 (5) | 7981 (4) | − 2357 (5) | 637 (25) |
| C6*B* | 5894 (5) | 6993 (4) | − 2374 (4) | 506 (22) |
| C7*B* | 5355 (5) | 6020 (4) | − 1607 (3) | 506 (20) |
| C8*B* | 3856 (4) | 5184 (3) | − 2785 (3) | 429 (19) |
| C9*B* | 3886 (4) | 3948 (3) | − 3106 (3) | 430 (19) |
| C10*B* | 5576 (5) | 4250 (4) | − 2426 (4) | 537 (22) |
| C11*B* | 6206 (5) | 5256 (4) | − 1290 (4) | 580 (23) |
| C12*B* | 2202 (5) | 1691 (4) | − 3568 (4) | 581 (23) |
| C13*B* | 787 (6) | 732 (4) | − 3433 (4) | 694 (26) |
| C14*B* | 1574 (6) | 1938 (4) | − 1553 (4) | 638 (26) |
| C15*B* | 3011 (5) | 2924 (4) | − 1641 (3) | 521 (22) |
| Compound (5) | | | | |
| N | 7071 (3) | − 1253 (1) | 4153 (3) | 337 (10) |
| O1 | 4991 (3) | − 29 (1) | 2220 (3) | 423 (9) |
| O2 | 6824 (3) | − 2719 (1) | 4206 (3) | 634 (12) |
| O3 | 3141 (3) | 993 (1) | 2569 (4) | 568 (12) |
| C1 | 6896 (3) | 677 (1) | 4153 (3) | 320 (12) |
| C2 | 7254 (4) | 850 (2) | 5808 (4) | 387 (14) |
| C3 | 7855 (4) | 1480 (2) | 6431 (4) | 444 (15) |
| C4 | 8094 (4) | 1959 (2) | 5391 (4) | 455 (15) |
| C5 | 7750 (4) | 1794 (2) | 3747 (4) | 434 (15) |
| C6 | 7163 (4) | 1161 (2) | 3096 (4) | 360 (13) |
| C7 | 6915 (4) | 1031 (2) | 1281 (4) | 443 (15) |
| C8 | 6244 (3) | − 37 (2) | 3653 (4) | 329 (12) |
| C9 | 7315 (4) | − 576 (2) | 3462 (4) | 334 (13) |
| C10 | 7386 (4) | − 629 (2) | 1698 (4) | 380 (14) |
| C11 | 8816 (4) | − 413 (2) | 1593 (4) | 469 (16) |
| C12 | 8307 (4) | − 1708 (2) | 4438 (4) | 430 (15) |
| C13 | 8090 (5) | − 2376 (2) | 5205 (4) | 571 (18) |
| C14 | 5618 (4) | − 2277 (2) | 3950 (5) | 584 (18) |
| C15 | 5774 (4) | − 1610 (2) | 3128 (4) | 423 (14) |
| C16 | 9280 (4) | 328 (2) | 2078 (4) | 475 (15) |
| C17 | 8335 (4) | 889 (2) | 1004 (4) | 535 (17) |

Atomic scattering factors and anomalous-scattering coefficients were taken from *International Tables for X-ray Crystallography* (1974, Vol. IV, pp. 99–102, 149). The final atomic coordinates are given in Table 2.[*]

Throughout the paper, the averaged values are means weighted according to the reciprocals of the variances, and the corresponding e.s.d.'s are the largest of the values of the external and internal standard deviations (Topping, 1960). The atom–atom non-bonded potential-energy calculations were carried out with the *ROTENER* (Nardelli, 1988) program which makes use of a function of the type $E_{ij} = B_{ij}\exp(-Cr_{ij}) - A_{ij}r_{ij}^{-6}$ [the $A$, $B$, $C$, parameters are from Mirsky (1978)] disregarding the Coulombic energy. All calculations were carried out on the ENCORE-GOULD-POWERNODE 6040 computer of the 'Centro di Studio per la Strutturistica Diffrattometrica del CNR (Parma)'. In addition to the quoted programs, *LQPARM* (Nardelli & Mangia, 1984) and *ORTEP* (Johnson, 1965) were used.

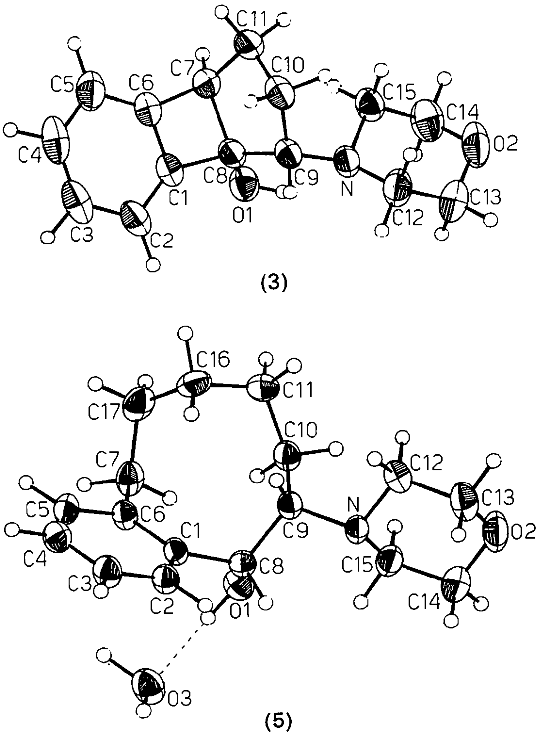


Fig. 2. *ORTEP* (Johnson, 1965) drawings of the molecules. Ellipsoids at 50% probability.

Table 3. *Bond distances* (Å) *and angles* (°) *with e.s.d.'s in parentheses*

| | Compound (3) | | Compound | |
|---|---|---|---|---|
| | Mol. *A* | Mol. *B* | (5) | Average |
| N—C9 | 1.471 (6) | 1.473 (5) | 1.498 (4) | - |
| N—C12 | 1.474 (6) | 1.469 (6) | 1.474 (4) | 1.473 (3) |
| N—C15 | 1.470 (5) | 1.474 (5) | 1.469 (4) | 1.471 (3) |
| O1—C8 | 1.408 (7) | 1.403 (6) | 1.426 (3) | 1.420 (7) |
| O2—C13 | 1.431 (7) | 1.433 (6) | 1.429 (4) | 1.430 (3) |
| O2—C14 | 1.427 (7) | 1.429 (6) | 1.437 (5) | 1.432 (3) |
| C1—C2 | 1.391 (7) | 1.387 (7) | 1.392 (4) | 1.391 (3) |
| C1—C6 | 1.377 (5) | 1.407 (5) | 1.403 (5) | 1.396 (9) |
| C1—C8 | 1.523 (7) | 1.514 (6) | 1.528 (4) | 1.524 (4) |
| C2—C3 | 1.387 (8) | 1.437 (7) | 1.386 (4) | - |
| C3—C4 | 1.401 (7) | 1.360 (7) | 1.373 (5) | - |
| C4—C5 | 1.401 (8) | 1.396 (9) | 1.381 (5) | - |
| C5—C6 | 1.386 (7) | 1.317 (6) | 1.393 (4) | - |
| C6—C7 | 1.527 (7) | 1.618 (7) | 1.526 (4) | 1.544 (26) |
| C7—C8 | 1.596 (5) | 1.604 (5) | - | 1.600 (4) |
| C7—C11 | 1.531 (7) | 1.526 (8) | - | 1.529 (5) |
| C8—C9 | 1.538 (6) | 1.538 (7) | 1.551 (5) | 1.544 (5) |
| C9—C10 | 1.549 (7) | 1.544 (6) | 1.559 (5) | 1.552 (5) |
| C10—C11 | 1.539 (6) | 1.540 (7) | 1.532 (6) | 1.537 (4) |
| C12—C13 | 1.502 (8) | 1.517 (7) | 1.507 (5) | 1.509 (4) |
| C14—C15 | 1.517 (7) | 1.518 (7) | 1.512 (5) | 1.515 (4) |
| C7—C17 | - | - | 1.554 (6) | - |
| C11—C16 | - | - | 1.525 (5) | - |
| C16—C17 | - | - | 1.528 (5) | - |
| | | | | |
| C12—N—C15 | 108.9 (4) | 109.4 (5) | 109.7 (2) | 109.5 (2) |
| C9—N—C15 | 115.1 (4) | 115.8 (5) | 114.0 (2) | 114.4 (5) |
| C9—N—C12 | 112.6 (5) | 112.7 (5) | 110.1 (3) | 111.2 (9) |
| C13—O2—C14 | 109.1 (5) | 110.1 (5) | 109.9 (3) | 109.8 (2) |
| C6—C1—C8 | 93.8 (5) | 97.0 (4) | 125.7 (3) | - |
| C2—C1—C8 | 143.7 (5) | 142.5 (5) | 116.2 (3) | - |
| C2—C1—C6 | 122.4 (5) | 120.3 (6) | 118.1 (3) | - |
| C1—C2—C3 | 115.4 (6) | 113.4 (5) | 122.3 (3) | - |
| C2—C3—C4 | 122.2 (6) | 122.4 (6) | 119.5 (3) | - |
| C3—C4—C5 | 122.0 (5) | 123.2 (7) | 118.9 (3) | - |
| C4—C5—C6 | 114.8 (6) | 113.6 (6) | 122.6 (3) | - |
| C1—C6—C5 | 123.2 (6) | 125.9 (5) | 118.5 (3) | - |
| C5—C6—C7 | 142.4 (6) | 142.0 (5) | 117.1 (3) | - |
| C1—C6—C7 | 94.4 (4) | 90.1 (4) | 124.3 (3) | - |
| C6—C7—C11 | 114.2 (5) | 117.2 (5) | - | 115.7 (15) |
| C6—C7—C8 | 85.5 (4) | 85.6 (4) | - | 85.6 (3) |
| C8—C7—C11 | 106.6 (4) | 107.0 (4) | - | 106.8 (3) |
| C1—C8—C7 | 86.3 (4) | 87.0 (4) | - | 86.7 (4) |
| O1—C8—C7 | 117.9 (6) | 118.5 (5) | - | 118.2 (4) |
| O1—C8—C1 | 114.8 (5) | 115.1 (5) | 113.4 (3) | 114.0 (5) |
| C7—C8—C9 | 106.8 (5) | 106.3 (4) | - | 106.5 (3) |
| C1—C8—C9 | 114.3 (5) | 114.4 (5) | 113.3 (3) | - |
| O1—C8—C9 | 113.8 (4) | 112.9 (6) | 110.5 (2) | - |
| N—C9—C8 | 110.0 (5) | 109.6 (5) | 109.3 (3) | 109.4 (3) |
| C8—C9—C10 | 104.3 (4) | 104.6 (5) | 114.9 (3) | - |
| N—C9—C10 | 117.6 (4) | 117.5 (5) | 113.9 (2) | - |
| C9—C10—C11 | 106.7 (5) | 107.1 (5) | 114.1 (3) | - |
| C7—C11—C10 | 104.8 (5) | 104.9 (5) | - | 104.8 (4) |
| N—C12—C13 | 110.2 (6) | 109.2 (5) | 110.1 (3) | 109.9 (3) |
| O2—C13—C12 | 110.6 (6) | 110.9 (4) | 111.7 (3) | 111.3 (3) |
| O2—C14—C15 | 110.8 (6) | 111.2 (5) | 111.2 (3) | 111.1 (2) |
| N—C15—C14 | 109.5 (5) | 108.7 (4) | 109.6 (3) | 109.3 (3) |
| C6—C7—C17 | - | - | 111.2 (3) | - |
| C10—C11—C16 | - | - | 116.3 (3) | - |
| C11—C16—C17 | - | - | 116.0 (3) | - |
| C7—C17—C16 | - | -- | 116.2 (3) | - |

## Discussion

In Table 3 bond distances and angles are compared and, when averaging is meaningful, the weighted means are given. *ORTEP* drawings of the molecules are displayed in Fig. 2.

### *Analysis of the anisotropic atomic displacements*

The most significant results of the analysis of the anisotropic atomic displacements are quoted in Table 4. This analysis was carried out in terms of the **LST** rigid-body model according to Schomaker &

---

[*] Lists of structure factors, anisotropic displacement parameters and H-atom parameters have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 54611 (32 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England. [CIF reference: GE0284]

Table 4. *Analysis of the anisotropic atomic displacements in terms of LST rigid-body motion and internal motions*

*MF* = centroid of the morpholine ring, *PF* = point on the normal to the mean plane through the morpholine ring at the centroid, *PF'* = normal at N to the morpholine plane, *BZ* = centroid of the benzene ring, *PZ* = normal at the centroid to the benzene plane. $\bar{\Delta}$ = mean difference of the mean-square vibrational amplitudes along the interatomic directions for all pairs of atoms; $\Delta U = U_{ij}(\text{obs.}) - U_{ij}(\text{calc.})$; $R_{wU} = [\Sigma(w\Delta U)^2/\Sigma(wU_o)^2]^{1/2}$; $\sigma(w\Delta U) = [\Sigma(w\Delta U)^2/\Sigma w^2]^{1/2}$; $\bar{\sigma}(U_o)$ = mean e.s.d. of $U_o$'s.

| | Treatment | $\bar{\Delta} \times 10^4$ (Å) | $\sigma(w\Delta U) \times 10^4$ | $\bar{\sigma}(U_o) \times 10^4$ | $R_{wU}$ |
|---|---|---|---|---|---|
| Compound (3) mol. *A* | Rigid-body | 31 (40) | 27 | 26 | 0.063 |
| | Internal motions | | 17 | | 0.039 |
| Compound (3) mol. *B* | Rigid-body | 32 (43) | 28 | 28 | 0.071 |
| | Internal motions | | 23 | | 0.059 |
| Compound (5) | Rigid-body | 31 (40) | 25 | 21 | 0.088 |
| | Internal motions | | 21 | | 0.069 |

Compound (3) mol. *A*

| Group librating | Libration Along | Libration Amplitude (°) |
|---|---|---|
| O1 | C1···C9 | 2.3 (8) |
| O2 | N···*PF'* | 2.0 (7) |
| C13 | N···C15 | 1.7 (16) |
| C14 | N···C12 | 0.3 (18) |
| C3, C4 | C2···C5 | 0.8 (13) |
| C2, C5 | C1–C6 | 1.6 (10) |
| C10 | C7···C9 | 1.2 (16) |

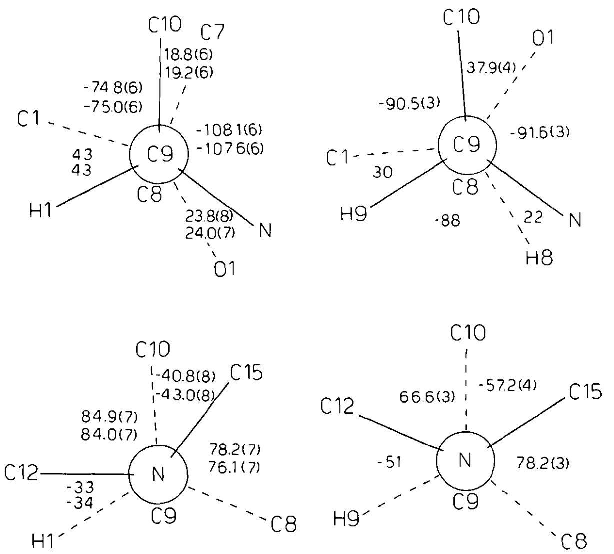
Compound (3) mol. *B*

| Group librating | Libration Along | Libration Amplitude (°) |
|---|---|---|
| O1 | C1···C9 | 3.1 (6) |
| N,...C15 | *MF*···*PF* | 1.0 (14) |
| C1,...C6 | *BZ*···*PZ* | 2.6 (6) |
| C10 | C7···C9 | 3.5 (10) |

Compound (5)

| Group librating | Libration Along | Libration Amplitude (°) |
|---|---|---|
| O1 | C1···C9 | 0.5 (34) |
| N,...C15 | *MF*···*PF* | 2.2 (7) |
| C1,...C6 | *BZ*···*PZ* | 1.9 (7) |
| C17 | C11···C16 | 2.4 (19) |
| C16 | C11···C17 | 4.0 (26) |
| C11 | C10···C17 | 3.3 (18) |

Trueblood (1968) and Trueblood (1978), also considering the internal motions according to Dunitz & White (1973) using the *THMV* program (Trueblood, 1984). As can be seen from the $U_{\text{eq}}$ values of Table 2, the ellipsoids of Fig. 2 and the data of Table 4, atomic displacements are more pronounced for both molecules of compound (3) and the internal motions (or static displacements) have some relevance particularly for the C—O—C terminal group of the morpholino ring in both compounds. In compound (5) displacements are less pronounced, presumably because the water molecule makes the crystal packing more rigid through hydrogen bonding. No correction of bond distances was considered for the data of Table 3.

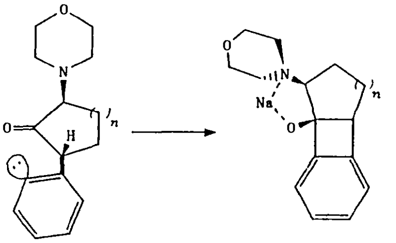


(*a*) (*b*)

Fig. 3. Newman projections along the C9—C8 and N—C9 bonds: (*a*) compound (3) (mol. *A* data above, mol. *B* data below); (*b*) compound (5).

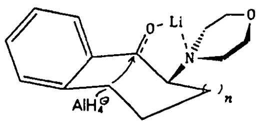
## *Configurations at the junctions and possible reaction mechanism*

From the molecular drawings of Fig. 2 and the Newman projections of Fig. 3 it appears that in compound (3) the C7—H, C8—O1, C9—N bonds are all *cis* with *R*, *R*, *S* configurations at the chiral C7, C8, C9 atoms respectively (also, of course, the *S*, *S*, *R* configurations of the enantiomer are present, the space group being centrosymmetric). This 'all *cis*' stereochemistry establishes that the second step of the arynic attack of the enolate only takes place on the less-hindered face according to the scheme below.



This indicates that some kind of chelation of the cation may reinforce the stereoselectivity of these condensations.

The stereochemistry of compound (5) at C8 and C9 is such that the C8—O1 and C9—N bonds are synclinal and this explains the stereoselective reduction of (4) to give '*cis*' (5). Indeed, it is well established (Pierre & Handel, 1974) that complexation of the carbonyl oxygen takes place during reduction with $LiAlH_4$. In this case the presence of nitrogen, which also strongly complexes lithium cations, leads to the formation of a chelate, forcing hydride attack of the carbonyl on the face opposite the amino group.



### *Conformation of the cyclopentane ring*

Fig. 4(*a*) shows the relevant parameters for the penta-atomic ring of compound (3) (averaged values for the two molecules). In the cyclopentane ring, a local pseudo-mirror runs through the midpoint of the junction (C7—C8) and the carbon (C10) opposite to it [minimum displacement asymmetry parameter (Nardelli, 1983*b*), DAP: $D_S$(C10) = 0.0042 (73) average], corresponding to an envelope conformation. The value of the total puckering amplitude (Cremer & Pople, 1975), $Q_T$ = 0.318 (5) Å average, is much smaller than that [$Q_T$ = 0.453 (2) Å] found for the same kind of ring when fused with a cyclohexene ring (Ianelli, Nardelli, Belletti, Geoffroy, Carré, Mouaddib & Caubère, 1990).

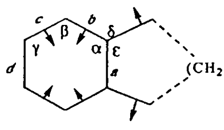
Of interest is the abnormally high C7—C8 bond distance, average value 1.600 (4) Å, which is significantly higher ($\Delta/\sigma$ = 14.1) than the expected C($sp^3$)—C($sp^3$) single-bond value, 1.542 (1) Å [from data in Dewar & Schmeising (1960); see also Allen, Kennard, Watson, Brammer, Orpen & Taylor (1987)]; a similar situation was found for the bond at the juction of a cyclobutene with a cyclohexene ring (Ianelli *et al.*, 1990).

### *Conformation of the cyclononene ring*

The relevant parameters concerning the cyclononene ring of compound (5) are given in Fig. 4(*b*). For this ring, $Q_T$ = 1.480 (4) Å and DAP is $D_2$(C8) = 0.1059 (10), the latter value indicating a local pseudo-twofold axis running along C17 and the midpoint of the C8—C9 bond. This conformation seems related to the one calculated by Bixon & Lifson (1967) for the minimum strain energy (59.4 kJ mol$^{-1}$) conformation of cyclonane. The fusion with a benzene ring, rather than the other substitutions, is the major reason for the observed changes.

### *Deformation of the benzene ring*

As shown in Table 5, in a previous paper of ours (Ianelli *et al.*, 1990) the discussion and conclusions apply to the benzocyclobutene moiety in compound (3). In particular the narrowing of the $\beta$ angle related to the narrowing of the $\varepsilon$ angle is observed, confirming the picture of a 'push–pull' effect pivoted on the atoms of the junction.



This effect seems to be inverted in the benzocyclononene moiety of compound (5) where the $\varepsilon$ and the $\beta$ angles (see scheme above) are larger, while the $\alpha$

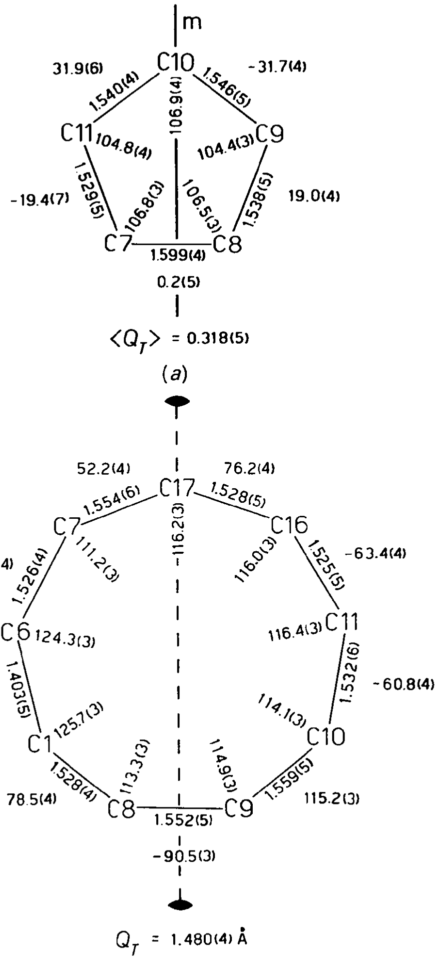


Fig. 4. Relevant parameters [bond distances $d$ (Å), bond angles $\alpha$ and torsion angles $\tau$ (°)] describing: (*a*) the cyclopentane ring of compound (3) (average values), $\langle d \rangle$ = 1.554 (13) Å, $\langle \alpha \rangle$ = 105.9 (5)°, $\Sigma\tau$ = 0.0°; (*b*) the cyclononene ring of compound (5), $\langle d \rangle$ = 1.523 (15) Å, $\langle \alpha \rangle$ = 116.9 (16)°, $\Sigma\tau$ = 0.6°.

and $\gamma$ angles are smaller than 120°. Systematic effects may also be present in the bond distances of the benzene ring: the *b* and *c* bonds are lengthened and shortened, respectively, by the same small value (0.004 Å) with respect to the average [1.388 (4) Å], and the same holds for bonds *a* and *d*, but by a much larger amount (0.015 Å). However, these differences are quite close to the significant threshold.

### *Morpholino moiety*

The morpholino substituent adopts a chair conformation with the average value of $Q_T = 0.574\,(4)$ Å; its structural parameters are not significantly different in the two compounds (Table 3). The orientation of this moiety is illustrated by the Newman projections of Fig. 3.

A better understanding of the conformation about the C9—N bond is obtained by considering the non-bonded energy profiles of Fig. 5, which show how the van der Waals energy for the free molecule varies with respect to that corresponding to the conformation found in the crystal, upon rotation of the morpholino group about the bond joining it to the rest of the molecule. In the calculation of these curves, the approximation is made that no other geometrical changes occur during rotation of the fragment, and the Coulombic energy is neglected. The energy barriers, which are higher in compound (3), are essentially due to the steric hindrance caused by the hydrogen atoms of the methylene groups bound to N and C9. Hindrance is caused also by the hydroxyl H in compound (3); this effect is not present in molecule (5) where that hydrogen is oriented away from the morpholino group as a consequence of the hydrogen bond formed by the hydroxyl group with the water molecule.

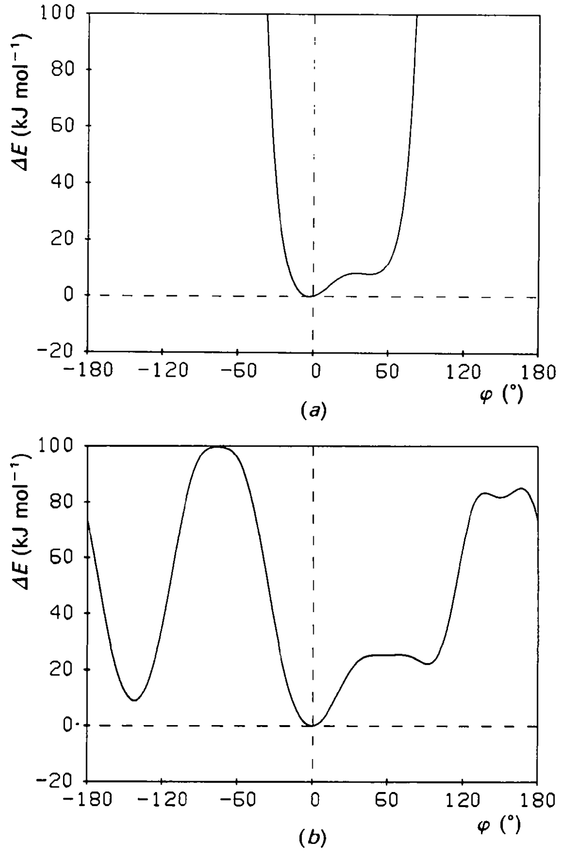


Fig. 5. Calculated potential-energy profiles for rotation of the morpholino moiety about the N—C9 bond: (*a*) compound (3) (mol. *A*, mol. *B* gives a similar plot) (*b*) compound (5). Zero corresponds to the conformation observed in the crystal.

### *Crystal packing*

The most important difference in the packing of the two independent molecules of compound (3) is as follows. The hydroxyl group of molecule *A* acts as a donor in a weak O—H···O hydrogen bond to an adjacent molecule *B* [the H positions are 'normalized' according to Jeffrey & Lewis (1978) and Taylor & Kennard (1983)]: O1*A*—H = 0.938, O1*A*···O1*B*$^{\mathrm{i}}$ = 3.276 (7), H···O1*B*$^{\mathrm{i}}$ = 2.633 Å, O1*A*—H···O1*B*$^{\mathrm{i}}$ = 126° [(i) = $1-x$, $1-y$, $-z$]. On the other hand, molecule *B* does not form such a bond. The other relevant packing contacts in the crystals of compound (3) are essentially of the van der Waals type. Fig. 6 shows a *PLUTO* drawing of the unit-cell contents for compound (3).

A quite different situation is found in compound (5), where the presence of the water molecule causes

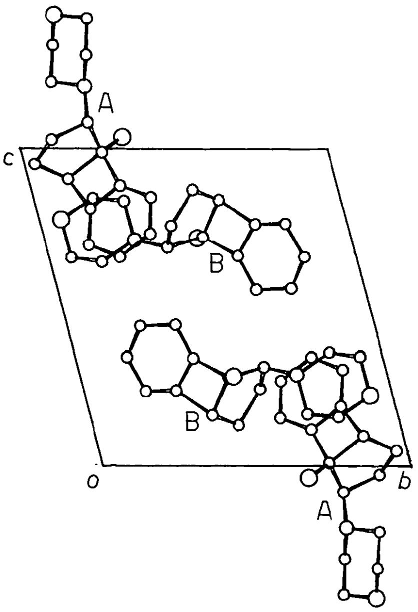


Fig. 6 Packing of the two independent molecules of compound (3) in the unit cell.

the formation of the following hydrogen bonds: O1—H = 0.938, O1···O3 = 2.807 (4), H···O3 = 1.872 Å, O1—H···O3 = 175°; O3—H1 = 0.938, $\mathrm{O3\cdots O2^{ii}}$ = 2.943 (4), $\mathrm{H1\cdots O2^{ii}}$ = 2.093 Å, $\mathrm{O3—H1\cdots O2^{ii}}$ = 150°; O3—H2 = 0.938, $\mathrm{O3\cdots N^{iii}}$ = 2.967 (5), $\mathrm{H2\cdots N^{iii}}$ = 2.031 Å, $\mathrm{O3—H2\cdots N^{iii}}$ = 175°; [where (ii) = $1 - x, \frac{1}{2} + y, \frac{1}{2} - z$; (iii) = $1 - x, -y, 1 - z$] which stabilize the packing of the molecules in the crystal. Other contacts are of the van der Waals type.

## References

Aatif, A., Mouaddib, A., Carré, M. C., Jamart-Grégoire, B., Geoffroy, P., Zouaoui, M. A., Caubère, P., Blanc, M., Gnassounou, J. P. & Advenier, C. (1990). *Eur. J. Med. Chem.* **25**, 441–445.

Abrahams, S. C. & Keve, E. T. (1971). *Acta Cryst.* **A27**, 157–165.

Allen, F. H., Kennard, O., Watson, D. G., Brammer, L., Orpen, G. & Taylor, R. (1987). *J. Chem. Soc. Perkin Trans.* 2, pp. S1–S19.

Belletti, D., Ugozzoli, F., Cantoni, A. & Pasquinelli, G. (1979). *Gestione on Line di Diffrattometro a Cristallo Singolo Siemens AED con Sistema General Automation Jumbo* 220. Internal Report 1-3/79. Centro di Studio per la Strutturistica Diffrattometrica del CNR, Parma, Italy.

Bixon, M. & Lipson, S. (1967). *Tetrahedron*, **23**, 769–784.

Cremer, D. & Pople, J. A. (1975). *J. Am. Chem. Soc.* **97**, 1354–1358.

De Camp, W. H. (1973). *Acta Cryst.* **A29**, 148–150.

Dewar, M. J. S. & Schmeising, H. N. (1960). *Tetrahedron*, **11**, 96–120.

Dunitz, J. D. & White, D. N. J. (1973). *Acta Cryst.* **A29**, 93–94.

Goodman, L. S. & Gilman, A. (1980). *The Pharmacological Basics of Therapeutics*, 6th ed. New York: MacMillan.

Ianelli, S., Nardelli, M., Belletti, D., Geoffroy, P., Carré, M. C., Mouaddib, A. & Caubère, P. (1990). *Acta Cryst.* **C46**, 1318–1324.

Jeffrey, G. A. & Lewis, L. (1978). *Carbohydr. Res.* **60**, 179–182.

Johnson, C. K. (1965). *ORTEP*. Report ORNL-3794. Oak Ridge National Laboratory, Tennessee, USA.

Lawton, S. L. & Jacobson, R. A. (1965). *The Reduced Cell and Its Crystallographic Applications*. Ames Laboratory. Available from the Clearinghouse for Federal Scientific and Technical Information, National Bureau of Standards, US Department of Commerce, Springfield, Virginia, USA.

Lehmann, M. S. & Larsen, F. K. (1974). *Acta Cryst.* **A30**, 580–589.

Le Page, Y. (1987). *J. Appl. Cryst.* **A20**, 264–269.

Mirsky, K. (1978). *Computing in Crystallography, Proceedings of an International Summer School in Crystallographic Computing*, p. 169. Delft Univ. Press.

Motherwell, W. D. S. & Clegg, W. (1976). *PLUTO*. Program for plotting molecular and crystal structures. Univ. of Cambridge, England.

Mugnoli, A. (1985). *J. Appl. Cryst.* **18**, 183–184.

Nardelli, M. (1983*a*). *Comput. Chem.* **7**, 95–98.

Nardelli, M. (1983*b*). *Acta Cryst.* **C39**, 1141–1142.

Nardelli, M. (1988). *ROTENER*. A Fortran routine for calculating non-bonded potential energy. Univ. of Parma, Italy.

Nardelli, M. & Mangia, A. (1984). *Ann. Chim. (Rome)*, **74**, 163–174.

Pierre, J. L. & Handel, H. (1974). *Tetrahedron Lett.* pp. 2317–2320.

Schomaker, V. & Trueblood, K. N. (1968). *Acta Cryst.* **B24**, 63–76.

Sheldrick, G. M. (1976). *SHELX76*. Program for crystal structure determination. Univ. of Cambridge, England.

Sheldrick, G. M. (1986). *SHELX86*. Program for crystal structure solution. Univ. of Göttingen, Germany.

Spek, A. L. (1988). *J. Appl. Cryst.* **21**, 578.

Taylor, R. & Kennard, O. (1983). *Acta Cryst.* **B39**, 133–138.

Topping, H. (1960). *Errors of Observation and their Treatment*, p. 91. London: Chapman & Hall.

Trueblood, K. N. (1978). *Acta Cryst.* **A34**, 950–954.

Trueblood, K. N. (1984). *THMV*. Univ. of California, Los Angeles, USA.

Zachariasen, W. H. (1963). *Acta Cryst.* **16**, 1139–1144.

---

*Acta Cryst.* (1992). **B48**, 185–191

# Structure of Ribonuclease $T_1$ Complexed with Zinc(II) at 1.8 Å Resolution: a $Zn^{2+}.6H_2O$.Carboxylate Clathrate

By Jianping Ding,* Hui-Woog Choe, Joachim Granzin and Wolfram Saenger†

*Institut für Kristallographie, Freie Universität Berlin, Takustraße 6, D-1000 Berlin 33, Germany*

(*Received* 2 *September* 1991; *accepted* 30 *October* 1991)

## Abstract

In order to study the inhibitory effect of $Zn^{2+}$ on ribonuclease $T_1$ [RNase $T_1$; Itaya & Inoue (1982). *Biochem. J.* **207**, 357–362], the enzyme was cocrystallized with 2 m*M* $Zn^{2+}$, pH 5.2, from a solution containing 55% (*v*/*v*) 2-methyl-2,4-pentanediol. The crystals are orthorhombic, $P2_12_12_1$, $a$ = 48.71 (1), $b$ = 46.51 (1), $c$ = 41.14 (1) Å, $Z$ = 4, $V$ = 93203 $Å^3$. The crystal structure was determined by molecular replacement and refined by restrained least-squares methods based on $F_{hkl}$ for 8291 unique reflections with $F_o \geq 1\sigma(F_o)$ in the resolution range 10 to 1.8 Å and converged at a crystallographic $R$ factor of 0.140. The $Zn^{2+}$ is *not* bonded to the active site of RNase $T_1$, probably because the His40 and His92 side chains are protonated. $Zn^{2+}$ occupies the

---

* Present address: CABM and Rutgers University, 679 Hoes Lanes, Piscataway, NJ 08854-5638, USA.

† Author to whom correspondence should be addressed.

0108-7681/92/020185-07$03.00