Molecular Crystals and Liquid Crystals

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/gmcl20

CRYSTAL STRUCTURE AND CONFORMATION OF A PAIR OF PIPERIDINE DERIVATIVES

A. Nallini [a], K. Saraboji [a], M. N. Ponnuswamy [a], M. Venkatraj [b] & R. Jeyaraman [b]

[a] Department of Crystallography and Biophysics, University of Madras, Guindy Campus, Chennai-600 025, India

[b] Department of Chemistry, Bharathidasan University, Tiruchirappalli-620 024, India

Version of record first published: 02 Feb 2011

To cite this article: A. Nallini, K. Saraboji, M. N. Ponnuswamy, M. Venkatraj & R. Jeyaraman (2003): CRYSTAL STRUCTURE AND CONFORMATION OF A PAIR OF PIPERIDINE DERIVATIVES, Molecular Crystals and Liquid Crystals, 403:1, 57-65

To link to this article: http://dx.doi.org/10.1080/15421400390234057

Mol. Cryst. Liq. Cryst., Vol. 403, pp. 57–65, 2003

ISSN: 1542-1406 print/1563-5287 online
DOI: 10.1080/ 15421400390234057

Taylor & Francis
Taylor & Francis Group

CRYSTAL STRUCTURE AND CONFORMATION OF A PAIR OF PIPERIDINE DERIVATIVES†

*A. Nallini, K. Saraboji, and M. N. Ponnuswamy**
Department of Crystallography and Biophysics, University of Madras, Guindy Campus, Chennai–600 025, India

M. Venkatraj and R. Jeyaraman
Department of Chemistry, Bharathidasan University, Tiruchirappalli–620 024, India

N-Morpholinoacetyl-3-methyl-2,6-diphenylpiperidin-4-one(MCAMPO), $C_{24}H_{28}N_2O_3$, F.W = 392.48, monoclinic, $P2_1/c$, $a = 9.5714(10)$ Å, $b = 19.7588(10)$Å, $c = 11.3961(10)$ Å, $\beta = 94.383(10)^\circ$, $V = 2148.9(3)$ Å^3, $Z = 4$, $D_{calc} = 1.213$ Mg/m^3, $\mu = 0.639$ mm^{-1}, $F_{000} = 840$, CuK$\alpha = 1.5418$ Å, final R1 and wR2 are 0.0509 and 0.1352, respectively.

N-Morpholinoacetyl-3-isopropyl-2,6-diphenylpiperidin-4-one(MCAIPO), $C_{26}H_{32}N_2O_3$, F.W = 420.54, orthorhombic, $P2_12_12_1$, $a = 9.0053(2)$Å, $b = 12.1942(10)$Å $c = 21.1742(2)$Å, $V = 2325.19(6)$Å^3, $Z = 4$, $D_{calc} = 1.201$ Mg/m^3, $\mu = 0.078$ mm^{-1}, $F_{000} = 904$, MoK$\alpha = 0.71073$Å final R1 and wR2 are 0.0595 and 0.1151, respectively.

The heterocyclic rings of the two ketopiperidines exhibit twist-boat and chair conformations, respectively. The morpholine ring poses an acceptor nitrogen atom for C–H . . . N interactions in both the structures.

Keywords: crystal structure; conformation; hydrogen bonding; MCAMPO; MCAIPO

INTRODUCTION

Functionalized piperdines are important heterocycles as they exhibit antidepressant, antiarrhythmic, antithrombogenic, spasmolytic, tranquilizing, and blood cholesterol-lowering activities [1]. Piperdine derivatives,

Received 1 January 2003; accepted 30 April 2003.

†The CDB reference Numbers: MCAMPO-CCDC 200346; MCAIPO-CCDC 200345.

The financial assistance to A. Nallini by the Jawaharlal Nehru Memorial Fund, Teen Murti House, New Delhi, India is acknowledged with thanks.

*Corresponding author. E-mail: mnpsy@hotmail.com

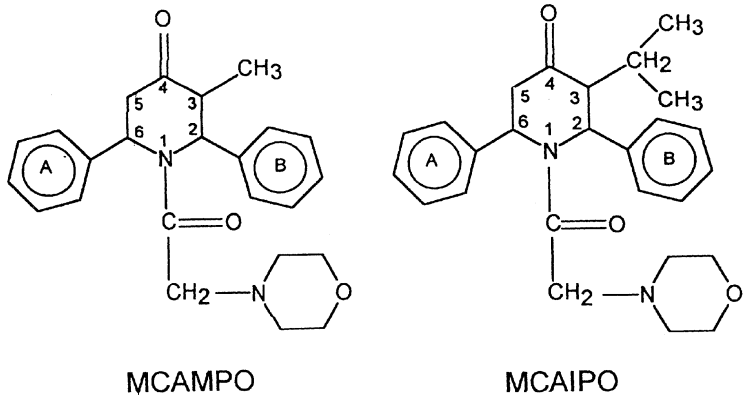

FIGURE 1 Chemical diagrams of MCAMPO and MCAIPO.

namely 4-piperidones, are synthetic intermediates in the preparation of various alkaloids and pharmaceutical products [2–3]. Recently it has been shown that a series of 3,5-bis arylylidene-4-piperidones and related N-Acryloyl analogues prepared as cytoxins may lead to drugs which are deprived of genotoxic properties [4].

Among the set of ketopiperidines, those which have the carbonyl oxygen at the 3rd and 4th positions behave as typical ketones. On the other hand, the 2-piperidones are devoid of ketonic properties and behave as cyclic amides. With relation to such ketopiperidines, structural studies on a pair of N-Morpholinoacetyl–substituted piperidin-4-ones by substituting different alkyl groups is dealt with in this study. The chemical diagrams of MCAMPO and MCAIPO are shown in Figure 1.

X-RAY DATA COLLECTION, STRUCTURE SOLUTION, AND REFINEMENT

Data Collection

MCAMPO

A crystal of dimension $0.04 \times 0.30 \times 0.22$ mm was used for collection of intensity data on an Enraf Nonius CAD4 diffractometer [5] with graphite monochromated CuKα radiation. The unit cell parameters were obtained from 25 reflections within the range of $15 \leq \theta \leq 25^{\circ}$ from least-squares refinement. Out of 4228 ($R_{int} = 0.0379$) independent reflections collected, 2582 reflections with $I \geq 2\sigma(I)$ were used for structure solution and analysis. Three standard reflections were selected for a constant check of

changes in orientation of the crystal and crystal decay. The intensities were corrected for Lorentz and polarization effects.

MCAIPO

A crystal of dimension $0.46 \times 0.26 \times 0.22$ mm was appropriately chosen and used for intensity data collection on a Siemens SMART CCD area detector [6]. The data collection was covered over a hemisphere of

TABLE 1 Crystal Data for MCAMPO and MCAIPO

Parameters	MCAMPO	MCAIPO
Empirical formula	$C_{24}H_{28}N_2O_3$	$C_{26}H_{32}N_2O_3$
Formula weight	392.48	420.54
Temperature(K)	293(2)	293(2)
Wavelength(Å)	1.54184	0.71073
Crystal system	Monoclinic	Orthorhombic
Space group	$P2_1/c$	$P2_12_12_1$
Unit cell dimensions		
a(Å)	9.5714(1)	9.0053(2)
b(Å)	19.7588(1)	12.1942(1)
c(Å)	11.3961(1)	21.1742(2)
β(°)	94.383(1)	
Volume (Å^3)	2148.9(3)	2325.19(6)
Z	4	4
Calculated density (Mg/m^3)	1.213	1.201
Absorption coefficient (mm^{-1})	0.0639	0.078
F(000)	840	904
Crystal size (mm)	$0.40 \times 0.30 \times 0.22$	$0.46 \times 0.26 \times 0.22$
Theta range (°)	4.48 to 71.88	1.92 to 28.25
Index ranges	$-10 \leq = h \leq = 11$ $0 \leq = k \leq = 24$ $0 \leq = l \leq = 14$	$-11 \leq = h \leq = 11$ $-14 \leq = k \leq = 16$ $-27 \leq = l \leq = 22$
Reflections collected/unique	4228/4043 [R(int) = 0.0323]	16525/5633 [R(int) = 0.1030]
Completeness	93.3%	99.2%
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Data/restraints/parameters	4043/0/263	5633/0/281
Goodness-of-fit on F^2	1.031	0.897
Observed reflections [I > 2σ(I)]	2582	2732
Final R indices [I > 2σ(I)]	R1 = 0.0509, wR2 = 0.1352	R1 = 0.0595, wR2 = 0.1151
R indices (all data)	R1 = 0.0894, wR2 = 0.1565	R1 = 0.1445, wR2 = 0.1419
Extinction coefficient	–	0.039(2)
Largest diff.peak and hole (eÅ^{-3})	0.196 and −0.184	0.217 and −0.187

reciprocal space by a combination of three sets of exposures, and each set had a different ϕ angle (0,88, and 180°) for the crystal and each exposure of 30 s covered at intervals of 0.3° in ω. The crystal-to-detector distance was 4 cm and the detector swing angle was −35°.

Structure Solution and Refinement (MCAMPO and MCAIPO)

The structures were solved by direct methods using the program SHELXS97 [7] and were subsequently refined by full-matrix least-squares using the program SHELXL97 [8]. All the hydrogen atoms were placed in geometrically idealized positions and allowed to ride on their parent atoms. The final cycle of refinement converged to R1 = 0.0509 and 0.0595,

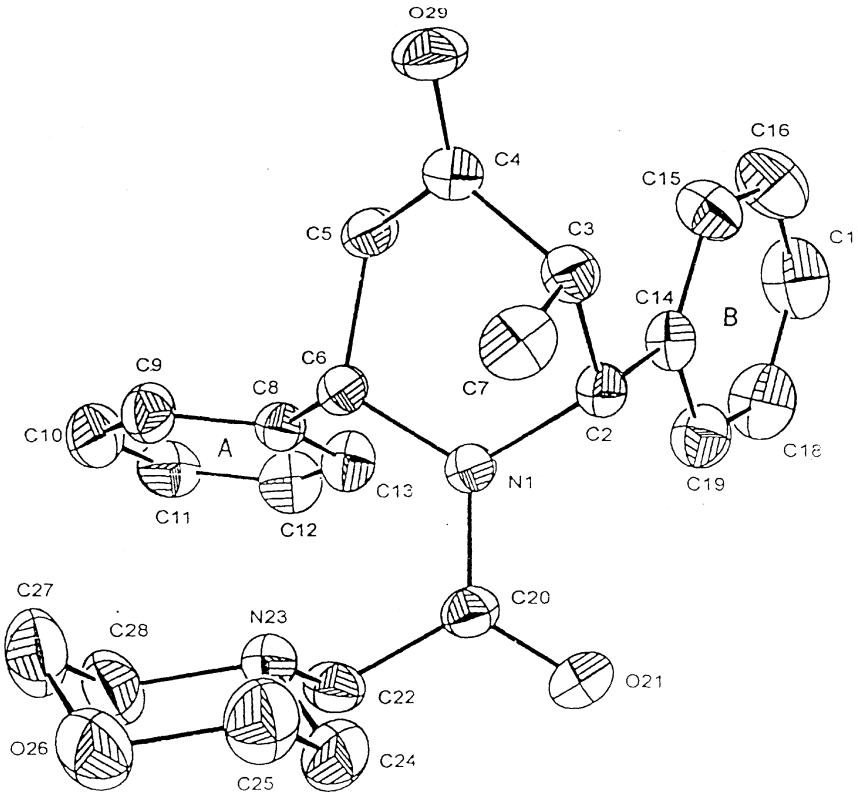

FIGURE 2 ORTEPIII diagram of MCAMPO showing the thermal ellipsoids at 30% probability level.

TABLE 2A Positional Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($Å^2 \times 10^3$) for the Nonhydrogen Atoms of MCAMPO

Atom	***x***	***y***	***z***	**$^{\$}$U(eq)**
N1	971(2)	5755(1)	3050(1)	44(1)
C2	−412(2)	5587(1)	3468(2)	47(1)
C3	−1119(2)	5058(1)	2636(2)	51(1)
C4	−1287(2)	5312(1)	1390(2)	51(1)
C5	−379(2)	5902(1)	1122(2)	53(1)
C6	1088(2)	5885(1)	1777(2)	45(1)
C7	−278(3)	4399(1)	2637(2)	67(1)
C8	1824(2)	6542(1)	1518(2)	47(1)
C9	2529(2)	6579(1)	505(2)	60(1)
C10	3161(3)	7172(1)	190(2)	73(1)
C11	3095(3)	7737(1)	878(2)	72(1)
C12	2398(3)	7706(1)	1889(3)	74(1)
C13	1764(3)	7115(1)	2206(2)	62(1)
C14	−1261(2)	6211(1)	3724(2)	53(1)
C15	−2608(3)	6329(1)	3265(2)	72(1)
C16	−3334(3)	6898(2)	3588(3)	92(1)
C17	−2730(4)	7351(2)	4367(3)	94(1)
C18	−1397(4)	7239(2)	4843(3)	86(1)
C19	−666(3)	6678(1)	4522(2)	66(1)
C20	2132(2)	5608(1)	3792(2)	51(1)
O21	2041(2)	5515(1)	4843(1)	69(1)
C22	3516(2)	5527(1)	3258(2)	58(1)
N23	3530(2)	4873(1)	2662(2)	52(1)
C24	3738(3)	4309(1)	3486(2)	72(1)
C25	3692(3)	3648(1)	2831(3)	78(1)
O26	4716(2)	3622(1)	1999(2)	81(1)
C27	4503(3)	4164(2)	1202(3)	85(1)
C28	4577(3)	4833(2)	1805(2)	74(1)
O29	−2087(2)	5053(1)	644(2)	71(1)

$^{\$}U(eq) = (1/3)\sum_i \sum_j U_{ij} a_i^* a_j^* a_i . a_j .$

wR2 = 0.1352 and 0.1151, respectively, for MCAMPO and MCAIPO. The geometrical parameters were obtained using the program PARST [9] and the figures representing the thermal ellipsoid plot were drawn using ORTEP-PIII [10]. The crystal data and refinement details are given in Table 1.

RESULTS AND DISCUSSION

The perspective view of the molecules MCAMPO and MCAIPO are shown in Figures 2 and 3, respectively. The atomic coordinates for the two molecules are presented in Table 2.

TABLE 2B Positional Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($Å^2 \times 10^3$) for the Nonhydrogen Atoms of MCAIPO

Atom	*x*	*y*	*z*	$^{\$}$U(eq)
N1	2416(2)	4729(2)	1706(1)	38(1)
C2	3461(3)	5662(2)	1743(1)	38(1)
C3	2599(3)	6754(2)	1678(1)	37(1)
C4	1263(3)	6783(2)	2114(1)	40(1)
C5	281(3)	5794(2)	2075(1)	46(1)
C6	1152(3)	4722(2)	2151(1)	42(1)
C7	2128(3)	6969(2)	981(1)	45(1)
C8	1070(4)	7945(3)	925(2)	73(1)
C9	3499(4)	7170(3)	568(2)	73(1)
C10	1677(3)	4455(2)	2818(1)	44(1)
C11	1381(4)	5089(3)	3342(2)	59(1)
C12	1927(5)	4797(4)	3937(2)	74(1)
C13	2790(4)	3882(4)	4000(2)	74(1)
C14	3060(4)	3225(3)	3493(2)	70(1)
C15	2518(3)	3507(2)	2910(2)	55(1)
C16	4534(3)	5628(2)	2307(1)	38(1)
C17	4520(3)	6381(2)	2797(1)	48(1)
C18	5595(3)	6334(3)	3272(2)	56(1)
C19	6689(3)	5559(3)	3253(2)	58(1)
C20	6724(3)	4811(3)	2766(2)	57(1)
C21	5655(3)	4835(2)	2297(2)	51(1)
C22	2582(3)	3985(2)	1230(1)	44(1)
O23	3701(3)	3987(2)	894(1)	70(1)
C24	1341(3)	3179(2)	1099(1)	50(1)
N25	41(3)	3761(2)	854(1)	45(1)
C26	307(4)	4162(3)	210(1)	58(1)
C27	−984(4)	4805(3)	−22(2)	74(1)
O28	−2304(3)	4168(2)	−22(1)	87(1)
C29	−2583(4)	3774(4)	602(2)	92(1)
C30	−1309(4)	3094(3)	840(2)	70(1)
O31	1023(2)	7537(2)	2474(1)	54(1)

$^{\$}U(eq) = (1/3)\sum_i \sum_j U_{ij} a_i^* a_j^* a_i . a_j$.

For the piperidine moieties in both the compounds, the delocalization of pi electrons in proximity to the nitrogen atom is implied from the bond lengths [N1–C20=] 1.374(2) Å in MCAMPO and [N1–C22=] 1.364(3) Å in MCAIPO.

The phenyl rings at positions 2 and 6 of MCAMPO are axial [C4–C3–C2–C14 = 70.5(2)°] and equatorial [C4–C5–C6–C8 = −174.34(18)°] with respect to the best plane of the piperidine ring. The two phenyl rings in MCAIPO are axially positioned, which is evident from the corresponding torsion angles [C4–C5–C6–C10=]−74.1(3)° and [C4–C3–C2–C16=]81.7(3)°.

TABLE 3 Possible Nonbonded Interactions (hydrogen bonds) for MCAMPO and MCAIPO

d(D-H)Å	d(H . . . A)Å	d(D . . . A)Å	< (DHA)°
MCAMPO			
C6-H6	H6 . . . N23	C6 . . . N23	C6-H6 . . . N23(i)
0.98(2)	2.54(2)	3.181(3)	122.8(2)
MCAIPO			
C6-H6	H6 . . . N25	C6 . . . N25	C6-H6 . . . N25(i)
1.03(3)	2.52(3)	3.149(4)	119(2)

Equivalent positions: (i)x,y,z.

The substitution of methyl group in MCAMPO and the isopropyl group in MCAIPO at C3 are in axial orientation, as can be seen from the conformation angles [N1–C2–C3–C7=] 62.1(2)° and 75.6(3)°, respectively.

The presence of the morpholinoacetyl group at the hetero atom in both the piperidine compounds shows the importance on their structural studies. Their acetyl groups acquire synclinal orientation. But, the respective dihedral angles between the best place of piperidine and the acetyl moiety,

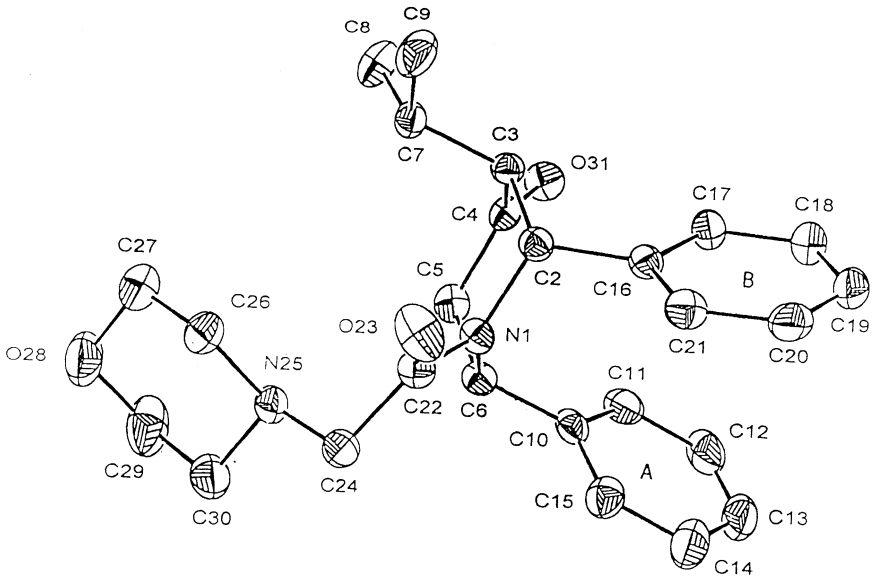

FIGURE 3 ORTEPIII diagram of MCAIPO showing the thermal ellipsoids at 30% probability level.

equal to 50.78(8)° in MCAMPO and 32.46(10)° in MCAIPO, show the degree of variation in their orientations.

The morpholino rings in the two compounds of piperidone adopt chair conformation. The deviations of the atoms C27 and C30 from the best plane in MCAIPO are 0.655(4) Å and −0.695(4) Å, respectively.

The piperidine rings of the two structures exhibit different conformations, namely the twist-boat in MCAMPO and the chair in MCAIPO. The least-squares plane calculation shows that the atoms C2 and C6 in MCAMPO deviate respectively in opposite directions by −0.768(2) Å and 0.517(2) Å. The chair conformation of piperidine ring in MCAIPO is seen from the deviations of the atoms C3[= −0.610(3) Å] and C6[= 0.641(3) Å] in relation to the best piperidine plane. The puckering parameters QT = 0.520(3), q2 = 0.021(3), q3 = 0.520(3), and $\phi 2 = -36.45(8)$ also favor chair conformation for the piperidine ring in MCAIPO [9].

The packing of the two piperidine structures is such that the morpholine rings pose an acceptor nitrogen atom for C–H . . . N interactions in both the structures (Table 3).

PREPARATION OF MCAMPO AND MCAIPO

The details of synthesis disclose the usage of common synthetic routes in the preparation of the two piperidones. Compounds MCAMPO and MCAIPO are outcomes of the synthesis which include their respective N-Chloroacetyl-substituted piperidones and morpholine as the two reactants. The same binary solvent mixture, benzene/petroleum ether in 1:2 ratio at a temperature of 333–353 K, yielded crystals of MCAMPO and MCAIPO under slow evaporation.

REFERENCES

[1] Comins, D.L., Brooks, C.A., & Ingalls, C.L. (2001). *J. Org. Chem. 66*, 2181.
[2] Wang, C.L., & Wuorola, M.A. (1992). *Org. Prep. Proceed. Int.*, *24*, 585.
[3] Grishina, G.V., Gaidarova, F.L., & Zefirov, N.S. (1994). *Chem. Heterocycl. Compd.*, *30*, 1401.
[4] Dimmock, J.R., Padmanilayam, M.P., Puthercode, R.N., Nazarati, A.J., Motaggnachalli, N.L., Zello, G.A., Quail, J.W., Oloo, E.O., Kraatz, H.-B., Prisciak, J.S., Allen, T.M., Santos, C.L., Balzarini, J., Clercq, E.D., & Manavathu, E.K. (2001). *J. Med. Chem.*, *44*, 586.
[5] Enraf-Nonius. (1994). *CAD-4 EXPRESS Software.* Delft, The Netherlands: Enraf-Nonius.
[6] Siemens. *SMART Software Reference Manual.* (1996). Madison, WI, Siemens Analytical X-ray Instruments Inc.
[7] Sheldrick, G.M. (1997). *SHELXS97. Program for the Crystal Structure Solution*, Göttingen, Germany: University of Göttingen.

[8] Sheldrick, G.M. (1997). ***SHELXS97. Program for the Crystal Structure Refinement***, Göttingen, Germany: University of Göttingen.
[9] Nardelli, M. (1983). ***Comput. Chem.***, ***7***, 95.
[10] Burnett, M.N., & Johnson, C.K. ***ORTEPIII.*** Report ORNL-6895, Oak Ridge National Laboratory, Oak Ridge, Tennessee, USA.