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2,6-Bis(4-nitrobenzylidene)cyclohexanone

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Key indicators

Single-crystal X-ray study
T = 123 K
Mean σ(C–C) = 0.004 Å
R factor = 0.056
wR factor = 0.132
Data-to-parameter ratio = 13.5

For details of how these key indicators were automatically derived from the article, see http://journals.iucr.org/e.

In the crystal structure of the title compound, $C_{20}H_{16}N_2O_5$, the cyclohexane ring assumes the sofa conformation. Steric repulsions between one of the *ortho*-H atoms of each of the aryl groups and the equatorial H atoms at positions 3 and 5 of the cyclohexane ring lead to large torsion angles between the aryl rings and the adjacent olefinic linkages. Various bond angles confirm this steric impedance between the aryl and cyclohexane rings.

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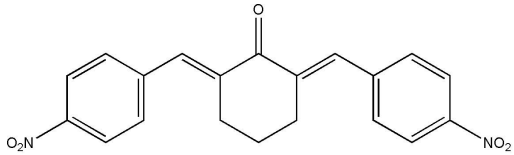
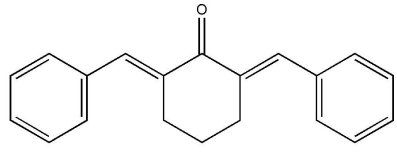
Comment

A major interest in our laboratories is the synthesis of conjugated arylidene ketones which are designed as thiol alkylators for evaluation as candidate cytotoxic and anticancer agents (Dimmock *et al.*, 2000, 2002). Recently, a series of 2,6-bis(arylidene)cyclohexanones was prepared and the compound with the lowest IC_{50} values towards human Molt 4/C8 and CEM T-lymphocytes, as well as murine P388 and L1210 cells, is 2,6-bis(4-nitrobenzylidene)cyclohexanone, (I) (Dimmock *et al.*, 2003). This compound possesses approximately one-third of the potency of the clinically useful antineoplastic alkylating agent melphalan towards these cell lines. Compound (I) is well tolerated in mice, in contrast to many other anticancer drugs, including melphalan (Quinn & Milne, 1986). The principal aim of the present X-ray crystallographic investigation of (I) is to obtain information pertaining to its shape and, in particular, to those structural features which may contribute to its significant potency towards malignant cells. In addition, the decision was made to compare its shape with that of the unsubstituted analogue (II) whose structure had been determined by X-ray crystallography previously (Jia *et al.*, 1989). In general, compound (I) possesses greater cytotoxic potency than (II) towards Molt 4/C8, CEM, P388 and L1210 cells (Dimmock *et al.*, 2003).



(I)



(II)

In (I), the central alicyclic ring adopts the sofa conformation. Atoms C1–C3/C5/C6 are coplanar, with an r.m.s. deviation of 0.043 Å; atom C4 is 0.666 (4) Å out of this plane. The *E* configuration of both olefinic double bonds is noted. Steric repulsions occur between the atom pairs H13/H5*e* and H20/H3*e* (the interatomic distances are 2.347 and 2.491 Å,

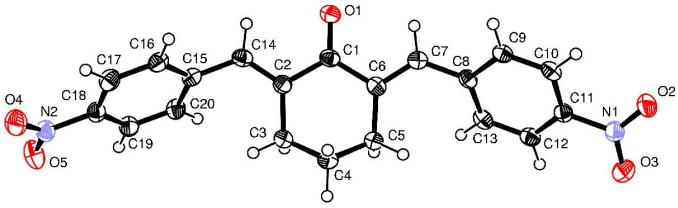


Figure 1
A general *ORTEP-3* view (Farrugia, 1997) of (I), with displacement ellipsoids for non-H atoms drawn at the 50% probability level. For clarity, the H atoms are drawn as small spheres of arbitrary size.

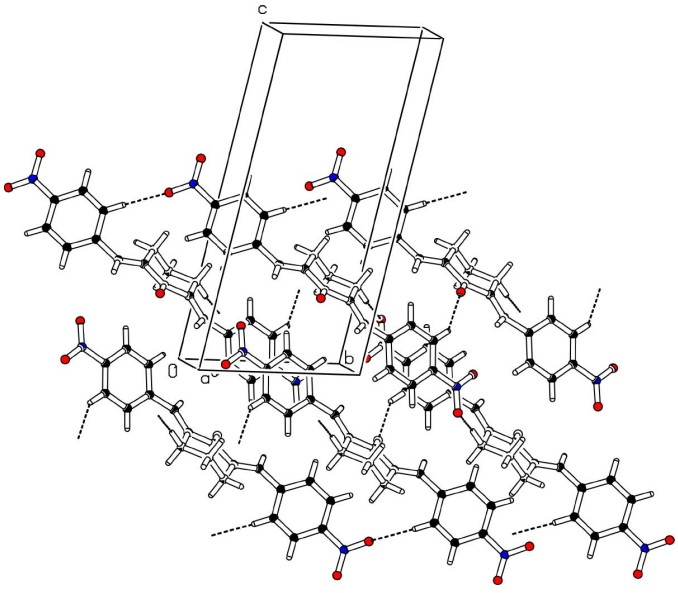


Figure 2
A packing diagram (Spek, 2003) of (I). The weak C—H···O interactions are indicated by dashed lines. The interleaved stacking of nitroaryl groups can be seen intersecting the bottom C face of the unit cell.

respectively) causing the two aryl rings to twist out of the plane of the adjacent olefinic linkages and creating torsion angles for C6—C7—C8—C13 (Θ_1) and C2—C14—C15—C20 (Θ_2) of 38.5 (4) and −47.4 (4)°, respectively. There are weak C—H···O interactions involving the carbonyl O atom and one O atom of each nitro group, as shown in Table 1. Furthermore, the relevant bond angles of (I) (Table 2) are all greater than 120°, confirming the repulsion between the aryl and cyclohexane rings.

In an attempt to ascertain the structural parameters contributing to the marked cytotoxicity of (I), its shape was compared with the less bioactive analogue (II). The Θ_1 and Θ_2 values of (II) are 40.1 (2) and −28.7 (2) (Jia *et al.*, 1989), *i.e.* one value is very similar and the other is significantly larger for (I). In solution, the two angles should be of the same magnitude with opposite signs. The significant differences must be due to crystal packing effects. The nitroaryl group corresponding to Θ_1 is interleaved with equivalent nitroaryl groups in the crystal structure of (I) [interlayer distances of 3.376 (4) and 3.300 (4) Å], with some weak C—H···O bonds from C—H units to carbonyl and nitro O atoms (Fig. 2). The greater lack of coplanarity of the aryl rings with the adjacent olefinic linkages in (I) than (II) may enable better alignments in narrow clefts at a binding site. Thus, in the future, the placement of nitro groups in the *ortho* and *meta* positions of the aryl rings, thereby creating even larger Θ values, may lead to a correlation between the Θ values and cytotoxic potencies. Second, as revealed in Table 2, certain bond angles are smaller in compound (I) than in (II). These data imply that the aryl rings are closer to the central alicyclic ring in (I) than in (II), which may be a contributing factor in the variation of potencies among the 2,6-bis(arylidene)cyclohexanones.

Experimental

A solution of sodium hydroxide (0.01 mol) in water (1 ml) was added to a solution of cyclohexanone (0.01 mol) and 4-nitrobenzaldehyde (0.02 mol) in ethanol (20 ml) at room temperature. After stirring the reaction mixture at room temperature for 4 h, the precipitate was collected and recrystallized from acetone to give the title compound [m.p. 477 K; literature m.p. 473–476 K (Dibella, 1968)] in 65% yield.

Crystal data

$C_{20}H_{16}N_2O_5$
M_r = 364.35
Triclinic, $P\overline{1}$
a = 7.5132 (5) Å
b = 7.8133 (3) Å
c = 16.1313 (11) Å
α = 77.537 (4)°
β = 89.546 (3)°
γ = 65.600 (3)°
V = 838.53 (9) Å^3
Z = 2
D_x = 1.443 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 3465 reflections
θ = 1.0–27.5°
μ = 0.11 mm^{-1}
T = 123 (2) K
Chip, yellow
0.20 × 0.20 × 0.10 mm

Data collection

Bruker–Nonius KappaCCD diffractometer
φ scans and ω scans with κ offsets
Absorption correction: none
6036 measured reflections
3290 independent reflections
2269 reflections with $I > 2\sigma(I)$
R_{int} = 0.040
θ_{max} = 26.0°
$h = -9 \rightarrow 9$
$k = -9 \rightarrow 9$
$l = -19 \rightarrow 19$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.056
$wR(F^2)$ = 0.132
S = 1.09
3290 reflections
244 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0405P)^2 + 0.5405P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.22 e Å^{-3}
$\Delta\rho_{min}$ = −0.23 e Å^{-3}

Table 1
Hydrogen-bonding geometry (Å, °).

D—H···A	D—H	H···A	D···A	D—H···A
C5—H5A···O2^{i}	0.99	2.54	3.441 (3)	152
C12—H12···O1^{ii}	0.95	2.35	3.192 (3)	147
C20—H20···O4^{iii}	0.95	2.47	3.368 (3)	158

Symmetry codes: (i) $-x, 3-y, -z$; (ii) $x-1, 1+y, z$; (iii) $x, 1+y, z$.

Table 2
Selected bond angles (°) for (I) and (II).

	(I)	(II)[a]
C3—C2—C14	124.2 (2)	125.5 (2)
C2—C14—C15	125.7 (2)	129.0 (2)
C14—C15—C20	120.5 (2)	123.0 (1)
C5—C6—C7	124.8 (2)	125.5 (1)
C6—C7—C8	127.5 (2)	130.5 (1)
C7—C8—C13	123.2 (2)	124.5 (2)

Note: (*a*) data taken from Jia *et al.* (1989).

H atoms were placed in calculated positions, with C—H distances ranging from 0.95 to 0.99 Å, and included in the refinement in riding-model approximation, with U_{iso}(H) values constrained to be 1.2 times U_{eq} of the carrier atom for all H atoms.

Data collection: *COLLECT* (Nonius, 1998); cell refinement: *SCALEPACK* (Otwinowski & Minor, 1997); data reduction: *SCALEPACK* and *DENZO* (Otwinowski & Minor, 1997); program(s) used to solve structure: *SIR97* (Altomare *et al.*, 1999); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *ORTEP-3 for Windows* (Farrugia, 1997) and *PLATON* (Spek, 2003); software used to prepare material for publication: *PLATON*.

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