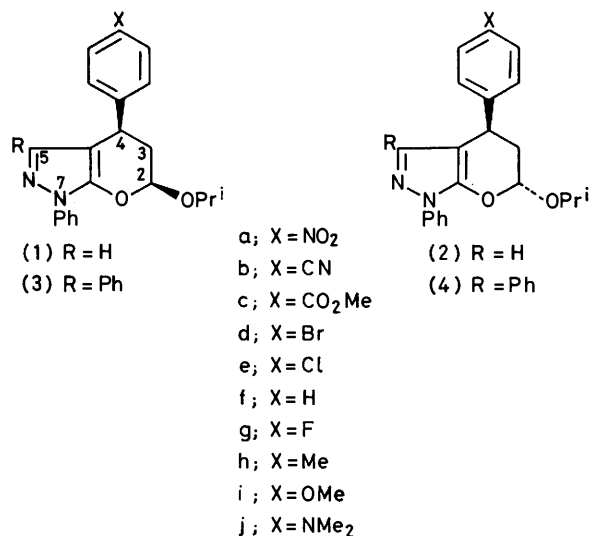# Conformational Preferences of 4-(*para*-Substituted Phenyl) 2-Isopropoxy-2,3-dihydropyran[2,3-*c*]pyrazoles: an Example of Dipole–Dipole Interaction

By **Giovanni Desimoni,** * **Anna Gamba Invernizzi, Pierpaolo Righetti,** and **Gianfranco Tacconi,** Istituto di Chimica Organica dell'Università, 27100 Pavia, Italy
Antonio Faucitano, Istituto di Chimica Generale dell'Università, 27100 Pavia, Italy

A linear dependence between conformational free energy and dipole moments was observed for a series of 4-(*para*-substituted phenyl)- *cis*[2,4]- and *trans*[2,4]-2-isopropoxy-2,3-dihydropyran[2,3-*c*]-pyrazoles. The interaction is rationalized in terms of dipole–dipole interactions, and this is supported to a certain extent by CNDO/2 calculation of electron densities in model compounds.

In a previous paper [1] we described the reaction between 4-(*para*-substituted benzylidene)-1-phenylpyrazol-5-ones and isopropyl vinyl ether which gives rise to two series of *cis*- and *trans*-adducts. Their configuration was determined by n.m.r. spectroscopy but some unusual variations in the coupling constants of the mobile dihydropyran fragment were noted. Since similar variations in coupling constants were also found in adducts from 4-(*para*-substituted benzylidene)-1,3-diphenylpyrazol-5-ones,[2] we examined the ^{1}H n.m.r. spectra of the two sets of *cis*- and *trans*-isomers (1—4a—j) in order to gain information on the forces, in addition to steric hindrance and the anomeric effect previously taken into account [3,4] and here assumed as constants, which play a relevant role in determining the conformational preferences.

^{1}H *N.m.r. and Energy Data.*—Results from both new † and previously published spectra are summarized in Table 1 and a wide variation of values is observed for (1) and (4), to a lesser extent in (3), and not in (2). In

(1) R = H
(3) R = Ph

a; X = NO₂
b; X = CN
c; X = CO₂Me
d; X = Br
e; X = Cl
f; X = H
g; X = F
h; X = Me
i; X = OMe
j; X = NMe₂

(2) R = H
(4) R = Ph

series (2) $J_{3,4}$ and $J_{2,3'}$ have a mean value of 11.08 and 2.54 Hz, respectively, with a standard deviation of 0.17

† Only *trans* coupling constants of the dihydropyran fragment are reported. Full data, available on request, will be published elsewhere with the synthetic and kinetic data.

[1] G. Desimoni, A. Gamba, M. Monticelli, M. Nicola, and G. Tacconi, *J. Amer. Chem. Soc.*, 1976, **98**, 2947.

and 0.16 Hz, which can be attributed to the electronegativity differences of the environments involved.

(I)   (II)

(III)   (IV)
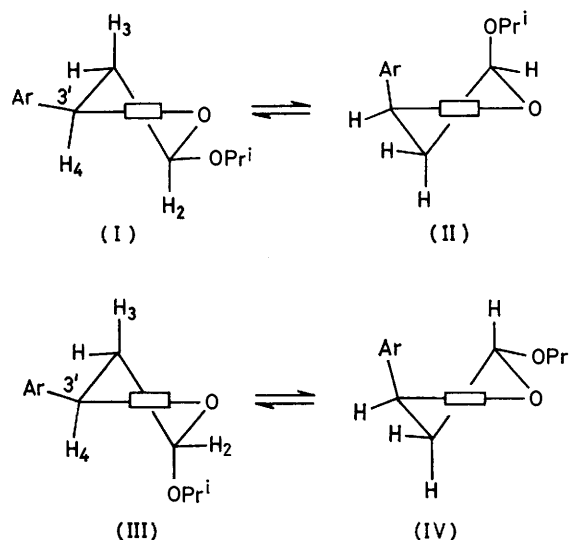
The *cis*-series (1a—j) shows $J_{2,3}$ values of 6.50—9.28 and $J_{3,4}$ of 7.47—10.37 Hz. In both cases the lower value occurs for the nitro- and cyano-substituted dihydropyrans (1a and b) and the higher value for the dimethylamino-compound (1j). Obviously a variation of *ca.* 3 Hz cannot be the result of the change in electronegativity involved in phenyl substitution and an explanation in terms of change in the conformational equilibrium (I) ⇌ (II) seems necessary.

Stabilization of conformation (II) by electron-attracting substituents X must involve the mutual interaction of the Ar and OPr^i groups when both are in the axial position since neither conformations (III) nor (IV) of the *trans*-isomers (2) show similar behaviour.

The change is dramatic when a phenyl group is in position 5 [adducts (3) and (4)] with the higher variations occurring in the *trans*-series (4a—j). Coupling constants are in the range 4.07—7.30 ($J_{2,3'}$) and 5.17—9.10 Hz ($J_{3,4}$). The lower values of the former occur for electron-attracting substituents and that of the latter for the electron-donating dimethylamino-group.

[2] G. Desimoni and G. Tacconi, unpublished work partly reported in *Chem. Rev.*, 1975, **75**, 651.
[3] M. J. Cook and G. Desimoni, *Tetrahedron*, 1971, **27**, 257.
[4] G. Desimoni, L. Astolfi, M. Cambieri, A. Gamba, and G. Tacconi, *Tetrahedron*, 1973, **29**, 2627.

The equilibrium between conformations (III) and (IV) can be explained by an interaction between the aryl group in the pseudoequatorial position and the 5-phenyl group which are close and nearly eclipsed.

In the *cis*-series (3a—j) both the above mentioned interactions can occur. Since both conformations (I) and (II) are favoured, the former by the XC_6H_4-Ph and the latter by the XC_6H_4-OPr^i interaction, the coupling constant variation is smaller (1.0—1.5 Hz).

action through space between the HOMO of the donor and the LUMO of the acceptor. If one is a constant (OPr^i or 5-phenyl group) and the only variation in the second is the phenyl substituent, there should be a quantitative dependence between the change in the energy level and the σ^+ constant of the substituent. Since a linear relationship between σ^+ values and the ionization potentials of substituted benzenes has been reported,[5] a similar linear relationship between σ^+ and

TABLE 1

trans-Coupling constants of (1)—(4) [a]

	(1) [b]		(2) [b]		(3)		(4)	
X	$J_{2,3}$/Hz	$J_{3,4}$/Hz	$J_{2,3'}$/Hz	$J_{3,4}$/Hz	$J_{2,3}$/Hz	$J_{3,4}$/Hz	$J_{2,3'}$/Hz	$J_{3,4}$/Hz
NO_2	6.60	7.47	2.36	11.30	4.27	4.89	4.13	9.10
CN	6.29	7.47	2.37	10.96	4.28	4.94	4.07	9.10
CO_2Me	7.39	8.52	2.45	11.10	4.58	5.87	5.18	7.70
Br	7.85	8.76	2.43	11.19	4.94	5.70	5.72	7.27
Cl	7.74	8.54	2.46	11.17	4.57	5.99	5.43	7.27
H [c]	8.53	9.47	2.76	10.99	5.77	6.65	5.86	6.55
F	8.13	8.89	2.36	11.26	5.35	6.00	5.65	7.46
Me	8.60	9.70	2.66	10.97	5.60	6.25	6.42	6.21
OMe	8.72	10.26	2.61	11.02	5.57	6.42	6.67	5.74
NMe_2	9.28	10.37	2.73	10.74	6.11	6.43	7.30	5.17

[a] N.m.r. spectra performed on a Perkin-Elmer R-12A spectrometer for 5—10% solutions in $CDCl_3$, and analysed as ABMX systems using the LAOCOON 3 computer program. Root mean square error < 0.10. [b] Values taken from ref. 1 (cyano-compounds excluded—see Experimental section). [c] Values taken from ref. 4.

TABLE 2

Equilibria and conformational free energies of (1), (3), and (4) at 35°

	(1)			(3)			(4)		
X	% Ph [b] pseudo-equatorial	k	$\Delta G°$/kcal mol^{-1}	% Ph [b] pseudo-equatorial	k	$\Delta G°$/kcal mol^{-1}	% Ph [b] pseudo-equatorial	k	$\Delta G°$/kcal mol^{-1}
NO_2	55.5	1.247	0.13	33	0.493	−0.43	70	2.333	0.52
CN	55.5	1.247	0.13	33.5	0.504	−0.42	70	2.333	0.52
CO_2Me	65	1.857	0.38	41.5	0.709	−0.21	57.5	1.353	0.19
Br	67	2.030	0.43	40	0.667	−0.25	54	1.174	0.10
Cl	65	1.857	0.38	42.5	0.739	−0.19	54	1.174	0.10
H [a]	73.5	2.774	0.63	48.5	0.942	−0.04	47.5	0.905	−0.06
F	68	2.125	0.46	42.5	0.739	−0.19	55.5	1.247	0.13
Me	75.5	3.082	0.69	45	0.818	−0.12	44.5	0.802	−0.13
OMe	80	4.000	0.85	46.5	0.869	−0.09	40.5	0.681	−0.24
NMe_2	81	4.263	0.89	46.5	0.869	−0.09	35.5	0.550	−0.37

[a] Data taken from ref. 4. [b] The error involved can be estimated to be in the range ±0.3 for values from 30 to 70% and *ca.* ±0.7 for values from 70 to 85%.

In order to determine the origin of the effect, to distinguish between a donor–acceptor or a dipole–dipole interaction, we have determined the conformational free energy $(\Delta G°)$ from individual equilibrium constants calculated from $J_{3,4}$ values. Equation (1) was used

$$J_{3,4} = x(J_{3a,4a} - J_{3e,4e}) + J_{3e,4e} \qquad (1)$$

with $J_{3a,4a}$ and $J_{3e,4e}$ the values of the coupling constant for 3- and 4-H in the axial–axial and equatorial–equatorial positions; these were taken [4] as 12.50 and 1.15 Hz, respectively.

Table 2 reports the values for each adduct calculated at 35° [the positive values of $\Delta G°$ indicate that the equilibria favour conformation (I) or (III)] and their reliability depends on the assumption that the change in electronegativity involve a variation of J similar to that found in series (2a—j).

A donor–acceptor interaction requires an orbital inter-

$\Delta G°$ can be expected. Every attempt to find this or a correlation with σ constants was unsatisfactory since the best result gave a correlation coefficient of 0.96.

However good linear correlations are obtained by plotting the $\Delta G°$ values for (1a—j) and (4a—j) against the values of the dipole moments of the *para*-substituted toluenes $(\mu_{Tol}{}^x)$ (Figure 1). These can be calculated by means of equation (2) simplified for the case of a

$$\mu_{Tol}{}^x = (\mu_{Me}{}^2 + \mu_x{}^2 + 2\mu_{Me}\mu_x \cos \theta_1 \cos \theta_2 \cos \omega_{12})^{1/2} \quad (2)$$

rigidly fixed $(\theta_1 \ 0°)$ and a sometimes freely rotating *para*-substituent $(\omega_{12} \ 0°)$; μ_{Me} and μ_x are the ' group moments ' [7] which, in the aromatic series, are the values of the dipole moments of monosubstituted benzenes.

[5] G. F. Crable and G. L. Kearns, *J. Phys. Chem.*, 1962, **66**, 436.
[6] V. I. Minkin, O. A. Osipov, and Y. A. Zhdanov, ' Dipole Moments in Organic Chemistry,' Plenum Press, New York, 1970, p. 100.
[7] Ref. 6, p. 91.

Both series (1) and (4) give good correlation co-efficients (0.996 and 0.991, respectively) but the slopes of the lines are opposite in sign (ρ 0.124 and -0.136,
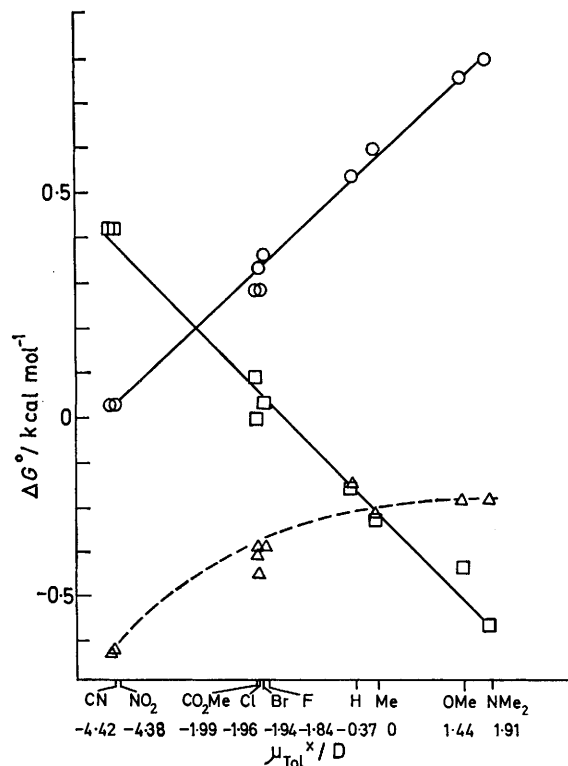

FIGURE 1   Plot of $\Delta G°$ against the dipole moments of *para*-substituted toluenes: ○, (1) (ρ 0.124; r 0.996); □, (4) (ρ -0.136; r 0.991); △, (3)

respectively). Since lower $\Delta G°$ values mean better stabilization of conformations (II) and (IV) with the aryl group in the pseudoaxial position, the slopes of opposite sign are evidence for the direct dependence of the equilibria on the dipole–dipole effect. In terms of classical electrostatic interactions between two dipoles, the XC_6H_4–OPr^i interaction stabilizes conformation (II) in series (1) if X induces a direction for the vector from the ring to the substituent (NO_2, CN). Conformation (IV) in series (4) is stabilized when the interaction XC_6H_4–Ph is unfavourable and hence the direction of the vector is from the substituent to the ring (NMe_2, OMe).

When both interactions operate, the overall effect is such that a parabolic shape results (3a—j). The variation of $\Delta G°$ is small (0.3 kcal mol^{-1}) compared with those of (1) and (4) but this is due to stabilization of both conformations (I) and (II) when the vector is directed from the ring to X (NO_2, CN).

Calculation of the Dipole–Dipole Interaction.—Quantitatively the interaction energy of two dipoles is given [8]

[8] E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, ' Conformational Analysis,' Interscience, New York, 1965, p. 460.
[9] J. M. Lehn and G. Ourisson, *Bull. Soc. chim. France*, 1963, 1113.

by equation (3).   In the correct formulation which was

$$E_\mu = \mu_1\mu_2 \,(\cos \chi - 3 \cos \alpha_1 \cos \alpha_2)/DR^3 \quad (3)$$

used to calculate the conformational equilibrium of 2-bromocyclohexanone,[9] μ_1 and μ_2 are the dipole moments, R is the distance between them, D the dielectric constant of the medium (in our case chloroform at 35°, which is the temperature of the n.m.r. probe and hence D is 4.55), and χ, α_1, and α_2 are respectively the angles determined by $\widehat{\mu_1\mu_2}$, $\widehat{\mu_1R}$, and $\widehat{\mu_2R}$.

Some calculations of E_μ were performed for the XC_6H_4–OPr^i interaction in conformation (II) taking dimethyl ether (μ_1 1.28 D with an angle of 124°) [7] and *para*-substituted toluenes as models for 2-isopropoxy and 4-aryl groups respectively. Figure 2 represents the geometry used as determined from Dreiding molecular models, taking a particular rotamer as the most populated for steric reasons. Calculations for the XC_6H_4–Ph interaction were not performed because of the difficulties in determining the dipole character of the 5-phenyl group, the correct geometry, and the conformation.

Only the so-called ' regular moments ' [7] (the moments of the groups whose resultants are directed along the C–X bond, here: NO_2, CN, Cl, F, H, and Me) were considered since the μ_2 vector coinciding with the C–X bond excludes the uncertainty connected with the angle θ_2. In order to determine R, it is necessary to determine the points of application of μ_2. Therefore the centres of gravity of charges in *para*-substituted toluenes were
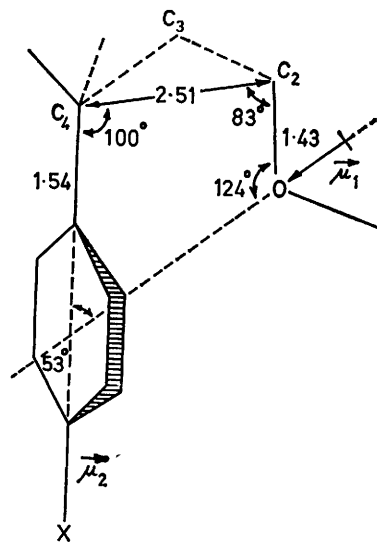

FIGURE 2   Schematic representation used to calculate E_μ [the fragment X–C(4)–C(2)–O was considered as planar in spite of a small deviation of C(2)–O $<10°$]. All lengths in Å

obtained from CNDO/2 calculations [10] of the charge densities. The atomic co-ordinates used were the best values taken from the literature for chlorotoluene,[11]

[10] A. Pople and O. L. Beveridge, 'Approximate Molecular Orbital Calculations,' McGraw-Hill, New York, 1970.
[11] J. Trotter, ' The Chemistry of the Carbon-Halogen Bond : Part 1,' ed. S. Patai, Wiley, London, 1973, p. 60.

fluorotoluene,[11] toluonitrile,[12] and nitrotoluene.[13] The resulting data are collected in Table 3.

TABLE 3

Net charge densities ($\times 10^4$) in *para*-substituted toluenes and dipole–dipole interaction energies ($E_\mu{}^x$)
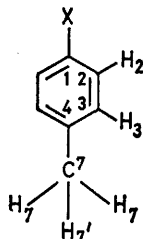
Atom or group	H	F [a]	Cl	CN	NO₂
C-1	−43	2 278	732	348	217
C-2	104	−511	186	153	257
C-3	−112	109	−109	−124	−121
C-4	412	212	494	445	630
2-H	−66	164	106	17	266
3-H	−63	−8	16	−8	78
C-7	−262	−224	−267	−275	−295
7-H	48	45	79	71	120
7′H	133	121	173	162	225
X	−63	−1 985	−1 692	660 [b]	4 735 [c]
				−1 567 [c]	−3 356 [d]
$E^x{}_\mu$ [e]/ kcal mol⁻¹	0.02	0.13	0.16	0.20	0.29

[a] Compare these with total charge densities in R. T. C. Brownlee and R. W. Taft, *J. Amer. Chem. Soc.*, 1970, **92**, 7007. [b] Carbon. [c] Nitrogen. [d] Each oxygen. [e] Details of $E_\mu{}^x$ calculations with all parameters involved are available on request.

The calculated ΔE_μ values [$E_\mu{}^{Me} - E_\mu{}^x$; $E_\mu{}^{Me} = 0$ since μ_2 is zero in equation (3)] can be plotted against the corresponding experimental $\Delta\Delta G°$ values (from Table 2) and if we exclude the low value for X = NO₂, which does not fit the observed trend presumably because the CNDO/2 method overestimates the electron-attracting power of the nitro-group, thus giving a high value for R, a very good linear correlation is obtained with a correlation coefficient of 0.998 and a ρ value of 0.527. Even if the calculated values are only half those expected (ρ should be 1.00), on account of the model used and the proximity of the dipole involved, they clearly support the experimental results.

EXPERIMENTAL

M.p.s are uncorrected. Microanalyses were performed by Dr. L. Maggi Dacrema.

Materials.—All compounds have been [1] or will be [2] described with the exception of those below.

4-p-Cyanobenzylidene-1-phenylpyrazol-5-one.—Prepared in accord with the literature method for similar compounds [14] from 1-phenylpyrazol-5-one and *p*-cyanobenzaldehyde this gave brick red *needles*, m.p. 255—256° (ethyl acetate) (Found: C, 74.8; H, 4.0; N, 15.55. C₁₇H₁₁N₃O requires C, 74.7; H, 4.05; N, 15.4%).

cis[2,4] *and* trans[2,4] *4-p-Cyanophenyl-2-isopropoxy-7-phenyl-2,3-dihydropyran[2,3-c]pyrazoles* (1b) *and* (2b).—These were prepared in accord with the literature method for similar compounds [1] from 4-*p*-cyanobenzylidene-1-phenylpyrazol-5-one and isopropyl vinyl ether. The mixture of adducts was crystallized from EtOH and the high yield *adduct* (1b) was separated as soft needles, m.p. 141—142° (EtOH) (Found: C, 73.25; H, 5.85; N, 11.55. C₂₂H₂₁N₃O₂ requires C, 73.5; H, 5.9; N, 11.7%), δ 5.51 (2-H), 2.03 (3-H), 2.27 (3′-H), and 4.17 (4-H) ($J_{2,3'}$ 2.28, $J_{3',4}$ 6.76, $J_{3,3'}$ −14.06 Hz), 7.20 (s, 5-H), 4.1 (m), 1.09 (d), and 1.14 (d) (OPrⁱ), diastereotopic due to the chiral centre at C-2. The ethanolic mother liquors, after evaporation to dryness, were chromatographed on silica gel with cyclohexane–AcOEt (9 : 1) as eluant. In addition to a second crop of (1b), the isomer (2b) was isolated. Crystallization from light petroleum gave small *prisms*, m.p. 151—152° (Found: C, 73.4; H, 6.0; N, 11.9%), δ 5.59 (2-H), 1.84 (3-H), 2.18 (3′-H), and 4.28 (4-H) ($J_{2,3}$ 2.50, $J_{3',4}$ 5.72, $J_{3,3'}$ −13.39 Hz), 7.14 (s, 5-H) and 4.1 (m), 1.10 (d), and 1.20 (d) (OPrⁱ).

N.m.r. Spectra.—These were taken as described in ref. 4.

CNDO/2 Calculations.—MO Calculations to the CNDO/2 [10] level of approximation were performed on a 6030 Honeywell computer by using a QCPE 141 Program. The atomic co-ordinates for selected models were derived by adopting the geometrical parameters reported in refs. 11—13. The CNDO/2 method does not include overlaps in the normalization steps; as a consequence the total probability density at the atoms are calculated by equation (4) where $P_{BB} =$

$$P_{BB} = \sum_\lambda^B \sum_i R_i C^2{}_{i\lambda} \qquad (4)$$

total electron density at atom B, λ = atomic orbitals on B, i = molecular orbital, R_i = number of electrons in the ith MO.

[12] W. A. Sheppard, 'The Chemistry of the Cyano Group,' ed. Z. Rapport, Interscience, London, 1970, p. 212.

[13] G. H. Wagniere, 'The Chemistry of the Nitro and Nitroso Groups. Part 1,' eds. H. Feuer and S. Patai, Interscience, New York, 1969, p. 40.

[14] G. Desimoni, A. Gamba, P. P. Righetti, and G. Tacconi, *Gazzetta*, 1972, **102**, 491.