Molecular Determinants for Drug–Receptor Interactions. Part 13.† X-Ray Molecular Structure of Naltrexone Malonate and Quantum Chemical Studies of the Conformations of the Pure Narcotic Antagonists Naloxone and Naltrexone

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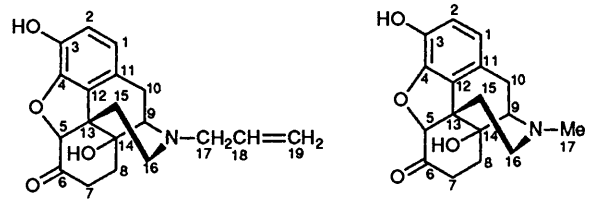
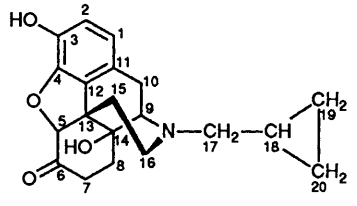
The X-ray molecular structure of naltrexone malonate $[(C_{20}H_{24}NO_4)^+(C_3H_3O_4)^-]$ was determined. In the T-shape molecule, the D and E rings adopt a chair conformation. Ring B is enveloped (C_s). The configuration of the *N*-cyclopropylmethyl group is equatorial. The preferred conformations and the energetics of the conformational processes of naloxone and naltrexone, as non-protonated (NLX and NTRX) and protonated ($NLXH^+$ and $NTRXH^+$) species, were studied using semiempirical MO calculations of the AM-1 type. The solid-state conformations about the *N*-substituent groups were not retained in calculations for isolated molecules. The $NTRXH^+$ species was more conformationally restricted than was $NLXH^+$ about the N–C(17) and, especially, C(17)–C(18) bonds. The conformational isoenergy maps calculated for NLX and NTRX showed that the energy barriers were lower, and that the minima zones were larger and shallower with respect to the cationic species. The present findings provided some insights into the possible conformation–activity requirements for μ-pure opioid antagonists.

In the framework of experimental and theoretical studies aimed at explaining the opiate–receptor interaction at a molecular level and to establish the conformation–activity relationships of opioid analgesics (agonists, antagonists, and dualists), the pure μ-antagonists naloxone (**1**) (NLX) and naltrexone (**2**) (NTRX)



(**1**)

(**3**)



(**2**)

Molecular formulae and atom-numbering scheme of naloxone (**1**), naltrexone (**2**), and oxymorphone (**3**).

are of particular interest for their different relative pharmacological potencies associated with their closely similar chemical structures.[1,2] Their structure-related analogue oxymorphone (**3**) is a potent μ-agonist, which differs from NLX and NTRX in having an *N*-methyl group in the place of *N*-allyl and *N*-cyclopropylmethyl groups, respectively. NLX is a pure μ-antagonist and NTRX is a much more potent μ-antagonist than is NLX.[2] Complete elucidation of the conformational profiles of NLX and NTRX is of fundamental importance in order to determine molecular requirements for the specific binding affinities of these drugs, particularly through the possible location of their pharmacophoric and haptophoric groups responsible for their pharmacological action.

While X-ray diffraction studies of the crystal-state were performed for naloxone (**1**),[3,4] the molecular structure and conformation data were not available for naltrexone (**2**) in the solid state.‡ Recent ^1H and ^{13}C NMR spectroscopic studies[7,8] established that both compounds are conformationally and configurationally homogeneous in solution (distorted chair conformation of the piperidine ring in the *N*-equatorial configuration). The conformation about N–C and C–C bonds of the *N*-alkyl moiety of the studied molecules in the liquid phase could not, however, be monitored by NMR methods. On the other hand, analysis of ^{13}C NMR spin-lattice relaxation times in terms of dynamics of internal motion[9,10] indicated a rigid conformation about the N–C and C–C bonds of the *N*-cyclopropylmethyl fragment of $NTRXH^+$ and a relatively higher flexibility about the corresponding bonds of the *N*-allyl group of $NLXH^+$. Previous theoretical work was concerned with conformations and electronic structures of the compounds under study using SCF-MO calculations,[11–13] and the PCILO method.[14] The objectives of this work were therefore to complement the available information and to provide additional insights into their molecular features which could be useful to clarify, in particular, the role played by the orientation and flexibility of the *N*-alkyl substituent in determining the action at the analgetic receptor. To this purpose we report here the molecular structure of NTRX (malonate salt) as determined by X-ray diffraction analysis, together with the results of detailed theoretical quantum mechanical MO calculations

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‡ Nitrogen protonation and equatorial configuration of the *N*-alkyl groups are requirements of the active form at the receptor.[5,6] Therefore, throughout the whole paperer the cationic species of maloxone and maltrexone will be denoted as $NLXH^+$ and $NTRXH^+$, respectively.

Table 1. Fractional atomic co-ordinates for compound (2)·$CH_2(CO_2H)_2$, with esds in parentheses.

	x	*y*	*z*
C(1)	−0.104 6(3)	0.049 2(3)	−0.472 4(5)
C(2)	−0.116 9(3)	−0.038 1(3)	−0.504 0(5)
C(3)	−0.106 4(2)	−0.103 1(2)	−0.390 3(5)
C(4)	−0.086 0(2)	−0.075 0(2)	−0.238 4(4)
C(5)	−0.025 2(3)	−0.068 5(2)	0.002 9(5)
C(6)	0.069 1(3)	−0.075 2(3)	−0.028 7(5)
C(7)	0.119 6(3)	0.003 4(3)	0.009 3(7)
C(8)	0.083 4(3)	0.084 1(3)	−0.071 0(6)
C(9)	−0.046 2(2)	0.178 2(5)	−0.089 0(5)
C(10)	−0.063 4(3)	0.167 6(3)	−0.269 1(5)
C(11)	−0.084 1(3)	0.075 5(2)	−0.317 2(5)
C(12)	−0.078 1(2)	0.011 8(2)	−0.205 1(4)
C(13)	−0.060 9(2)	0.022 1(2)	−0.029 5(4)
C(14)	−0.003 6(3)	0.100 2(2)	−0.006 4(5)
C(15)	−0.143 3(3)	0.038 1(3)	0.059 1(5)
C(16)	−0.185 8(3)	0.120 8(3)	0.004 3(6)
C(17)	−0.168 8(3)	0.278 3(3)	−0.035 9(5)
C(18)	−0.111 2(3)	0.353 6(3)	−0.029 9(5)
C(19)	−0.142 7(4)	0.437 4(3)	0.037 0(9)
C(20)	−0.082 8(4)	0.384 4(4)	0.129 3(7)
N	−0.125 1(2)	0.195 6(2)	0.006 3(4)
O(1)	−0.115 0(2)	−0.188 9(2)	−0.420 3(4)
O(2)	−0.067 9(2)	−0.126 5(2)	−0.107 8(3)
O(3)	0.098 9(2)	−0.140 6(2)	−0.080 3(5)
O(4)	0.000 0(2)	0.119 2(2)	0.161 0(3)
C(21)	−0.162 1(3)	−0.235 5(3)	−0.823 2(5)
C(22)	−0.164 0(4)	−0.301 1(3)	−0.957 2(6)
C(23)	−0.224 7(3)	−0.285 9(4)	−1.095 2(6)
O(5)	−0.113 9(2)	−0.250 9(2)	−0.712 0(4)
O(6)	−0.207 3(2)	−0.169 8(2)	−0.830 0(4)
O(7)	−0.264 5(2)	−0.212 6(3)	−1.098 8(5)
O(8)	−0.230 7(3)	−0.340 6(3)	−1.195 9(5)

Table 2. Selected bond distances (Å) for compound (2)·$CH_2(CO_2H)_2$, with esds in parentheses.

C(1)–C(2)	1.391(6)	C(12)–C(13)	1.515(5)
C(1)–C(11)	1.410(6)	C(13)–C(15)	1.539(6)
C(2)–C(3)	1.399(6)	C(14)–C(9)	1.551(6)
O(2)–C(5)	1.465(5)	C(14)–C(13)	1.532(5)
C(3)–C(4)	1.391(6)	C(14)–O(4)	1.444(5)
C(3)–O(1)	1.359(5)	C(15)–C(16)	1.521(6)
C(4)–C(12)	1.378(5)	C(16)–N	1.512(5)
C(4)–O(2)	1.390(5)	C(17)–C(18)	1.488(6)
C(5)–C(6)	1.540(6)	N–C(17)	1.503(5)
C(5)–C(13)	1.538(5)	C(18)–C(19)	1.501(7)
C(6)–C(7)	1.497(6)	C(18)–C(20)	1.495(7)
C(6)–O(3)	1.201(6)	C(19)–C(20)	1.484(9)
C(7)–C(8)	1.535(7)	C(21)–C(22)	1.520(7)
C(8)–C(14)	1.519(6)	O(5)–C(21)	1.239(6)
C(9)–C(10)	1.553(6)	O(6)–C(21)	1.249(5)
C(9)–N	1.523(5)	C(22)–C(23)	1.536(8)
C(11)–C(10)	1.517(5)	C(23)–O(7)	1.302(7)
C(12)–C(11)	1.369(5)	C(23)–O(8)	1.203(7)

(AM-1 type) of the conformational energies of the internal rotations of the *N*-substitutent groups in $NLXH^+$ and $NTRXH^+$ cationic species and in NLX and NTRX free bases.

Experimental

Sample.—In spite of considerable efforts it was not possible to obtain crystals of good quality from commercial naltrexone hydrochloride, while naltrexone, as its malonate, was obtained as transparent, bright prisms of quality high enough to permit structure analysis. The crystal used for intensity measurements was *ca.* 0.3 mm on edge and no correction for absorption was made [μ(Mo-K_α) = 0.7 cm^{-1}]. Intensities and cell dimensions were determined, at room temperature, with a Philips PW 1100 computer-controlled automatic diffractometer.

Table 3. Selected bond angles (°) for compound (2)·$CH_2(CO_2H)_2$, with esds in parentheses.

C(2)–C(1)–C(11)	119.4(4)	C(1)–C(2)–C(3)	123.3(4)
C(2)–C(3)–O(1)	124.2(4)	C(1)–C(11)–C(10)	124.7(4)
C(3)–C(4)–C(12)	120.8(4)	C(1)–C(11)–C(12)	116.7(4)
C(4)–O(2)–C(5)	104.6(3)	C(2)–C(3)–C(4)	115.8(4)
C(4)–C(3)–O(1)	120.0(4)	O(2)–C(5)–C(13)	105.7(3)
C(4)–C(12)–C(13)	108.5(3)	C(3)–C(4)–O(2)	126.9(3)
C(5)–C(6)–O(3)	120.8(4)	C(4)–C(12)–C(11)	123.7(4)
O(2)–C(5)–C(6)	107.9(3)	C(5)–C(6)–C(7)	116.2(4)
C(7)–C(6)–O(3)	123.1(4)	C(5)–C(13)–C(14)	118.2(3)
C(7)–C(8)–C(14)	108.9(4)	C(5)–C(13)–C(15)	112.4(3)
C(8)–C(14)–C(9)	111.8(3)	C(6)–C(5)–C(13)	113.4(3)
C(9)–C(14)–O(4)	107.4(3)	C(6)–C(7)–C(8)	111.2(4)
C(11)–C(10)–C(9)	113.5(3)	C(8)–C(14)–C(13)	112.1(3)
C(11)–C(12)–C(13)	127.8(3)	C(8)–C(14)–O(4)	110.3(3)
C(12)–C(11)–C(10)	118.4(3)	C(9)–N–C(16)	113.2(3)
C(12)–C(13)–C(14)	108.4(3)	C(9)–N–C(17)	114.4(3)
C(12)–C(13)–C(15)	109.6(3)	C(10)–C(9)–N	112.8(3)
C(13)–C(14)–C(9)	107.0(3)	C(12)–C(13)–C(5)	98.4(3)
C(14)–C(9)–C(10)	115.8(3)	C(12)–C(4)–O(2)	112.2(3)
C(14)–C(13)–C(15)	109.1(3)	C(13)–C(15)–C(16)	111.9(3)
C(15)–C(16)–N	110.6(3)	C(13)–C(14)–O(4)	108.0(3)
C(16)–N–C(17)	110.4(3)	C(14)–C(9)–N	105.5(3)
N–C(17)–C(18)	111.6(4)	C(17)–C(18)–C(20)	117.9(4)
C(17)–C(18)–C(19)	118.6(4)	C(18)–C(20)–C(19)	60.5(4)
C(18)–C(19)–C(20)	60.1(4)	C(19)–C(18)–C(20)	59.4(4)
O(6)–C(21)–O(5)	123.6(4)	O(5)–C(21)–C(22)	116.6(4)
O(6)–C(21)–C(22)	119.8(4)	C(21)–C(22)–C(23)	118.3(4)
C(22)–C(23)–O(7)	117.6(4)	C(22)–C(23)–O(8)	118.5(5)
O(8)–C(23)–O(7)	123.9(5)		

Crystal Data.—$(C_{20}H_{24}NO_4)^+(C_3H_3O_4)^-$, M = 445.5, orthorhombic, $P2_12_12_1$, a = 16.047(4), b = 15.469(4), c = 8.434(3) Å, V = 2 093.6(1.1) Å^3; Z = 4, D_m = 1.40 g cm^{-3} (by flotation in CCl_4–C_6H_6), D_c = 1.41 g cm^{-3}, λ(Mo-K_α) = 0.7107 Å, F(000) = 944.

3 463 Independent reflections ($2\theta < 60°$) were collected using θ–2θ scans; of these, 762 were rejected because of low intensity [$I < 3\sigma(I)$]. The data were corrected for Lorentz and polarization effects.

Structure Analysis.—The structure was determined by direct methods using the program SHELXS-86.[15] The *E*-map, computed from the unambiguous set of phases (CFOM = 0.063), gave a model which fitted the geometry of the naltrexone malonate molecule and from which all 32 non-hydrogen atoms could be obtained (R = 0.25). Full-matrix least-squares refinement gave R = 0.067, and at this stage all the hydrogen atoms, except for the three hydroxy-group hydrogen atoms, were localized in a difference Fourier-map, and only their isotropic thermal parameters were refined. The refinement converged at R = 0.060 for the 2 701 observed reflections (no. variables 313; G index 1.04). During the refinement the function minimized was $\Sigma w(\Delta F)^2$, unit weights were applied throughout, and the highest residual in the final ΔF-map was 0.46 e Å^{-3}. The structure was refined using the SHELX-76[16] program system on a Digital Microvax-3300 computer.

Final positional parameters for the non-hydrogen atoms are listed in Table 1, while bond distances and angles are reported in Table 2 and 3 and other geometrical data are shown in Table 4.

Table 4.

(*a*) Torsional angles/°.

Ring A	C(1)–C(2)–C(3)–C(4)	2.6
	C(2)–C(3)–C(4)–C(12)	0.9
	C(3)–C(4)–C(12)–C(11)	−4.4
	C(4)–C(12)–C(11)–C(1)	4.1
	C(11)–C(1)–C(2)–C(3)	−2.8
	C(12)–C(11)–C(1)–C(2)	−0.5
Ring B	C(4)–O(7)–C(5)–C(13)	29.8
	O(2)–C(5)–C(13)–C(12)	−31.5
	C(5)–C(13)–C(12)–C(4)	22.9
	C(13)–C(12)–C(4)–O(2)	−6.0
	C(12)–C(4)–O(2)–C(5)	−15.2
Ring C	C(9)–C(10)–C(11)–C(12)	−5.9
	C(10)–C(11)–C(12)–C(13)	6.5
	C(11)–C(12)–C(13)–C(14)	−32.5
	C(12)–C(13)–C(14)–C(9)	54.2
	C(13)–C(14)–C(9)–C(10)	−59.1
	C(14)–C(9)–C(10)–C(11)	33.6
Ring D	C(5)–C(6)–C(7)–C(8)	−52.4
	C(6)–C(7)–C(8)–C(14)	62.6
	C(7)–C(8)–C(14)–C(13)	−56.7
	C(8)–C(14)–C(13)–C(5)	42.0
	C(13)–C(5)–C(6)–C(7)	35.0
	C(14)–C(13)–C(5)–C(6)	−29.8
Ring E	C(9)–C(14)–C(13)–C(15)	−65.0
	N–C(9)–C(14)–C(13)	66.3
	C(13)–C(15)–C(16)–N	−50.3
	C(14)–C(13)–C(15)–C(16)	57.0
	C(15)–C(16)–N–C(9)	54.6
	C(16)–N–C(9)–C(14)	−62.4
	O(2)–C(4)–C(12)–C(11)	173.0
	C(5)–O(2)–C(4)–C(12)	−15.2
	C(6)–C(5)–O(2)–C(4)	−91.8
	C(7)–C(6)–C(5)–O(2)	151.7
	C(8)–C(7)–C(6)–C(5)	−52.4
	C(9)–C(14)–C(8)–C(7)	−176.9
	C(10)–C(9)–C(14)–C(8)	64.0
	C(13)–C(14)–C(8)–C(7)	−56.7
	C(14)–C(8)–C(7)–C(6)	62.6
	C(15)–C(13)–C(14)–C(8)	172.0
	C(16)–C(15)–C(13)–C(14)	57.0
	N–C(16)–C(15)–C(13)	−50.3
	C(17)–N–C(16)–C(15)	−175.7
	C(18)–C(17)–N–C(16)	−178.2
	C(19)–C(18)–C(17)–N	−140.2
	C(19)–C(20)–C(18)–C(17)	−108.4

(*b*) Deviation (Å) of atoms in rings A, B, and C (mean plane I) and in rings D and E (mean plane II). Atoms marked with an asterisk do not define the plane.

Plane I	C(1) 0.08; C(2) 0.09; O(2) −0.05; C(3) 0.05; C(4) −0.06; C(12) −0.14; C(5) 0.25; C(13) −0.33; C(14) 0.38; C(9) −0.16; C(10) 0.05; C(11) −0.03
Plane II	C(5) 0.07; C(6) 0.08; C(7) −0.52; C(8) 0.08; C(9) 0.41; C(13) 0.26; C(14) −0.24; C(15) −0.27; C(16) 0.14; N −0.19
Plane A	C(1) 0.01; O(1)* 0.03; C(2) −0.02; O(2)* 0.11; C(3) 0.01; C(4) 0.01; C(11) 0.01; C(12) −0.02; C(13)* −0.09; C(10)* 0.14
Plane C	C(4)* 0.21; C(5)* 0.43; C(8)* 1.88; C(9) −0.23; C(10) 0.03; C(11) 0.08; C(12) 0.02; C(13) −0.24; C(14) 0.36; N* −1.72; O(4)* −0.09

(*c*) Dihedral angles between the planes (°).

(I)–(II)	82.1	(I)–(F)	35.7
(I)–(A)	4.9	(II)–(F)	76.9
(II)–(A)	86.9	(B)–(C)	10.2
(D)–(A)	79.7	(D)–(E)	12.1
(E)–(A)	90.8		

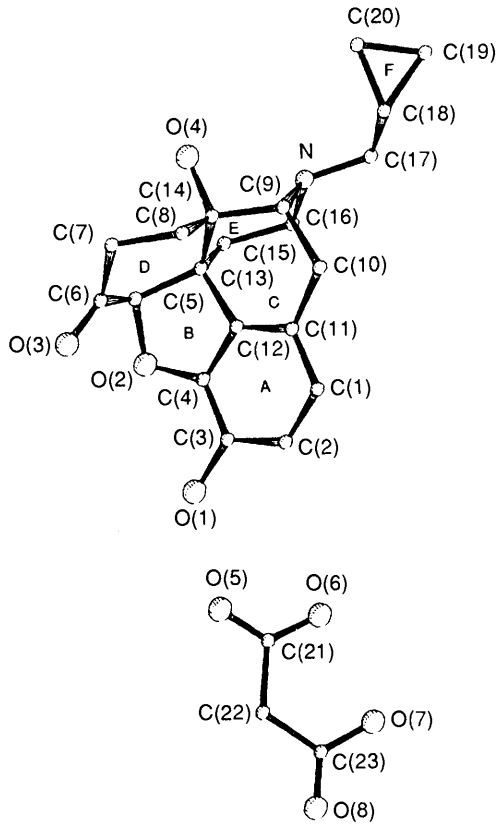

Figure 1. Perspective view of the naltrexone malonate molecule in the crystal state.

A perspective view of the molecule in the solid state is given in Figure 1.*

Quantum Mechanical Calculations.—Calculations of the conformational energies for the species NLX, $NLXH^+$, NTRX, and $NTRXH^+$ were performed through the AM-1 semiempirical method[17] using the AMPAC package[18] run on a Digital VAX 11/750 computer system. The X-ray structure data (taken from ref. 5 and from the present work) were initially used as input parameters for full optimization of geometries by the AM-1 method. The chair conformation of the piperidine ring and the *N*-equatorial configuration of the alkyl group of the molecular backbones in the solid (refs. 3, 4, and present work) and in the liquid[7] states were assumed as retained for isolated molecules. The optimized geometries were then used as input for calculations of conformational energies as a function of the rotation angles ω_1, ω_2 about the N–C and C–C bonds, respectively, of the *N*-substituent groups (see Figure 2 for definition of angles). The conformational iso-energy contour maps were generated by 360° rotations of ω_1, ω_2, with scans of 18°. The cationic and non-cationic species were treated as semirigid rotors in which the C–H bond angles of the *N*-allyl and *N*-cyclopropylmethyl groups, as well as the twisting angles C(8)–C(14)–O(4)–H(4), C(17)–N(1)–C(16)–C(15), and H(1)–O(1)–C(3)–C(2) in both molecular backbones, were simultaneously adjustable parameters during the rotations. Optimization of the rotational angles ω_1, ω_2 was performed within each local minimum zone of the maps.

* *Supplementary data* (see section 5.6.3 of Instructions to Authors, in the January issue). Anisotropic thermal parameters for non-hydrogen atoms and positional parameters for the hydrogen atoms have been deposited at the Cambridge Crystallographic Data Centre.

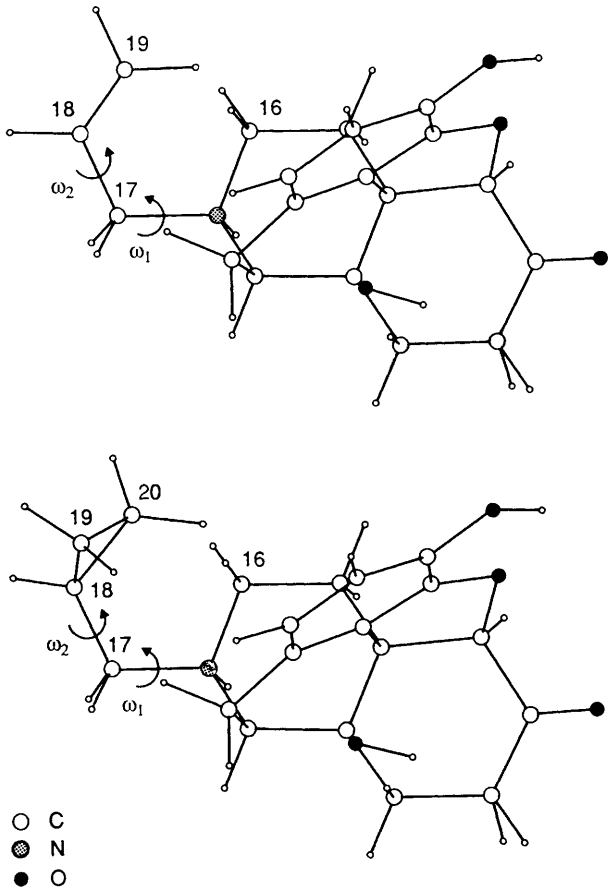

Figure 2. Perspective drawing of $NLXH^+$ (upper) and $NTRXH^+$ (lower) in the conformation ω_1, $\omega_2 = 0$ defined by coplanar arrangement of the C(16)–N–C(17)–C(18) (ω_1) and N–C(17)–C(18)–C(19) (ω_2) atoms. The projection is made along the perpendicular to these planes. The usual convention applies for the definition of torsion angles (negative sign of angle A–B–C–D when, looking through B toward C, D is anticlockwise from A).

Results and Discussion

The X-ray structure analysis of the $NTRXH^+$ species showed the well established T-shape (Figure 1) of the fairly rigid morphine-related compounds with a 4,5-epoxymorphinan skeleton.[19] The five-ring system may be considered in terms of two planes, one comprising the A, B, C rings (the stock of the T), and the second comprising the D, E rings (the arms of the T) The dihedral angle between the two planes is 82.1°, as compared with 86.6° in morphine·HCl·$3H_2O$,[20] 90.9° in morphine·H_2O,[21] 88.4° in codeine·HBr·$2H_2O$,[22] and 82.6° in naloxone·HCl·$2H_2O$,[3,4].

The overall molecular shape of protonated naltrexone is virtually identical with that of naloxone,[3,4] and the dihedral angles (Table 4) agree with the corresponding angles in naloxone with deviations <4.9° (mean value 1.8°).

The D and E rings assume a chair conformation, while the saturated C ring, having five atoms roughly in a plane (maximum deviation 0.03 Å) with C(12) 0.69 Å out of the plane, is in a sofa form. The substituent group at N is in the equatorial configuration, leaving the lone pair at *N*-axial, as shown in Figure 1. This situation is in line with that of $NLXH^+$ [3,4] and with those of the three substituted 6,7-benzomorphan compounds gemazocine·HBr,[23] M_r 1526, and M_r 2034.[24]

Ring B is in the envelope (C_s) conformation, but somewhat twisted [puckering co-ordinate[25] q_2 −0.316(4), φ_2 82.6(7)].

The cyclopropylmethyl side-chain adopts the same conformation as in gemazocine·HBr,[23] ketazocine·HCl·H_2O,[26] and bremazocine·HCl,[27] different from those observed in cyclazocine·HBr·H_2O and cyclazocine base,[28] and the cyclopropyl ring is almost perpendicular (80.4°) to the piperidine ring.

Bond lengths and interbond angles have expected values, including somewhat lengthened C–C single bonds and a large range of tetrahedral angles (98.4–118.2°) at the quaternary carbon atom C(13).

Packing of the $NTRXH^+$ cation and the malonate anion is determined primarily by the hydrogen bonding between the phenolic hydroxy-group H at O(1) and the O(5) atom of the malonate [O(1)···O(5) 2.64 Å] and this short distance represents a genuine hydrogen bond. Apart from this short distance and that intramolecular bond involving the quaternary N atom and the OH group on C(14) [N···O(4) 2.67 Å], there are no intermolecular contacts less than 3 Å between the non-hydrogen atoms.

The following results of the theoretical calculations, which apply to molecules in the gas phase, do not reproduce the conformations found in the solid state for either compound. This indicates that the torsion angles assumed by the *N*-alkyl moieties in the crystal state of both $NLXH^+$ and $NTRXH^+$ cations are essentially determined by intermolecular crystal-packing forces.

A comparison of the two sets of four low-energy conformations yielded by the surfaces generated by the two cations (Table 5) shows that: (i) the conformations (**4**) for $NLXH^+$ and (**3**) for $NTRXH^+$ are nearly coincident; (ii) only the conformational preferences about the C(17)–C(18) bond are significantly affected on passing from $NLXH^+$ to $NTRXH^+$.

It is noteworthy that although the present results are not directly comparable to those from previously cited theoretical work because of the differences in the methods and optimization procedures used for the search for the conformational minima, the preferred conformations (**1**)–(**4**) of $NLXH^+$ and NLX approximately resemble those obtained up *ab initio* calculations.[11]

As illustrated in Figure 3, the pairs of minima (1), (4) and (2), (3) ($NLXH^+$) and (1), (3) and (2), (4) ($NTRXH^+$) appear (within oscillations of ±20° allowed by the torsional energy barriers about ω_1, ω_2 angles) as made by two pairs of conformations which are 'mirror images' of each other with respect to the plane bisecting the piperidine ring through C(13), N, and C(17). An additional interesting feature is that, in the two analogous molecular backbones, the different *N*-alkyl moieties in the conformations corresponding to the four minima of each set have atoms which, with good approximation, can match one another. This should support the hypothesis by which both should engage the receptor in some of their preferred conformations.

The torsion barrier heights are low enough to allow easy interconversion of $NLXH^+$, through ω_1 rotations, from conformer (1) to (3) and *vice versa* ($\leq$3 kcal mol^{-1}) * as well as from conformer (2) to (4) and *vice versa* ($\leq$1 kcal mol^{-1}). The calculated interconversion barriers between the two pairs of minima about the C(17)–C(18) bond attain the maximum value of 5 kcal mol^{-1}. In the case of $NTRXH^+$ the energy barrier for jumping the C(17)–C(18) bond from the conformational states (1), (4) to conformers (2), (3), and *vice versa*, attained a value (>8 kcal mol^{-1}) which is somewhat higher than that in $NLXH^+$, thus indicating a rigid C(17)–C(18) bond and 'isolated' conformer pairs. This is an important result which is fairly consistent with findings from ^{13}C NMR spin-lattice relaxation time (T_1) studies [9,10] in solution. These report, as an inherent feature of $NTRXH^+$, the internal diffusion rate (D_R)

* 1 cal = 4.184 J.

Table 5. Conformations in the solid- and in the gas-phase. Results of statistical analysis (made using the Boltzman factor and assuming no significant entropic or solvation differences between conformers) are also quoted.

	Theoretical energy minimum	ω_1/°, ω_2/°	Relative energy/ kcal mol^{-1}	% Population (at 308 K) of the conformational states	ω_1, ω_2 (solid phase)/°
NLXH$^+$					
	(1)	80.7, 119.2	0	40	−179.6, −97.9[a]
	(2)	86.6, −112.5	0.01	37	
	(3)	180, 126	0.71	13	
	(4)	173.1, −70.9	0.80	10	
NTRXH$^+$					
	(1)	77.7, 140.4	0	44	−178.2, −140.2[b]
	(2)	84.3, −89	0.19	32	
	(3)	173.2, −70.6	0.65	15	
	(4)	173, 163.4	1.06	8	
NLX					
	(1)	180, 144	0	39	
	(2)	84, −137	0.30	24	
	(3)	162, 162	0.39	20.5	
	(4)	90, 144	0.51	16.5	
NTRX					
	(1)	175, 167,6	0	25	
	(2)	174.2, −173.6	0.22	17.4	
	(3)	78.7, −114.4	0.23	17.3	
	(4)	−174.1, −63.1	0.25	16.5	
	(5)	177 −73.1	0.34	14.2	
	(6)	79.3, 129.8	0.58	9.6	

[a] Ref. 4. [b] This work.

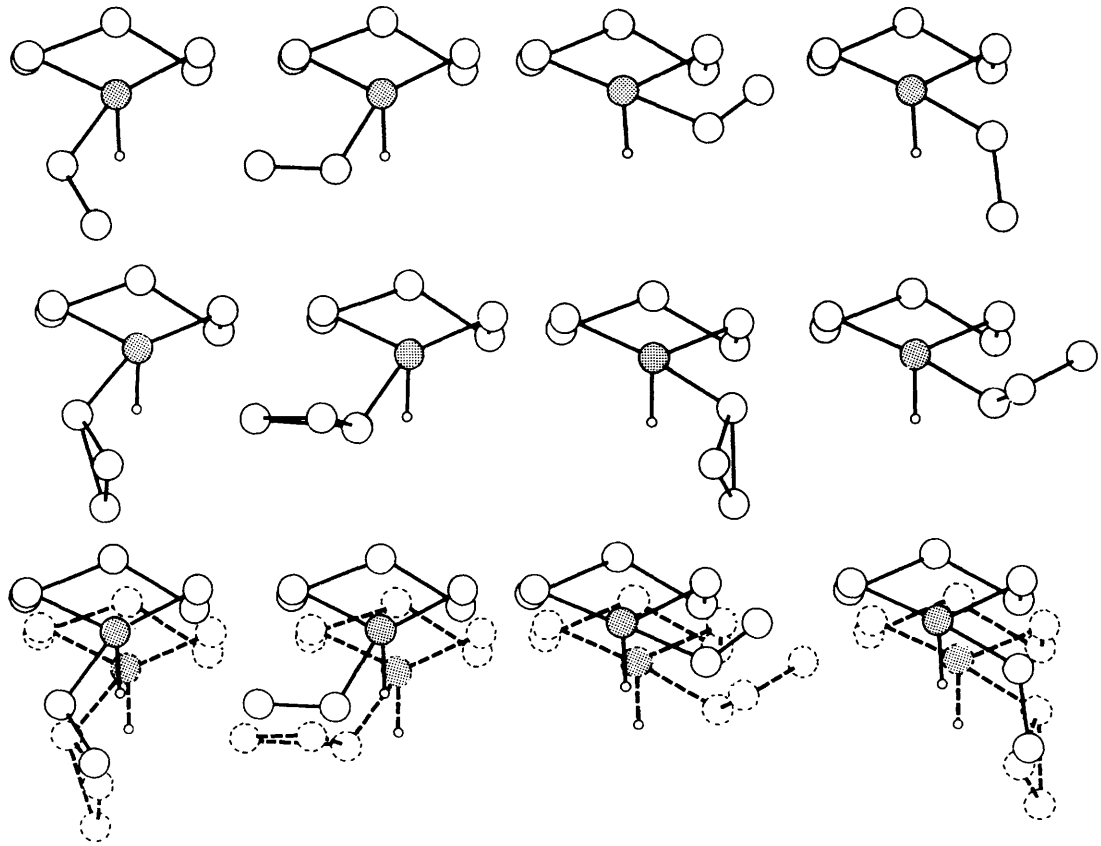

Figure 3. Comparison of the energetically preferred conformations (**1**)–(**4**) (in that order) of the *N*-alkylpiperidine moiety of NLXH$^+$ (upper) and NTRXH$^+$ (lower). The molecular backbone and hydrogen atoms are excluded for simplicity. The common perspective view is along the C(17)–N bond that is projected perpendicularly to the plane of the drawing. The lowest section of the figure shows graphic superposition of the preferred conformations of NLXH$^+$ on those of NTRXH$^+$.

value of zero for motion around the C(17)–C(18). Based on a simple relationship[29] which correlates the D_R-value for complete rotational diffusion motion to the interconversion constant (K_{int}) for jumping motion, the found ($D_R = 0$) value will correspond to $K_{int} = 0$ in the jump-motion frame, *i.e.* to 'lack of motion' about C(17)–C(18) and, accordingly, to effectively high interconversion energy barriers between separate conformations.

The calculated minima for NLX and NTRX (Table 5) are considerably larger and shallower with respect to those of $NLXH^+$ and $NTRXH^+$, respectively. For NTRX two additional low-energy conformations (**5**), and (**6**) became accessible.

The difference could be reasonably accounted for in terms of delocalization effects of the positive charge over the cations, thus causing increase of torsion barriers. This is consistent with (i) calculated zero charge on the nitrogen of $NLXH^+$ and $NTRXH^+$ in preferred conformations given by the present work; (ii) recent valuable findings from high-resolution X-ray diffraction measurements of electron density distribution of naloxone hydrochloride[30] which provided evidence of net negative charge on the protonated nitrogen atom. Therefore the conformational minima of cationic species may be reasonably expected to be narrower than those of non-protonated molecules. In the non-cationic species the pure steric effects predominate in determining low-energy conformations.

The conformationally more restricted *N*-alkyl group of $NTRXH^+$ relative to $NLXH^+$ appears in line with a proposed dynamic model of regulation of the opioid receptor,[10] accounting for its higher μ-pure antagonistic potency with respect to $NLXH^+$. The common stereochemical arrangement of atoms of the alkyl groups in the most populated conformations of $NTRXH^+$ and $NLXH^+$ may also constitute a basis for modelling of the haptophoric group which determines the antagonist response of the receptor.

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References

1 A. F. Casy and R. T. Parfitt, 'Opioid Analgesics,' Plenum, New York, 1986, p. 445 (see also refs. therein and refs. 7–10, 12 of this paper).
2 M. S. Gold, C. A. Dackis, A. L. C. Pottash, H. H. Sternbach, and W. J. Anitto, *Med. Res. Rev.*, 1982, **2**, 211.
3 I. Karle, *Acta Crystallogr., Sect. B*, 1974, **30**, 1682.
4 R. L. Sime, R. Forehand, and R. J. Sime, *Acta Crystallogr., Sect. B*, 1975, **31**, 2326.
5 A. F. Casy, 'Guide to Molecular Pharmacology–Toxicology,' Part 1, ed. R. M. Featherstone, Marcel Dekker, New York, 1973, p. 217.
6 R. Y. Kobylecky, A. C. Lane, C. F. C. Smith, L. P. G. Wakelin, W. B. T. Cruse, E. Egert, and O. Kennart, *J. Med. Chem.*, 1982, **25**, 1280.
7 B. Perly, G. C. Pappalardo, and A. Grassi, *Z. Naturforsch., Teil B*, 1986, **41**, 231.
8 E. L. Eliel, S. Morris-Natschke, and V. M. Kolb, *Org. Magn. Reson.*, 1984, **22**, 258.
9 G. C. Pappalardo, L. Radics, M. Baldo, and A. Grassi, *J. Chem. Soc., Perkin Trans. 2*, 1985, 955.
10 A. Grassi, B. Perly, and G. C. Pappalardo, *Chem. Phys.*, 1989, **130**, 335.
11 B. V. Cheney and D. A. Zichi, *Int. J. Quantum Chem., Quantum Biol. Symp.*, 1981, **8**, 201.
12 B. V. Cheney, J. Szmuszkovicz, R. A. Lahti, and D. A. Zichi, *J. Med. Chem.*, 1985, **28**, 1853.
13 B. V. Cheney, D. J. Duchamp, and R. E. Christoffersen, 'NIDA Research Monograph 22,' eds. G. Barnett, M. Trsic, and R. E. Willette, National Institute on Drug Abuse, Washington, DC, 1978, pp. 218–249.
14 G. H. Loew and D. S. Berkowitz, *J. Med. Chem.*, 1978, **21**, 101.
15 G. M. Sheldrick, 'Crystallographic Computing 3', eds. G. M. Sheldrick, C. Kruger, and R. Goddard, University Press, Oxford, 1985, pp. 175–189.
16 G. M. Sheldrick, SHELX-76, Programs for Crystal Structure Determination, University of Cambridge, Cambridge, England, 1976.
17 M. J. Dewar, E. G. Zoebisch, E. F. Healy, and J. J. P. Stewart, *J. Am. Chem. Soc.*, 1985, **107**, 3902.
18 QCPE Program No. 506, Indiana University.
19 J. P. Tollenaere, H. Moereels, and L. A. Raymaekers, 'Atlas of the Three-dimensional Structure of Drugs,' Elsevier/North-Holland, Amsterdam, 1979, pp. 167–181.
20 L. Gylbert, *Acta Crystallogr., Sect. B*, 1973, **29**, 1630.
21 E. Bye, *Acta Chem. Scand., Ser. B*, 1976, **30**, 549.
22 G. Kartha, F. R. Ahmed, and W. H. Barnes, *Acta Crystallogr., Sect. B*, 1962, **15**, 326.
23 Y. G. Gelders, C. J. De Ranter, and H. Schenk, *Acta Crystallogr., Sect. B*, 1979, **35**, 699.
24 O. M. Peeters, C. J. De Ranter, and N. M. Blaton, *Acta Crystallogr., Sect. B*, 1982, **38**, 3055.
25 D. Cremer and J. A. Pople, *J. Am. Chem. Soc.*, 1975, **97**, 1354.
26 C. L. Verlinde and C. J. De Ranter, *Acta Crystallogr., Sect. C*, 1983, **39**, 1703.
27 C. L. Verlinde, N. M. Blaton, C. J. De Ranter, and O. M. Peeters, *Acta Crystallogr., Sect. C*, 1984, **40**, 1759.
28 I. L. Karle, R. D. Gilardi, A. V. Fratini, and J. Karle, *Acta Crystallogr., Sect. B*, 1969, **25**, 1469.
29 M. Baldo, A. Grassi, and A. Raudino, *Phys. Rev. A*, 1989, **40**, 1017, and refs. therein.
30 C. L. Klein, R. J. Majeste, and E. D. Stevensen, *J. Am. Chem. Soc.*, 1987, **109**, 6675.

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