

The Structures of Two Rubazoic Acid Derivatives

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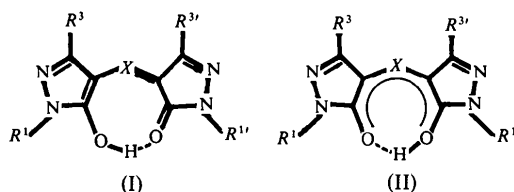
Abstract

Rubazoic acid derivatives form a strong chelated hydrogen bond in an eight-membered ring. The structures of 4-(5-hydroxy-1,3-dimethyl-4-pyrazolylmethylene)-1,3-dimethyl-2-pyrazolin-5-one, $C_{11}H_{14}N_4O_2$ (CRA), and of 4-(5-hydroxy-1,3-dimethyl-4-pyrazolylimino)-1,3-dimethyl-2-pyrazolin-5-one, $C_{10}H_{13}N_5O_2$ (NRA), have been determined from single-crystal X-ray diffraction data. CRA is orthorhombic, space group $Pnma$, with $a = 8.420$ (9), $b = 6.736$ (9), $c = 20.68$ (2) Å and $Z = 4$; NRA is orthorhombic, space group $Pbca$, with $a = 8.524$ (2), $b = 13.320$ (8), $c = 40.44$ (2) Å and $Z = 16$. Both structures were solved by direct methods and refined by least squares. H atoms were located from difference Fourier syntheses and partially included in the refinement. The final R value for CRA is 0.068, for NRA 0.089. The eight-membered chelate ring of CRA is completely planar, as is the whole molecular frame, whereas the chelate ring of NRA shows a torsion at the imino group. CRA and NRA contain strong *intra-molecular* hydrogen bonds with O–O distances of 2.425 and 2.44 Å respectively.

Introduction

Rubazoic acid derivatives have recently been the subject of extended synthetic studies (Hänsel, 1976*a,b*). They show a strong tendency to form stable metal chelates. Thus rubazoic acid, which is the renal secretion product of Pyramidon (Gradnik & Fleischmann, 1973), seems to inhibit certain metal-containing enzymes (Meltzer, 1978). Spectral studies (Bratan-Mayer, Strobusch & Hänsel, 1976) showed these compounds to exist only as OH tautomers (II) with a strong intramolecular hydrogen bond in non-polar solvents. To answer the question regarding the degree of tautomerism and the geometric form of the eight-membered ring, a methylene-bridged [4-(5-hydroxy-

1,3-dimethyl-4-pyrazolylmethylene)-1,3-dimethyl-2-pyrazolin-5-one: CRA] and an imino-bridged [4-(5-hydroxy-1,3-dimethyl-4-pyrazolylimino)-1,3-dimethyl-2-pyrazolin-5-one: NRA] rubazoic acid derivative were submitted to an X-ray structure analysis.



Rubazoic acid: $X \cong R^1 = R^{1'} \cong \text{Ph}$, $R^3 = R^{3'} \cong \text{CH}_3$
 CRA: $X \cong \text{CH}$, $R^1 = R^{1'} = R^3 = R^{3'} \cong \text{CH}_3$
 NRA: $X \cong \text{N}$, $R^1 = R^{1'} = R^3 = R^{3'} \cong \text{CH}_3$

Experimental

Both compounds were crystallized from petrol, CRA as long yellow needles, NRA as short dark-red prisms. The space groups were determined with Weissenberg and precession techniques and precise lattice parameters were obtained by the least-squares fitting of the powder patterns.

X-ray intensities were measured on an automatic Nonius CAD-4 diffractometer with graphite-monochromated $\text{Mo } K\alpha$ radiation and pulse-height discrimination. Of the 6477 intensities measured in the range $2^\circ < \theta < 60^\circ$ for CRA, 1362 were considered as observed according to the criterion $I > 2\sigma(I)$, the corresponding values for NRA being 3896 intensities, range $1^\circ < \theta < 25^\circ$, observed reflexions 2137. The intensities of both compounds were corrected for absorption. Two reflexions were monitored periodically during each data collection and showed no crystal or electronic instabilities.

Determination and refinement of the structures

CRA

The structure was solved with the *MULTAN* 74 system (Main, Woolfson, Declercq & Germain, 1974) using 131 normalized structure factors with $E > 2.54$. The resulting E map with the highest figure of merit

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showed all non-hydrogen atoms lying on the mirror plane. Isotropic least-squares refinement using atomic form-factor curves from *International Tables for X-ray Crystallography* (1974) resulted in an R value of 0.167; further anisotropic refinement gave $R = 0.116$. At this point reflexions in the range $\sin \theta/\lambda > 0.67 \text{ \AA}^{-1}$ were discarded. Further refinement of all parameters along with the isotropic extinction coefficient gave an R of 0.095 for the now 811 observed reflexions. A corresponding difference Fourier synthesis with $\sin \theta/\lambda \leq 0.5 \text{ \AA}^{-1}$ showed all the H atoms as the most prominent peaks.

A good weighting scheme for further refinement was $W = w_1 w_2$ with $w_1 = 1/\sigma_1^2$ and $w_2 = 1/\sigma_2^2$ where $\sigma_1 = a + b|F_o|$ and $\sigma_2 = c + d(\sin \theta/\lambda)$, calculated by the program *PESOS* (Martinez-Ripoll & Cano, 1975). Weighted refinement of all parameters (C, O, N anisotropic, H isotropic, scale factor, extinction coefficient) gave unweighted and weighted disagreement indices $R = 0.068$ and $R_w = 0.074$.* The final fractional coordinates are given in Table 1; Fig. 1 shows the molecule with its atomic numbering scheme.

* Lists of structure factors, thermal parameters and coefficients of the weighting scheme for both compounds have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 35227 (25 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 1. Fractional coordinates ($\times 10^4$, for H $\times 10^3$) and thermal parameters ($\times 10^3$, for H $\times 10^4$) for CRA

	x	y	z	B (\AA^2)
N(1)	5652 (4)	7500	11581 (1)	59 (2)
N(2)	7299 (4)	7500	11564 (2)	62 (2)
C(3)	7667 (5)	7500	10954 (2)	51 (2)
C(4)	6294 (4)	7500	10545 (2)	43 (2)
C(5)	4986 (5)	7500	10993 (2)	48 (2)
O(1)	3480 (3)	7500	10918 (1)	64 (2)
C(10)	9352 (6)	7500	10739 (3)	74 (3)
C(11)	4833 (8)	7500	12195 (2)	80 (4)
C(6)	6363 (4)	7500	9869 (2)	43 (2)
N(3)	3146 (4)	7500	8737 (1)	56 (2)
N(4)	4449 (4)	7500	8318 (1)	61 (2)
C(7)	3551 (5)	7500	9360 (2)	48 (2)
C(8)	5270 (4)	7500	9369 (2)	46 (2)
C(9)	5673 (5)	7500	8696 (2)	52 (2)
O(2)	2520 (3)	7500	9812 (1)	62 (2)
C(12)	7335 (5)	7500	8432 (2)	78 (3)
C(13)	1555 (5)	7500	8473 (3)	72 (4)
H(1)	747 (4)	750	971 (1)	0 (0)
H(9)	829 (13)	750	871 (5)	16 (0)
H(10)	743 (7)	628 (12)	814 (3)	16 (0)
H(2)	300 (13)	750	1041 (5)	15 (4)
H(3)	995 (6)	750	1105 (2)	2 (1)
H(4)	958 (5)	636 (8)	1043 (2)	8 (1)
H(6)	366 (9)	750	1214 (3)	8 (2)
H(7)	516 (5)	627 (7)	1247 (2)	7 (1)
H(12)	88 (9)	750	889 (4)	9 (2)
H(13)	137 (4)	624 (7)	821 (2)	6 (1)

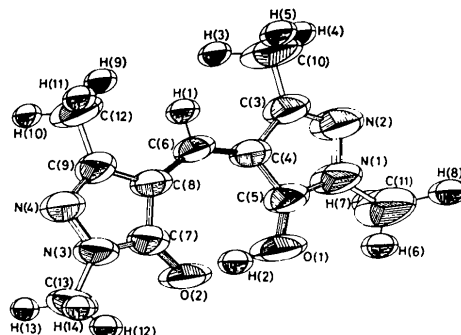


Fig. 1. A molecule and the numbering scheme of CRA. The thermal ellipsoids are scaled to the 50% probability level; H atoms have a radius of 0.1 Å.

NRA

With 499 E 's > 1.45 *MULTAN* computed a phase set, whose corresponding E map revealed one molecule of the asymmetric unit. Tangent-formula phase refinement with 100 E 's > 2.49 led in 10 cycles to an E map which allowed all non-hydrogen atoms of the two molecules to be recognized. With these coordinates and isotropic temperature factors of 3.5 \AA^2 for all atoms, the R value was 0.449. This high value is astonishing, because the following six cycles of full-matrix isotropic least-squares refinement brought no great parameter shifts but reduced the R value to 0.138. Further blocked refinement with anisotropic thermal parameters gave $R = 0.105$. A difference Fourier synthesis

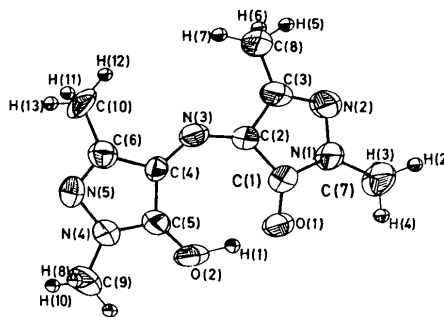


Fig. 2. Molecule A of NRA (same parameters as for CRA).

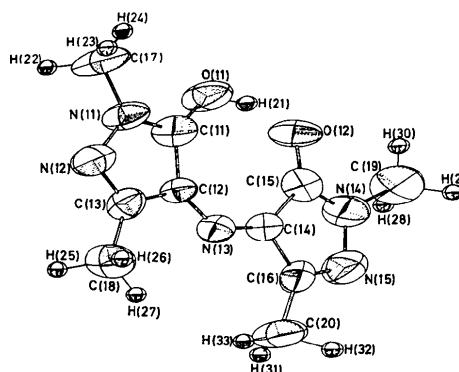


Fig. 3. Molecule B of NRA.

calculated at this stage in the range $\sin \theta/\lambda \leq 0.5 \text{ \AA}^{-1}$ showed the chelate H atoms as prominent peaks; the H atoms of the methyl groups were difficult to detect and

Table 2. Fractional coordinates ($\times 10^4$, for H $\times 10^3$) and thermal parameters ($\times 10^3$, for H $\times 10^4$) for NRA

	x	y	z	B (\AA^2)
N(1)	2775 (8)	272 (5)	7045 (1)	44 (4)
N(2)	4431 (8)	251 (5)	7020 (1)	51 (4)
C(1)	2053 (9)	202 (7)	6752 (2)	44 (5)
C(2)	3340 (9)	129 (6)	6514 (1)	38 (4)
C(3)	4742 (10)	163 (7)	6708 (2)	47 (5)
O(1)	581 (6)	191 (5)	6724 (1)	49 (3)
C(7)	2050 (11)	303 (8)	7368 (2)	60 (6)
C(8)	6381 (10)	154 (9)	6579 (2)	69 (7)
N(3)	3417 (7)	13 (5)	6192 (1)	39 (4)
N(4)	287 (8)	-21 (5)	5619 (1)	46 (4)
N(5)	1597 (9)	-178 (5)	5410 (1)	51 (4)
C(4)	2349 (9)	-43 (5)	5955 (1)	34 (4)
C(5)	633 (9)	49 (6)	5939 (1)	41 (5)
C(6)	2792 (10)	-156 (6)	5614 (2)	45 (5)
O(2)	-405 (6)	169 (5)	6154 (1)	57 (3)
C(9)	-1265 (11)	60 (8)	5467 (2)	66 (6)
C(10)	4452 (11)	-315 (8)	5492 (2)	60 (6)
N(11)	8699 (8)	7683 (5)	8114 (1)	48 (4)
N(12)	7390 (9)	7789 (6)	7898 (1)	57 (4)
C(11)	8313 (10)	7606 (6)	8426 (2)	47 (5)
C(12)	6602 (9)	7654 (6)	8440 (2)	38 (5)
C(13)	6173 (10)	7786 (7)	8096 (1)	43 (5)
O(11)	9354 (6)	7478 (5)	8650 (1)	59 (4)
C(17)	10269 (10)	7615 (9)	7977 (3)	72 (7)
C(18)	4516 (10)	7876 (8)	7982 (2)	60 (6)
N(13)	5539 (7)	7602 (4)	8679 (1)	39 (4)
N(14)	6165 (8)	7311 (5)	9537 (1)	50 (4)
N(15)	4523 (8)	7369 (6)	9515 (1)	55 (4)
C(14)	5631 (9)	7488 (6)	8998 (2)	40 (5)
C(15)	6882 (10)	7389 (6)	9247 (2)	44 (5)
C(16)	4228 (10)	7470 (6)	9203 (2)	44 (5)
O(12)	8377 (6)	7353 (4)	9212 (1)	54 (4)
C(19)	6935 (12)	7266 (8)	9858 (2)	67 (6)
C(20)	2582 (11)	7473 (8)	9071 (2)	60 (5)
H(1)	-7 (12)	26 (7)	640 (2)	68 (36)
H(2)	246	91	748	63
H(3)	243	-31	749	63
H(4)	89	31	738	63
H(5)	696	-37	668	63
H(6)	686	83	664	63
H(7)	663	11	633	63
H(8)	-145	-58	534	63
H(9)	-218	15	561	63
H(10)	-122	63	531	63
H(11)	471	18	532	63
H(12)	451	-101	538	63
H(13)	540	-32	564	63
H(21)	914 (8)	757 (5)	885 (1)	15 (22)
H(22)	1042	825	783	63
H(23)	1027	703	781	63
H(24)	1118	755	812	63
H(25)	433	733	782	63
H(26)	447	855	786	63
H(27)	358	789	813	63
H(28)	649	666	998	63
H(29)	659	789	998	63
H(30)	808	722	987	63
H(31)	211	816	919	63
H(32)	201	695	915	63
H(33)	234	764	883	63

were rather low broad maxima. They were placed in the expected positions with the program *HSEARCH* (Fayos & Martinez-Ripoll, 1975). The last cycles of blocked refinement with a fixed isotropic $B = 5.0 \text{ \AA}^2$ for the H atoms of the methyl groups and with their positional parameters fixed resulted in the following unweighted and weighted disagreement indices: $R = 0.089$ and $R_w = 0.080$ (unit weights).^{*} Figs. 2 and 3 show the two molecules of the asymmetric unit and their atomic numbering scheme; Table 2 gives the atomic coordinates in cell fractions.

Description and discussion of the two structures

Molecular structure

CRA. All the heavy atoms of the molecule and six of the 14 H atoms lie on special positions, on the mirror plane. This is an astonishing result for a quite large organic molecule and can only be explained through a high gain of resonance energy. Fig. 4 shows the important bond lengths and angles of *CRA* (top values) and of *NRA* (middle values molecule *A*, bottom values molecule *B*); the values for the methyl groups of *CRA* are given in Table 3. The bond lengths N(2)—C(3) (1.300 Å) and N(4)—C(9) (1.293 Å) can be compared with those found for the five-membered rings of two azomethine dyes (Smith & Barrett, 1971). They seem to correspond to a N—C double bond (1.29 Å: Pauling, 1960), whereas the bonds C(4)—C(5), C(8)—C(7), C(3)—C(4) and C(8)—C(9) are shorter than an sp^2 — sp^2 single bond (1.488 Å: Dewar & Schmeising, 1960). The C—O distances are much longer than a C—O double bond and even longer than in 2-acetyl-3-indazolinone (Smith & Barrett, 1969), where the O

^{*} See previous footnote.

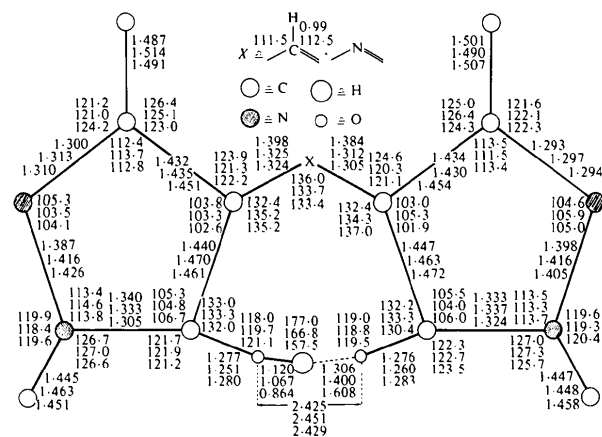


Fig. 4. Bond lengths (\AA) and angles ($^\circ$) for *CRA* (top values) and *NRA* (middle values molecule *A*, bottom values molecule *B*).

Table 3. Bond lengths (Å) and angles (°) of the methyl hydrogens of CRA

C(10)—H(3)	0.83	C(3)—C(10)—H(3)	110
C(10)—H(4)	1.02	C(3)—C(10)—H(4)	112
C(10)—H(5)	1.02	C(3)—C(10)—H(5)	112
		H(3)—C(10)—H(4)	112
		H(3)—C(10)—H(5)	112
		H(4)—C(10)—H(5)	98
C(11)—H(6)	0.98	N(1) C(11)—H(6)	98
C(11)—H(7)	1.04	N(1)—C(11)—H(7)	111
C(11)—H(8)	1.04	N(1)—C(11)—H(8)	111
		H(6)—C(11)—H(7)	109
		H(6)—C(11)—H(8)	109
		H(7)—C(11)—H(8)	105
C(12)—H(9)	0.99	C(9)—C(12)—H(9)	123
C(12)—H(10)	1.02	C(9)—C(12)—H(10)	107
C(12)—H(11)	1.02	C(9)—C(12)—H(11)	107
		H(9)—C(12)—H(10)	106
		H(9)—C(12)—H(11)	106
		H(10)—C(12)—H(11)	106
C(13)—H(12)	1.03	N(3)—C(13)—H(12)	101
C(13)—H(13)	1.01	N(3)—C(13)—H(12)	110
C(13)—H(14)	1.01	N(3)—C(13)—H(12)	110
		H(12)—C(13)—H(13)	111
		H(12)—C(13)—H(14)	111
		H(13)—C(13)—H(14)	113

Estimated standard deviations of bond distances (Å) and angles (°) for CRA

	Bond or angle	Average	Range
Distances	Heavy-heavy	0.006	0.006–0.007
	Hydrogen bond	0.12	0.12–0.12
	Methylene C—H	0.04	—
	Methyl C—H	0.07	0.05–0.12
Angles	Heavy-heavy	0.41	0.36–0.45
	Hydrogen bond	5.4	4.9–5.7
	Methylene C—H	2.3	2.3–2.3
	Methyl C—H	3.9	2.4–6.8

participates in an intermolecular hydrogen bond. These facts in connexion with the 'aromatic' bond lengths to atom C(6) favour a formulation of the structure as in (II), although the short N—N and N—C(methyl) distances show that canonic structures other than (II) are also of great importance.

The O—O distance (2.425 Å) is extremely short compared with the van der Waals distance (2.80 Å), but the steric pressure is still so strong that the bond angle at C(6) is widened to 136°. The gain of resonance energy in a planar system allows no torsion at the bridging atom.

NRA. Although this compound shows an even stronger structural similarity with the two azomethine dyes than does CRA, there are significant differences in the bond lengths of the five-membered rings. The bonds to atoms C(1), C(5), C(15) and C(11) (see Fig. 4) are shorter than the comparable bonds in the two dyes (C—C 1.499, 1.494 Å; C—N 1.369, 1.377 Å); the C—O distances are longer (dyes: 1.219, 1.217 Å). The two azine bonds are also more nearly equal in *NRA*

Table 4. Bond lengths (Å) of the methyl hydrogens of *NRA*

C(7)—H(2)	1.00	C(17)—H(22)	1.03
C(7)—H(3)	1.02	C(17)—H(23)	1.01
C(7)—H(4)	0.99	C(17)—H(24)	0.98
C(8)—H(5)	0.98	C(18)—H(25)	0.98
C(8)—H(6)	1.04	C(18)—H(26)	1.02
C(8)—H(7)	1.01	C(18)—H(27)	1.00
C(9)—H(8)	1.01	C(19)—H(28)	1.01
C(9)—H(9)	1.00	C(19)—H(29)	1.02
C(9)—H(10)	0.99	C(19)—H(30)	0.99
C(10)—H(11)	0.99	C(20)—H(31)	1.01
C(10)—H(12)	1.03	C(20)—H(32)	1.01
C(10)—H(13)	1.03	C(20)—H(33)	0.98

Estimated standard deviations of bond distances (Å) and angles (°) for *NRA*

	Bond or angle	Average	Range
Distances	Heavy-heavy	0.014	0.010–0.1
	Hydrogen bond	0.09	0.077–0.11
Angles	Heavy-heavy	0.73	0.63–0.83
	Hydrogen bond	6.2	3.9–9.6

than in the two mentioned compounds. This is the result of the strong conjugation effect in *NRA*, which is reflected in the short O—O distances. The C—H lengths of the methyl groups are in Table 4.

As Fig. 4 demonstrates, there are small differences between molecule *A* and molecule *B*. Most remarkable are the differences in the torsion angles at the bridging N. In the case of molecule *A* the values are C(1)—C(2)—N(3)—C(4) 3.2° ($\pm 1.2^\circ$), C(2)—N(3)—C(4)—C(5) 4.0° ($\pm 1.3^\circ$), corresponding to values in molecule *B* of C(15)—C(14)—N(13)—C(12) 1.8° ($\pm 1.4^\circ$) and C(14)—N(13)—C(12)—C(11) 0.2° ($\pm 1.2^\circ$). Because of the smaller torsion angle in molecule *B* the chelate proton is forced out of the plane of the eight-membered ring (see also Table 5) and the angle at the imino group is widened. Molecule *B* seems to be less conjugated than molecule *A*, an effect which can only be explained by the two different electronic neighbourhoods in the crystal. Table 5 shows that the atoms of the five-membered rings lie in ideal planes, which are approximately parallel. Nearly parallel to these planes are the planes of the chelate rings. The two least-squares planes of both molecules (heavy atoms and chelate H atoms) form an angle of 11.7°. Between the N-methyl H atoms pointing to the centre of the molecules and the O atoms there are surely weak interactions, the corresponding distances being 2.7 [O(1)—H(4), O(12)—H(30)] and 2.6 Å [O(2)—H(9), O(11)—H(24)]. Comparable distances are also found in 2-acetyl-3-indazolinone.

The most striking difference between CRA and *NRA* is the loss of the molecular symmetry *m* as a result of the shorter azine bonds. In a planar configuration the O atoms would come too close together and

Table 5. *Least-squares planes in NRA and deviations ($\text{\AA} \times 10^5$) of atoms from them*

Atoms marked with asterisks were not included in the computations of the planes. The average e.s.d. is 0.009 \AA .

$A = 0.12692$	N(1) -16	$A = 0.35608$	N(14) -675
$B = 13.26938$	N(2) 143	$B = 13.24408$	N(15) 299
$C = -3.47054$	C(1) -98	$C = 3.96672$	C(14) -490
$D = -2.04837$	C(2) 179	$D = 13.69335$	C(15) 718
	C(3) -207		C(16) 148
	O(1)* -2412		O(12)* -88
	N(3)* -3977		N(13)* 1572
	C(7)* -8064		C(19)* 8824
	C(8)* 5017		C(20)* 2816
$A = 0.72213$	N(4) 1100	$A = 0.47458$	N(11) 155
$B = 13.20252$	N(5) -1627	$B = 13.23490$	N(12) -732
$C = -4.12096$	C(4) -790	$C = 3.96996$	C(11) 394
$D = -2.33419$	C(5) -216	$D = 13.80231$	C(12) -805
	C(6) 1534		C(13) 987
	O(2)* -726		O(11)* -2652
	N(3)* 4658		N(13)* -3176
	C(9)* 6904		C(17)* -6851
	C(10)* -2442		C(18)* 499
$A = 0.54274$	H(1) 7398	$A = 0.22255$	H(21) 12978
$B = 13.24879$	O(1) -8636	$B = 13.24926$	O(11) -7744
$C = -3.28755$	C(1) -153	$C = 4.01999$	C(11) -2167
$D = 1.83929$	C(2) 5053	$D = 13.67163$	C(12) 961
	N(3) 653		N(13) 1379
	C(4) -4884		C(14) -641
	C(5) -1316		C(15) -977
	O(2) 1885		O(12) -3799

the repulsion would be too strong. This is avoided through torsion at the imino group and stretching of the bond angles at C(4), C(2) and C(12), C(14) respectively. Therefore, the widened bond angle of the bridging methine group in CRA can be reduced in NRA. This loss of planarity implies less possibility for conjugative interactions. NRA favours asymmetric canonic structures more than CRA.

As to the symmetric double minimum proposed by Bratan-Mayer, Strobusch & Hänsel (1976) for the chelate proton in symmetrically substituted rubazoic acid derivatives, the X-ray structure analysis cannot support this statement. Although in this report the e.s.d. of the chelate bond lengths (0.1 \AA) does not reach the necessary accuracy (0.003 \AA ; Rundle, 1964) to allow definite statements to be made concerning the positions of the H atoms, the differences between comparable bonds in the five-membered rings and between the bridging bonds and, last but not least, the two different torsion angles in NRA imply that the chelate H must be more strongly bound to one of the two O atoms. Neither CRA nor NRA can be regarded as the formulation (II) in the crystalline state; *i.e.* as an eight-membered chelate ring with a 'smeared' six- π -electron system.

Crystal structure

CRA. Fig. 5 shows the packing of the molecules in the unit cell. A striking feature is the formation of a

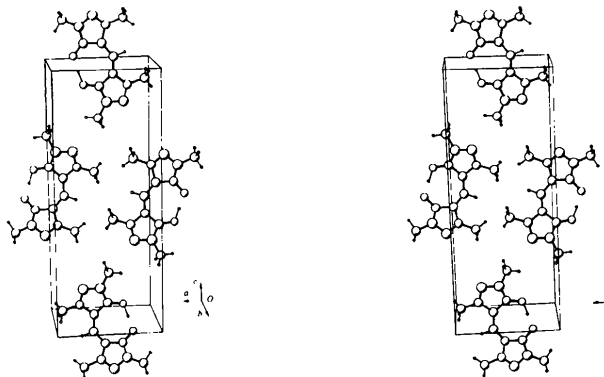


Fig. 5. Stereoscopic view of CRA down the b axis.

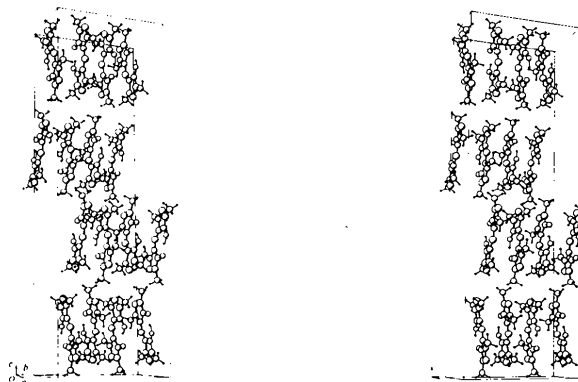


Fig. 6. Stereoscopic views of NRA down the a axis.

hydrophilic zone between the unit cells through the chelate groups and of a hydrophobic zone inside the unit cells through the methyl groups – a common packing principle found in living nature. All intermolecular distances are greater than the van der Waals contact distances.

NRA. Fig. 6 shows the layer structure of this compound. The two molecules of the asymmetric unit form alternate wavy sheets parallel to the plane (010). In each sheet the molecules build up infinite chains, ordered in a zigzag way perpendicular to (100). Comparison of the two crystal structures shows their strong crystallographic relationship. Through the loss of the molecular symmetry m in NRA the mirror plane turns into a glide plane and the cell constants in directions b and c are doubled. In the gaps thus formed a second molecule is incorporated.

Most of the computations required in this analysis were performed with the XRAY 70 system (Stewart, Kundell & Baldwin, 1970) on the Univac 1106 computer of the Rechenzentrum der Universität Freiburg. This work was supported by a grant from the Deutsche Forschungsgemeinschaft. The authors thank Professor W. Hänsel and Dr F. Strobusch who supplied the crystals. The technical assistance of Mr L. Feuchte is gratefully acknowledged.

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The Structure of Triclinic Bilirubin Chloroform–Methanol Solvate

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Abstract

Crystals of bilirubin ($C_{33}H_{36}N_4O_6$) grown from a chloroform–methanol solution are triclinic [space group $P\bar{1}$, $a = 9.58$ (4), $b = 11.96$ (4), $c = 15.60$ (5) Å, $\alpha = 93.3$ (1), $\beta = 99.9$ (1), $\gamma = 84.8$ (1)°, $Z = 2$, at 223 K]. Solvent molecules are present in the crystal structure. The structure was solved by direct methods and was refined to $R = 0.11$ for 2140 unique diffractometer data, with $F_{obs} \geq 4\sigma$. The refinement with individual atomic parameters gave satisfactory bond lengths for the bilirubin molecule; the determination of the positions of the H atoms makes possible an unequivocal assignment of the bilirubin formulation. Bilirubin is shown to have two molecular planes interrelated by a non-crystallographic 2 axis; the lactam configuration involves six intramolecular hydrogen bonds. The vinyl groups appear to be disordered.

man and most animals; excess of bilirubin provokes the yellow colour in all jaundices. Neonatal jaundice is particularly frequent and, although usually benign, if there is a high concentration of this pigment it may diffuse into the brain and cause irreversible damage. Bilirubin is removed from infants by exchange transfusion and irradiation to avoid intoxication.

Among other unusual physical and chemical properties, bilirubin presents a remarkable Cotton effect when complexed with serum albumin. This extremely large Cotton effect in the visible region is 'very likely associated with a high degree of inherent dissymmetry' as in the case of hexahelicene (Blauer & King, 1970).

Fischer, Plieninger & Weissbarth (1941) first elucidated the basic structure of bilirubin (Fig. 1). Several spectroscopic studies were devoted to the conformation of bilirubin, and Kuenzle proposed (Kuenzle, 1970; Kuenzle, Weibel, Pelloni & Hemmerich, 1973) a model consisting of two molecular planes separated by the central methylene bridge. This model, stabilized by strong intramolecular hydrogen bonds, is corroborated by subsequent spectroscopic

Bilirubin, one of the most important components of the bile pigments, is the end product of hæm catabolism in