FULL PAPER

Molecular Mechanics: The Cross-conjugated Carbonyl Group in Heterocyclic Compounds. 1. Parameterisation (MM2) of the >C=O Bond

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Abstract A new type of carbon atom has been included in the MM2 force field when it is part of a carbonyl group cross-conjugated in a heterocyclic molecule. This carbon atom is fully included in the π system calculation. New stretching parameters for the C=O bond have been estimated by a statistical process from X-ray molecular structures recorded in the Cambridge Structural Database System.
The proposed parameters have been found appropriate for compounds in which the atoms adjacent to the carbonyl are a carbon and a heteroatom i.e. mainly for the α-pyrone ring and the conjugated "lactams". They are inappropriate for carbonates and oxazo-ones but should be valid for quinones provided that they are not involved in a charge transfer complex. The mean unsigned deviation for 111 bond lengths (89 cyclic molecules) is 0.01Å but the maximum deviation can reach ± 0.03Å. Part of the observed dispersion could be the result of the variation of the effective dielectric constant D from one crystal to another.

Keywords Molecular mechanics, MM2, Parameterisation, Carbonyl group, Heterocyclic molecules

Introduction

In pharmacology, numerous active compounds are carbonyl containing aromatics or heterocyclics. In the MM2 and MM3 force fields [1] the carbonyl moiety which involves the C=O bond (respective atom type numbers 3 and 7) has been parameterised. The π bond order is taken into account for it is anticipated that the carbonyl group might be conjugated through another carbon atom (type number 2) as in the chain:

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(>C=C-XC=O). The length of the polar C=O bond, is sensitive to the inductive effects of the X substituent. That is why l_0 (natural bond length) and k_0 (stretching force constant) parameters are X-dependent and different sets of parameters have been accordingly set up for ketones (X: CRR'R''), esters (X: OR) and amides (X: NRR'). The polarity of the carbonyl bond makes its length also dependent on the effective dielectric constant D. This leads to the use of variable parameter sets for the different domains of variation of D [2].

Modeling the carbonyl bond is therefore not an easy task. The present philosophy and the proposed parameters imply that the mesomeric effects only bring about a slight variation of the >C=O bond order in any case much lower than

the inductive and dielectric effects. That is the reason why, for esters and amides, the conjugation with the O atom (type 6) or N atom (type 9) is not explicitly taken into account. This philosophy has also led, in the MM3 force field, to the definition of numerous oxygen atom types [2].

The situation is, *a priori*, somewhat different when the carbon atom of the carbonyl is cross-conjugated: X-C(O)-Y which is, for instance, the case in the α-pyrone ring where X = C_{sp}^2 (type 2) and Y = O (type 41). Delocalisation possibilities are greater and may be no longer negligible compared to the other effects. Poor results obtained with the current parameters for α-pyrones and γ-pyrones (flavones) prompted the present study of a large set of molecules in which the C=O group is cross-conjugated through diverse X and Y atoms. We report here an attempt to find a set of parameters, for the C=O bond, resulting from calculations in which at least the C, O, X and Y atoms are all included in the π system, thus implying a new type of C_{sp}^2 atom.

Parameterisation of the carbonyl bond (C cross-conjugated)

In the MMP2 method (MM2 method for conjugated molecules), a self-consistent-field (SCF/PP) calculation is undertaken on the π system to obtain the bond orders, which are used to assign stretching and torsional parameters [3]. Resonance integrals between bonded atoms are calculated by the method of Lo and Whitehead [4] and the two centers repulsion integrals γ_{ij} are evaluated using Ohno's empirical formula [5].

In the MM2(91) force field, the only bonds involving the C (type 3) atom and which are π bond order dependent, are: C(3)-C(2), C(3)=O(7) and C(3)-C(3). This was insufficient for our purposes and as we also did not want to alter the present parameters in situations where they work well, we had to define a new type of carbon atom which could describe all or at least most of the cases where the C atom is cross-conjugated.

Because type number 44 was free in our program, we attributed it to the new C atom.

Modifications of the source code

Introduction of a new type of atom does not generally imply major modifications of the MM2 code. Input and parameter files (CPD.MM2, PARA.MM2) give information to the program. Here, minor modifications were nevertheless necessary to indicate that the new type of atom was to be submitted to π quantum calculations. The main modification is to declare in the SCF.f subroutine that atom types 44 and 3 are equivalent.

Further modifications

All the force field parameters implying the 44 type number are, of course, missing from the data. But it must be considered that this type of atom is not completely new but an adaptation of the type 3 atom. The force field was thus not completely reparameterised. At least in a first step, all the parameters which do not depend explicitly on the π bond order were transferred from type 3 to type 44 and our effort was mostly applied to bond dipole moments and stretching parameters. As a first guess, it was also assumed that the π bond parameters for the C(2)-C(3) bond were also valid for the C(2)-C(44) bond. This will be discussed farther on.

σ bond dipole moments

Estimation of the σ dipole moment of the C(44)-O(7) bond was performed by use of some α-pyrone type molecules (Fig.1).

As can be seen, the σ bond dipole moments involved are: C(2)-O(41); O(41)-Lp(20); O(41)-C(44); C(44)-O(7) and C(2)-C(44).

Parameters concerning the first two bonds are already present in MM2 data. The other bonds involving the new C atom type and the corresponding σ dipole moments also had to be estimated in accordance also with the related π dipole moments. In agreement with the MM2 philosophy the C(2)-C(2) and C(2)-C(44) bond moments were assumed to be zero.

σ dipole moments for the C-O (2-41) and O-Lp (41-20) bonds

Partition of the C-O (2-41) bond dipole moment into σ and π components is already done in MM2(91). But, due to the correction of the π bond moments that we suggested in a previous paper [6], (which introduces a reduction factor of 0.46) the σ bond moment had to be reestimated.
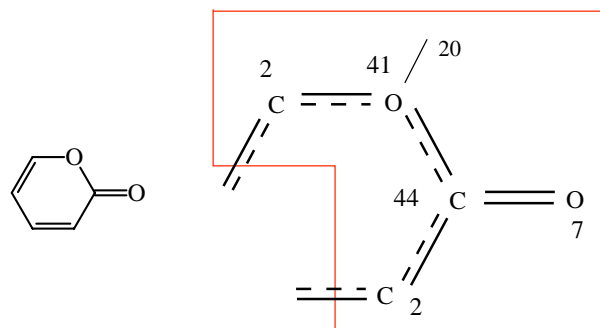

Figure 1 *Topology and atom types of α-pyrones*

Table 1 *List of the molecules cited in this work. The Refcode is mentioned when their geometry comes from the C.S.D.S. Compounds **16** and **18** to **70** are α pyrones or conjugated δ lactones. Compounds **71** to **91** conjugated lactams, **92** to **102** conjugated thiolactones, **103** and **104** a quinone and an analogue*

No.	Name	Refcode
1	Furan	**FURANE 10**
2	Benzofuran	
3	Nitrofuran	
4	Phenoxathine	
5	Phenol	**PHENOL 03**
6	Vinyl alcool	
7	Trans-acrolein	
8	Cis-acrolein	
9	Methacrolein	
10	Crotonaldehyde	
11	Methyl-vinyl-ketone	
12	Benzaldehyde	**HAMDII**
13	Coumarin	**COUMAR 02**
14	Maleic anhydride	**MLEICA**
15	Tropone	
16	1-Oxa-azulen-2-one	**OXAZUL**
17	Phtalic anhydride	
18	N-Acetyl-5,6-dihydrofuro(2,3-b)pyrid-2-one	**AFURPO 10**
19	4-Methoxy-6-(2,4-dihydroxy-6-methylphenyl)-2-pyrone	**ALOAGL 10**
20	5-Crotonoyl-4-methoxy-6-methyl-pyrone	**BABNIB**
21	7,8-Dihydro-4,7,7-trimethyl-2H,5H-pyrano(4,3-b)pyran-2,5-dione	**BINTUN**
22	6-Ethoxycarbonylamino-4-chloro-5-methyl thio carbonyl-2-oxo-3H-pyran	**CATMOZ**
23	3-Acetyl-5-(alpha-methylbenzylidene)-2,4-oxolanedione	**CIJHOS**
24	Coarctatin dibromide	**COARDB**
25	5-Benzylidene-3-acetyl-oxolan-2,4-dione	**COCVIZ**
26	(Z)-3-Bromo-5-(bromonitromethylene)-furan-2(5H)-one	**COLJUI**
27	5Z-Carboxymethylene-3-chloro-4-methyl-2(5H)furanone	**COMFRN**
28	cis-Octa-2,4,6-triene-1,4,5,8-diolide	**COTROL 10**
29	3-Acetyl-4-hydroxy-6-phenyl-2-pyrone	**CUZXUQ**
30	Methyl alpha-(3-hydroxy-5-oxo-4-phenyl-2H-2-furylidene)-phenyl acetate	**DADTEH**
31	5-(trans-(Z)-beta,gamma-Epoxy-alpha-methoxy-cinnamylidene)-4-methoxy-furan-2(5H)-one	**EPMCMF 10**
32	3,3'-Diacetyl-5,5'-bis(ethoxycarbonyl)-glaucyrone	**ETGLAU 01**
33	(-)-Dimethyl 1-acetyl-1,2,3,7-tetrahydro-7-oxopyrano(3,4-b)pyrrol-2,5-dicarboxylate	**FAFYEQ**
34	(E,E)-7-(2-Butenylidene)-1,7-dihydro-1-oxo-cyclopenta(c)pyran-4-carboxylic acid methyl ester	**FIJHIP**
35	3-Chloro-5,6-dihydro-4-methylphenylaminoangelicin	**FIVRIL**
36	3,9-Dimethyl-2,5,6,7-tetrahydrofuro (2,3-b)indolizin-2-one	**GAKGOO**
37	7-(Dimethylamino)-3,4-dihydro-N,N-dimethyl-5-oxo-2H,5H-pyrano(4,3-b) pyran-8-carboxamide	**GEWBOZ**
38	4-Chloro-5-dichloromethylene-2-furanone	**GEXWUB**
39	3-(1-(ethylamino)ethylidene)-6-methyl-3H-pyran-2,4-dione	**HABNED**
40	2-(beta-Hydroxyisopropyl)-2,3-dihydro-6,7-furano-coumarin	**JECPUC**
41	alpha-3(1-Phenyl-N-(dimethylcarboxamide)methylimine)-4,5-trimethylene-pyran-2-one	**JEDYAS**
42	4-Hydroxy-6-methyl-3-(3-dimethylaminoacryloyl)-2H-pyran-2-one	**JIHJOZ**
43	4,5,6,7-Tetrafluoro-8-methoxy-2H-cyclohepta (b) furan-2-one	**JIYJAC**
44	8-Benzyl-3-phenyl-2H-indeno (2,1-b) furan-2-one	**JOPDIB**
45	3-Benzoylamino-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydrocoumarin	**JUKZUK**
46	3,4-Dichloro-2-(methoxycarbonyl(chloro)methylene)furan-4-one	**JUNFUT**
47	3,7-Dimethyl-1H,9H,10H-dipyrano(4,3-b:3',4'-e)pyran-1,9-dione	**KEMZUX**
48	Acetylmelodorinol	**KETDOC**
49	trans-7,8-Dihydro-7-hydroxy-4-methoxy-7,8-dimethyl-2H,5H-pyrano(4,3-b)pyran-2-one (Benzene solvate)	**KITRIO**
50	2-Cyclohexenyl-4-cyclohexylidene-2-butenolide	**KUPXIC**
51	6-t-Butyl-2-(dipivaloymethylene)-5-pivaloyl-1,3-dioxin-4(2H)-one	**LACVAM**

Table 1 (continued)

No.	Name	Refcode
52	5-(p-Methoxyphenyl)-3-methoxy-penta-2,4-dien-4-olide	**MXPENO**
53	3-(1-(Phenylamino)ethylidene)-6-methyl-2,4-dioxo-2,3-dihydro-4H-pyran	**PAEXPY**
54	5-(4-Acetoxy-6-methyl-2-pyron-3-yl)-3ethoxycarbonyl-1-phenylpyrazole	**PANDEN**
55	DL-4-Hydroxy-4H-furo(3,2-c)pyran-2(6H)-one	**PATULO**
56	3-Acetoacetyl-7-methyl-2H,5H-pyrano(4,3-b)pyran-2,5-dione	**POCRAA**
57	Reductiomycin	**RDCTMC**
58	N-(2-Phenyl-4Z,6E-2,4,6-heptatriene-4-olide-7-yl)morpholine	**SAMGOC**
59	4-Methoxy-6-(2-(2-furyl)ethenyl)pyran-2-one	**SOWBOV**
60	trans-Octa-2,4,6-triene-1,4,5,8-diolide	**TOTROL 10**
61	2,6-Dimethyl-5H-furo(3,2-b)pyran-5-one	**VASDOI**
62	2,7-Dimethyl-5H-furo(3,2-b)pyran-5-one	**VASDUO**
63	3-Diphenylmethylene-7-phenyl-9-oxabicyclo(4.3.0)non-1,4,6-trien-8-one	**VOBRUZ**
64	7-Methyl-7-methoxy-5-phenyl-oxatricyclo(6.3.0.0)undeca-1,5-dien-4-one	**VOCREK**
65	(4Z,6Z)-6-Acetyl-7-hydroxy-2,4,6-octatriene-4-olide	**VOXGOE**
66	9-Hydroxy-3-methyl-2H-naphto(2,3-b)pyran-2,5,10-trione	**VUTDAP**
67	3-(5-Chloro-2-benzoxazolyl)-7-diethylamino-2H-1benzopyran-2-one	**VUWZUI**
68	3-Acetyl-6-methyl-2H-pyrano(2,3-b)indolizin-2-one	**WANPAC**
69	alpha Pyrone	**WIKCAU**
70	Methyl-4,5dichloro-3-methyl-2-oxo-2H-pyran-6-carboxylate	**YABYIJ**
71	7-Chloro-8-methyl-2(1H)-quinolinone	**BAWVAW**
72	8-Acetoxy-2-quinolone	**BIMSIZ**
73	alpha-Bromo-gamma-phenyl-gamma-ethylglutaconimide	**BPEGIM**
74	4-Bromo-1-methyl-3,5-diphenyl-2-pyridone	**CANRAK**
75	4-Hydroxy-2-pyridone	**CAXKOB**
75	4-Hydroxy-2-pyridone (neutron study)	**CAXKOB 11**
76	1-Phenyl-1,2-dihydro-2-quinolinone	**CIPGIR**
77	5-Chloro-2-pyridone	**CLPYRO**
78	4-Chloro-5-methylamino-2,3,6-pyridinetrione monohydrate	**CMPYTO**
79	N,N-Dimethyl-1-hydroxy-2(1H)-pyridinone-6-carboxamide	**DAHBAP**
80	4-Benzoyloxy-5-chloro-2-pyridone	**HATKAO**
81	2-Quinolone	**HXQUIO 01**
82	Cerpegin	**JEGVOG**
83	1-Hydroxypyridine-2-one	**JEMJUG**
84	2-Methyl-6,7-bis(dimethylthio)isoquinoline-3,5,8(2H)-trione	**KUNKUZ**
85	7,8-Dihydro-7-methyl-2,5(1H,6H)-quinoline-1,5-dione	**PEXLEJ**
86	2-Pyridone	**PYRIDO 04**
87	2-Methylpyrrolo(3,4-c)pyrrole-1,3(2H,5H)-dione	**SIWDAD**
88	2-Methylpyrrolo(3,4-c)pyrrole-1,3(2H,5H)-dione (2nd conformation)	**SIWDAD**
89	1-Acetylindone-2,3-dione	**TARGEY**
90	3-Ethyl-4-oxa-1,5,6-trihydrophtalimide	**VOBDEV**
91	4-(4-Bromophenylamino)-3a,4-dihydro-9-dimethylamino-2-phenylbenzo(f) isoindoline-1,3-dione	**YESPOB**
92	(4R,(2E,5E))-3-Hydroxy-2,4,6-trimethyl-2,5,7-octatriene-4-thiolide	**BIHKIM 10**
93	Dibromo-(maleic acid)-thioanhydride	**BMLTAA**
94	Di-iodo-(maleic acid)-thioanhydride	**BMLTAB**
95	trans-3,6-Dimethyl-thieno(3,2-b)thiophene-2,5(3H,8H)-dione	**DMTTDO**
96	(5R)-2,5-Dihydro-4-hydroxy-5-methyl-3-phenyl-5-(prop-1'-enyl)-2-oxothiophene	**FIVKEA**
98	Dithieno(3,4-b;3',4'-e)(1,4)dithiine-1,3,5,7-tetraone	**FOWVES**
99	3-((3-Hydroxy-5-(hydroxymethyl)-2-methyl-4-pyridyl)methylamino)-2(5H)-thiophenone	**FURKAE**
100	5-Benzylidene-3,4-dichlorothiophen-2(5H)-one	**JUYHAN**
101	3,6-Dibromo-thieno(3,2-b)thiophene-2,5-dione	**LERGUK**
102	17beta-Acetoxy-18-methyl-1-thia-A-norestra-3,9(10),11-trien-2-one	**WANCAP**
103	2,6-Dimethyl-4H-1-thiapyran-4-one	**DEFYES**
104	Tetrabromo-p-benzoquinone	**TBBENQ**

Table 2 *Experimental and calculated dipole moments for 5 test molecules containing an oxygen (type 41) atom*

Molecule	μ_{exp} (D)	Ref.	μ_σ^{MM2} [a] (D)	μ_π^{MM2} [a] (D)	μ_{tot}^{MM2} [a] (D)	$\mu_{tot\_opt}^{MM2}$ [b] (D)	$\mu_{tot\_opt}^{MM2\,(91)}$ [c] (D)
1	0.66	[7b,8]	1.19	0.53	0.66	0.63	0.68
2	0.79	[7b]	1.19	0.48		0.75	0.96
3	4.41	[8]	2.41	2.58		4.72	4.18
4	0.93 - 1.10	[8]	0.33	0.34		0.01	0.01
5	1.28	[9,7b]	1.44	0.32	1.33	1.32	1.37
6	1.02	[9,7b]	1.40	0.35	1.10	1.10	0.96

[a] Calculated for the crystalline geometry
[b] Calculated with a reduction factor (MM2 full optimisation)
[c] Calculated without reduction factor (MM2(91) full optimisation)

For that, a reference molecule - furan-**1** for which we had both the geometry (FURANE10 [7]) and the experimental molecular dipole moment (0.66D [8]), was chosen. Assuming that the O-Lp (41-20) bond moment remains unchanged (0.750D), by geometrical considerations similar to those described in a previous paper [6], an estimation of the σ moment of the C-O (2-41) bond was found: 0.366D (Fig. 2).

The parameter thus obtained was tested on five extra molecules for which the experimental molecular dipole moment was known as well as the geometry [7b, 8, 9]. Results are gathered in Table 2. They are globally as good as those used in MM2(91).

σ dipole moments for the O-C (41-44) and C=O (44-7) bonds

For comparison purposes, it was first necessary to reevaluate the σ dipole moment of the usual carbonyl bond (3-7). Previous parameters were determined by Allinger et al [10, 11] from simple conjugated molecules (see Scheme 1). At that time the correction factor we suggested for the π dipole moments had not been introduced. Methylvinylketone, chosen as the reference molecule was used to reevaluate the σ moment by the procedure already described leading to:
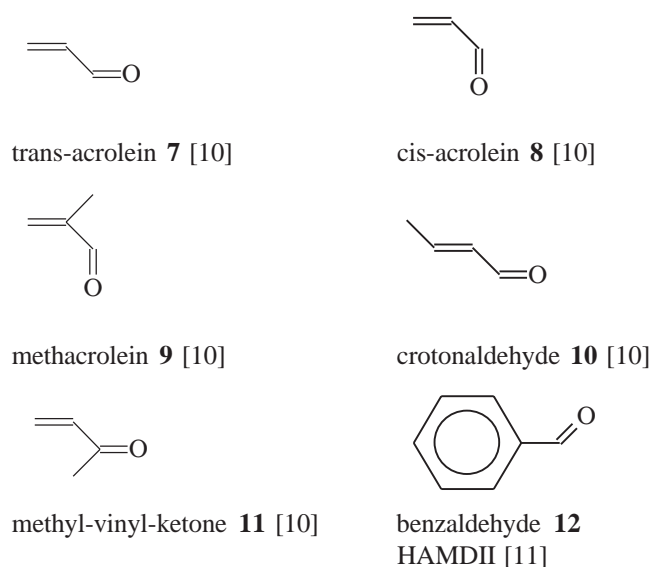

Figure 2 *σ and π bond moments involved in the furan molecular dipole moment*

Scheme 1 *Reference and test molecules for the determination of the corrected σ-bond moment for the C(3)=O(7) bond*

Table 3 *Experimental and calculated dipole moments for 6 molecules containing the C(3)=O(7) bond*

Molecule	μ_{exp} (D)	Ref.	μ_{σ}^{MM2} [a] (D)	μ_{π}^{MM2} [a] (D)	μ_{tot}^{MM2} [a] (D)	$\mu_{tot\_opt}^{MM2}$ [b] (D)	$\mu_{tot\_opt}^{MM2\,(91)}$ [c] (D)
11	3.16	[10]	1.56	1.62	3.16	3.19	6.34
7	3.17	[10]	1.38	1.64	3.02	3.04	6.21
8	2.55	[10]	1.38	1.38	2.71	2.75	5.51
9	2.80	[10]	1.28	1.63	2.91	2.93	6.10
10	3.72	[10]	1.60	1.75	3.33	3.26	6.41
12	2.78 - 2.99	[8,11]	1.38	1.62	2.96	2.99	6.09

[a] Calculated for the crystalline geometry
[b] Calculated with a reduction factor (MM2 full optimisation)
[c] Calculated without reduction factor (MM2(91) full optimisation)

$\mu_{\sigma.cor}^{3-7} = 1.38D$ (experimental molecular dipole moment: 3.16D)

Application of the parameter found in this way to the molecules in Scheme 1 led to more satisfying results than those obtained with the classical MM2(91) (see Table 3).

The determination of the σ dipole moment for the C(44)-O(7) bond by use of α-pyrone molecules first required the estimation of the σ dipole moment of the C(44)-O(41) bond. Very scarce experimental information on the molecular dipole moments of α-pyrones is available. The only compound of that type for which we had both the structure and the dipole moment was coumarin **13** (COUMAR02.[12]). So we had to turn to some extra molecules.

Because of its symetry, maleic anhydride **14** is interesting (see Scheme 2) and from it, by geometrical considerations a relation between $\mu_{\sigma.cor}^{44-7}$ and $\mu_{\sigma.cor}^{44-41}$ was set up:

$$\mu_{\sigma.cor}^{44-41} = 3.18 - 0.66 \times \mu_{\sigma.cor}^{44-7} \tag{1}$$

For a complete determination of the unknowns, a further molecule was needed.

Tropone **15** ($\mu_{exp} = 4.30D$) was chosen because, in accordance with the MM2 philosophy here its μ_{π}^{total} is only due to the C(44)=O(7) bond. As μ_{π}^{total} is calculated to be 4.79D, we have, after correction:
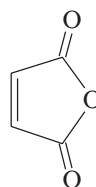
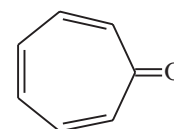$$\mu_{\pi.cor}^{total} = 0.46 \times 4.79 = 2.20D \tag{2}$$

and then

Scheme 2 *Molecules involved in the determination of the dipole moments of the O(41)-C(44) and C(44)=O(7) bonds*
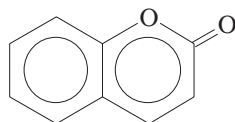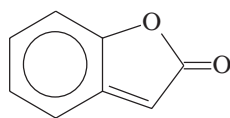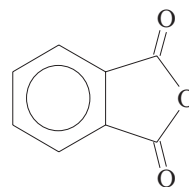

coumarin **13**
COUMARO2[12]

maleic anhydride **14**
MLEICA[13]

tropone **15** [8]

1-oxa-azulen-2-one **16**
OXAZUL[14]

phthalic anhydride **17** [8]

Table 4 *σ dipole moments for various conjugated bonds (corresponding π dipole moments corrected)*

Topology	Atom Types	Moments(D)
=N-Lp	37-20	0.600(a)
C-N=	2-37	1.129
=N-H	37-23	0.600(a)
>N-C	40-2	0.156
>N-H	40-23	-0.550(a)
>N-C	40-1	-0.741
=N-N<	37-40	-0.88
S-C	42-2	1.147
C-O	2-41	0.366
O-Lp	41-20	0.750(a)
C=O	3-7	1.38
C-O	3-41	1.23
C=O	44-7	2.10
C-O	44-41	1.79
C=C	44-2	0.0

[a] Unchanged

$$\mu_{\sigma.cor}^{total} = 4.30 - 2.20 = 2.10 D \tag{3}$$

Use of the previous relation and geometrical considerations led to:

$$\mu_{\sigma.cor}^{44-7} = 2.10 D \tag{4}$$

$$\mu_{\sigma.cor}^{44-41} = 1.79 D \tag{5}$$

Application of these parameters to coumarin led to a molecular dipole moment of 4.50D for an experimental value of 4.52D [12]. As expected, the use of the value of $\mu_{\sigma.cor}^{C=O}$ for the 3-7 bond (1.38D) led to worse results (3.89D) showing
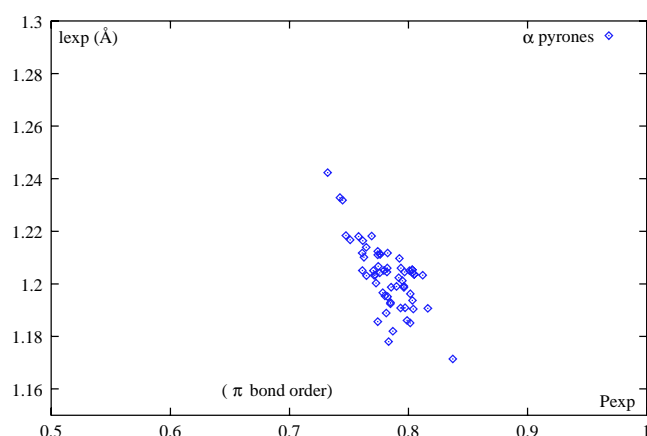
Figure 3 *Plot of l_{exp} versus P_{exp} for the C(44)=O(7) bond in α-pyrones*

that, even corrected, the parameters of the 3-7 bond are not appropriate.

Unfortunately only two molecules were available to test the parameters: 1-oxa-azulen-2-one **16** and phthalic anhydride **17** (Scheme 2). Here the discrepancies between calculated and experimental values are larger:

	Exp. (D)	Calc. (D)
1-oxa-azulen-2-one **16**	5.64	5.10
phthalic anhydride **17**	5.29	6.30

As already mentioned, the correction of the π bond moments, led to the reestimation of some σ bond moments implying or not the new C type 44. This occurred for the test molecules but also for all those which will be used later in the statistical study. These corrected σ bond moments are reported in Table 4.

First estimation of the l_2, k_2, TSLOPE and SSLOPE parameters of the C(44)=O(7) bond

Let l_0 and k_0 be respectively the «natural» bond length and force constant of the C(44)=O(7) bond, both parameters are dependent on the π bond order P. For a limited domain a linear relationship is a good approximation and we have:

$$l_0 = (l_2 + TSLOPE) - TSLOPE \times P \tag{6}$$

$$k_0 = (k_2 - SSLOPE) + SSLOPE \times P \tag{7}$$

where l_2 and k_2 are the extrapolated parameters for the double bond (P = 1) and TSLOPE and SSLOPE the slopes of the corresponding graphs.

Equivalent equations can be written:

$$l_0 = l_1 - TSLOPE \times P \tag{8}$$

$$k_0 = k_1 + SSLOPE \times P \tag{9}$$

Here l_1 and k_1 are the extrapolated parameters for the single bond (P = 0).

The estimation of the parameters proceeded as for the nitrogroup [4]. As we were mostly interested in α-pyrones, we first selected, a series of molecules of that class whose structures have been determined and are recorded in the Cambridge Structural Data System (C.S.D.S.) [20]. The selection criteria were a reliability factor less than 0.10 and the existence of one or several C=CO-O groups. This way, 54 reference «conjugated lactones» were retained containing 61 >C(44)=O(7) bonds (compounds **16** and **18** to **70**: Table 1).

The π bond orders – which will be called P_{exp} – were calculated, without optimisation, by the MM2 program using the crystalline geometries. Fig. 3 shows that there is a correlation between l_{exp} (bond length in the crystal) and P_{exp}:

One can observe that the variation domain of the π bond order is small (0.73 - 0.84) but that the correlated variation of l_{exp} is rather large (1.171 - 1.242). Quite strong dispersion

Figure 4 *Some classes of molecules in which the carbon atom of the carbonyl group is cross-conjugated*

Figure 5 *Plot of l_{exp} versus P_{exp} for the C(44)=O(7) bond for the whole set of reference molecules*
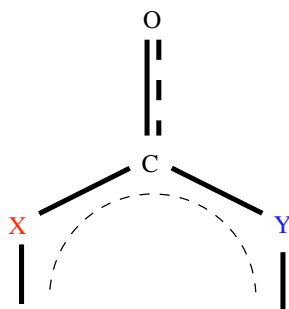
of the dots is also observable, but, at the present stage of the study, it is not possible to attribute it either to steric or to other effects. Extension of the variation domain of P_{exp} was seen to be impossible using only α-pyrones. Because it was also interesting to know to what extent the 44 carbon type is general (cross-conjugated C) the exploration was extended to other classes of compounds (Fig. 4).

Conjugated lactams (21 molecules **71** to **91** Table 1) and thiolactones (11 molecules **92** to **102** Table 1) gave (l_{exp}, P_{exp}) dots close to the best fit straight line and permitted the extension of the P_{exp} domain (0.66-0.86). They were thus included in the study (see Fig. 5).

Compounds in which X and Y are heteroatoms, seem to exhibit different correlations as can be seen in Fig 6. They have thus been omitted in the present study.

The case of quinones is more complex. Most often, their X-ray structure has been determined as part of a charge transfer complex. There was one clearly distinct exception **104**, which was thus retained. We added to it compound **103** which, strictly speaking, is not a quinone(see Fig. 6).

Finally the 111 bonds included in the 88 selected reference molecules led to the best fit straight line (Fig. 5) whose equation is:

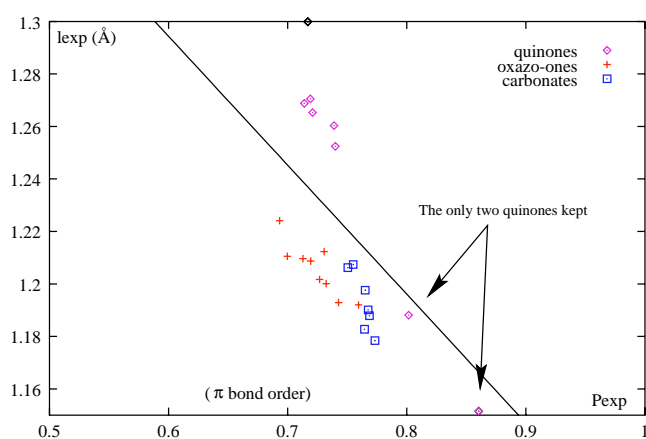$$l_{exp} = 1.589 - 0.491 \times P_{exp} \qquad (10)$$

with the correlation factor r = -0.90046

For the first estimations of k_1 and SSLOPE we used Badger's rule (see ref [1] and references there in):

$$k_{exp} \times \left[A_{ij} \times \left(l_{exp} - B_{ij} \right) \right]^3 = 10 \qquad (11)$$

with Allinger's parameters for the C(3)=O(7) bond: i.e. $A_{ij} = 1.75$, $B_{ij} = 0.64$.

Thus:

$$k_{exp} \times \left(l_{exp} - 0.64 \right)^3 = 1.865 \qquad (12)$$

Fig. 7 shows:
- The theoretical graph of

$$k_{exp}^{theor} = \frac{1.865}{\left[(1.589 - 0.64) - 0.491 \times P_{exp} \right]^3} \qquad (13)$$

obtained by combining (10) and (12).

- Dots representative of the (k_{exp}, P_{exp}) couples obtained by direct use of equation (12) and effective X-ray bond lengths.

The proximity of the dots to the curve confirms the value of equation (10). In the P_{exp} domain**,** the curvature of the graph of equation (8) is rather small and a linear approximation is justified. The best fit straight line is also shown in Fig. 7. Its equation is:

$$k_{exp} = -9.42 + 25.35 \times P_{exp} \qquad (14)$$

r = 0.87794
k_1 = –9.42
SSLOPE = 25.35 md·Å^{-1}

Figure 6 *Location of the dots (P_{exp}, l_{exp}) for the quinones, oxazo-ones and carbonates around the best fit straight line set up for the 88 reference molecules*
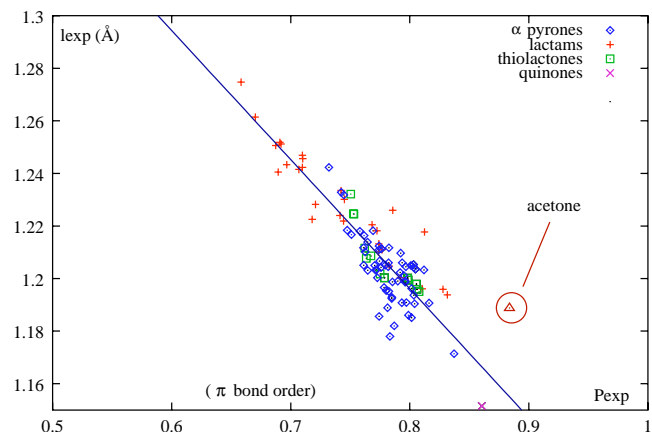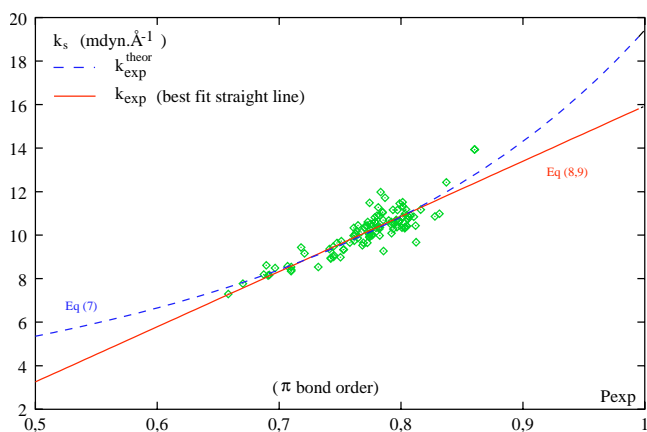
Figure 7 *Plot of k_{exp} versus P_{exp} for the C(44)=O(7) bonds*

Figure 8 *Extension of Fig. 7 exhibiting the negative value of k_1 and its artificial character*

The negative value of k_1 is somewhat confusing. With k_2 the same relation is:

$$k_{exp} = 15.93 + 25.35 \times P_{exp} \quad k_2 = 15.93 \text{md}\text{Å}^{-1} \quad (15)$$

which looks more reasonable. In fact, it must be kept in mind that k_1 and k_2 are extrapolated values in regions where equation (10) is not valid as shown in Fig. 8.

Refinement of the stretching parameters for the C(44) = O(7) bond

Equations (10) and (15) are based on P_{exp} and l_{exp}. «Natural» parameters l_0 and k_0 are distinct from l_{exp} and k_{exp} which are dependent on their surroundings. So, the parameters estimated so far l_2, TSLOPE, k_2, SSLOPE, can be considered only as first estimations of the parameters in equations (6) and (7). The goal of their refinement is thus to find a set of natural parameters which, used in optimisation processes, would led to calculated bond lengths l_{calc} identical or close to l_{exp}.

If we plot on a graph $l_{calc}(estimated\ parameters) = f(l_{exp})$, the best fit straight line which expresses the correlation can be written:

$$l_{calc} = \alpha \times l_{exp} + \beta \quad (16)$$

For a bond which has a π character l_{calc} is dependent on l_2, k_2, TSLOPE and SSLOPE but also on steric effects due to the surroundings. So, the external constraints have to be taken into account in the search of the best values for these four parameters. This can be obtained in the present case, (because the C=O bond is a terminal bond), by letting the C=O bond length vary in the optimisation processes while the rest of the molecule is frozen.

The solution is found when:
• α is close to 1
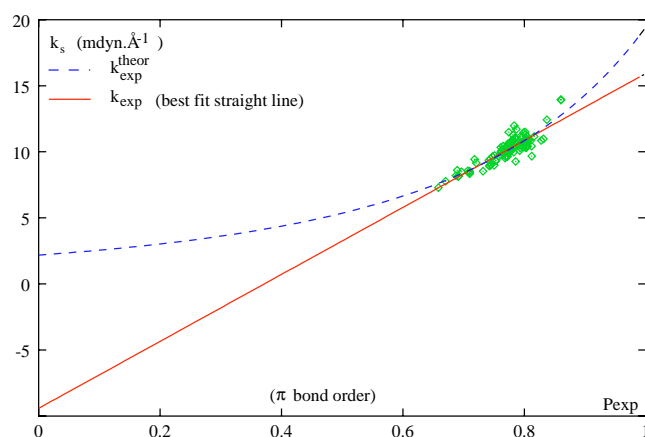• β is close to 0   for the whole set of reference molecules.

It is also desirable that the dispersion of dots around the best fit straight line (eq. 16) be the least possible: i.e. that a correlation factor r is good or that:

$$\delta = \sum_{i=1}^{N} \left| l_{exp}^i - l_{calc}^i \right| \text{ is minimum} \quad (17)$$

N = number of considered bonds.

The large number of reference molecules prompted us to build a series of programs which successively:

For each molecule:
- introduces or modifies l_2 and TSLOPE in the extra-parameters file PARA.MM2
- proceeds to geometry optimisation
- reads l_{calc} in the output file TAPE4.MM2.

For the whole set of molecules:
- evaluates the best fit straight line (eq. 16) and thus α, β and r
- calculates δ
- repeats the process after modifications of the tested parameters.

As the hydrogen atoms are generaly poorly located by X-rays, their position has also been allowed to move in the process of optimisation. Moreover, to prevent out-of-plane relaxation of the C=O bond, we fixed a dihedral angle to which it participates.

Within these conditions, a series of refinements was performed on the preliminary estimation. The first grid was defined by:

$l_2 \in [1.070 ; 1.105]$ by steps of 0.005Å.

The TSLOPE domain was adjusted to the l_2 values to omit calculations in unsuitable regions. For instance,

for $l_2 = 1.070$ TSLOPE $\in [0.600 ; 0.650]$ by steps of 0.05
for $l_2 = 1.105$ TSLOPE $\in [0.420 ; 0.515]$ by steps of 0.05

Further refinements were made on narrower grids with smaller steps.

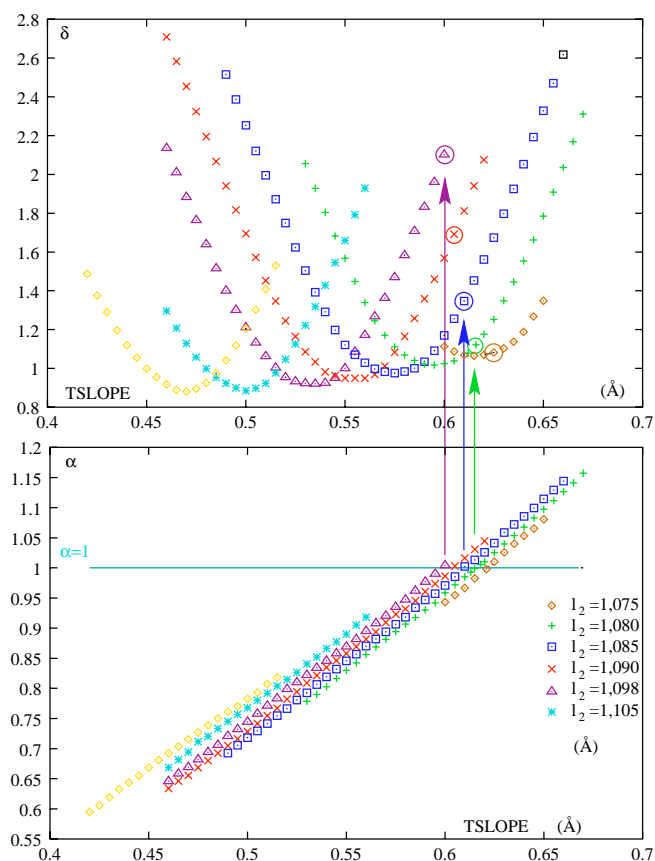Fig. 9 represents the evolution of the two criteria α and δ for various values of l_2 and TSLOPE. It clearly shows re-

Figure 9 *Graphical exploitation of the data from the refinement cycle of the stretching parameters for the C(44)=O(7) bond*

Figure 10 *Determination of the best values of the l_2 and TSLOPE parameters for the C(44)=O(7) bond by use of the statistical parameters α and δ*

also be adequate for quinones provided they are not engaged in a charge-transfer complex.

Despite our efforts to enlarge the π index P_{exp} domain, it remained limited to 0.66 - 0.86. Within that domain TSLOPE and SSLOPE parameters are high. Extrapolation toward P = 1 leads to l_2 and k_2 values which still have some physical meaning. Use of the parameters here proposed for π indices less than 0.5 would be unreasonable and absurd for P = 0 (single bond).

The proposed parameters are satisfying in that the mean unsigned derivation $\bar{\delta}$ is approximately 0.01Å, but the maximum deviations can reach ±0.03Å. They are also conceptualy satisfying in that they explicitly express their dependence on the π character of the bond. But, because they are based on experimental bond lengths in crystals, they implicitly take into account a medium value of the effective dielectric constant D.

gions where the criteria are not satisfied and a region $l_2 \in$ [1.075 ; 1.085] TSLOPE $\in$ [0.600 ; 0.625] in which a futher refinement was performed with a step of 0.001Å. In this way, it was deduced (see Fig. 10) that the best parameters were $l_0 = 1.070$Å and TSLOPE = 0.622 Å for:

$\alpha = 1.0017$
$\beta = -0.13.10^{-2}$
$r = 0.85019$
$\delta = 1.075$Å for 111 bonds $\bar{\delta} = 0.0097$Å

Fig. 11 shows $l_{exp} = f(l_{calc})$ for the best parameters. The cloud of dots is rather well balanced around the bisektrix. Maximal dispersion is ±0.03Å which is rather large but was to be expected from the curve $l_{exp} = f(P_{exp})$. The proposed parameters are shown in Table 5.

Discussion and conclusion

Statistical study, in the solid state, of 89 cyclic molecules containing a cross-conjugated >C=O group (111 bonds) has shown that it is possible to define a new carbon type (44) appropriate to α-pyrones, conjugated lactame and thiolactones but not to carbonates and oxazo-ones. It seems that it would
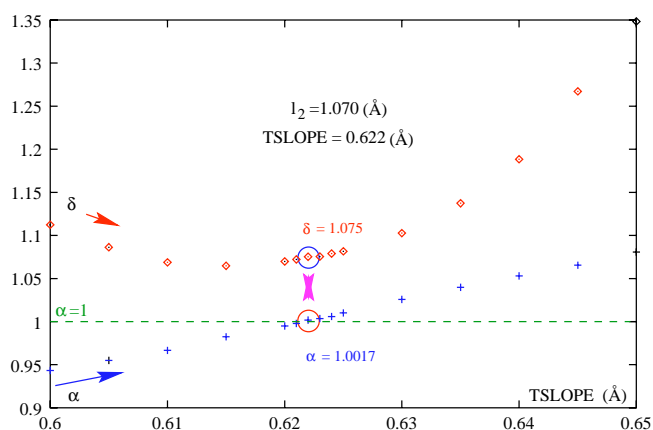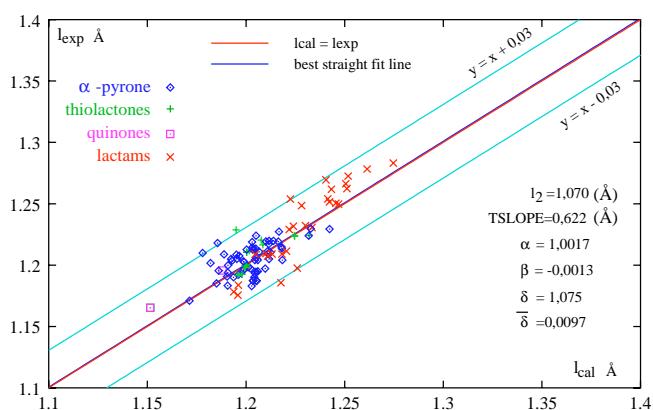

Figure 11 *Comparison of l_{exp} and l_{calc} for the 111 C(44)=O(7) bonds of the 88 reference molecules. Results obtained with the parameters proposed here*

Table 5 *Stretching parameters for the C(44)=O(7) bond*

Atom types	k_2 (mdyn.Å^{-1})	l_2 (Å)	σ bond moment (D)	SSLOPE (Å)	TSLOPE (mdyn.Å^{-1})
44 7	15.93	1.070	2.10	6.927	0.218

In a crystal, deviation of D from that mean value results in a deviation from l_{calc} versus l_{exp} and is possibly the source of a part of the observed dispersion.

Theoretically, another factor of deviation could be the following. In all MM Allinger's force fields, the definition of the «bond length» is the thermal average value (at room temperature) of the internuclear distance (r_g) which, is experimentally given by gas phase electron diffraction. However, X-ray diffraction experiments give the average nuclear positions of heavy atoms at thermal equilibrium and from these the internuclear distance (r_α) is determined. The r_g and rα bond lengths differ from the consequences of the perpendicular vibrations [14]. We do not suspect that this factor is important here because the rigidity of the ring system constrains, by extension of the conjugation, the perpendicular vibrational motions of the carbonyl.

Introduction of the type 44 C atom to replace the type 3 C atom in some cases also implies reparameterisation of the C=Y= bonds adjacent to the carbonyl. This was done for Y=O and N and will be published later on.

Unsaturated lactone rings have also been studied by several authors within the MM2 force field [15,16]. In both these papers however, the lactones studied do not exhibit a comparable delocalisation. The type number of the intracyclic oxygen atom is 6 and the π calculations imply either the MMX program [15] (MM2+MMPI subroutines) or the MMP2 method with tentative parameters [16]. No lactams studied so far have been conjugated [17,18].

Technical considerations

As already mentioned, handling a large number of molecules led us to write several programs in C-shell or Fortran for Unix systems. Because of their technical character, they will be published elsewhere but are available from the authors upon request.

Modification of the MM2 source-code will also be described. An important difficulty encountered with the standard MM2 program was the lack of convergence of the SCF calculations due, most of the time, to the size of the π system and accumulation of heteroatoms. To remedy to that we introduced in MM2 the SCFCHK subroutine developed by Bacon and Zerner [19] for ZINDO. Thanks to that modification we increased the successful calculations by approximately 25%.

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