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Molecular mechanics: the cross-conjugated carbonyl group in heterocyclic compounds. 3. Parameterisation (MM2) of the adjacent C=C bond: evaluation tests

Abstract In the MM2 force field, the definition of a new type of carbon (carbonyl atom, when it is cross-conjugated) has led to the reestimation of the mechanical parameters of the adjacent C(O)-O and C(O)-N bonds in fully-conjugated cyclic compounds: α-pyrones, δ-lactones, and conjugated "lactams". New parameters, based on the study of 97 bonds, are presented here for the similar adjacent C(O)-C bond in the same compounds. Comparison of calculated bond lengths to experimental X-ray bond lengths shows that, statistically, the results are substantially improved but the dispersion remains large. Full optimisation of the molecules concerned shows that in some cases the errors accumulate on the C(O)-O bond which is more sensitive to errors in the evaluation of its own π bond order. The origins of the discrepancies are discussed. Using caffeine as a test molecule, the MM2 method with the parameters proposed here, appears less acurate than the ab initio and DFT methods (both with 6–31G**basis) but still better than the semi-empirical methods (AM1-PM3).

Introduction

The simulation, by molecular mechanics, of heterocyclic compounds in which a carbonyl group is cross-conjugated has led us to define a new type of carbon (carbonyl) atom effective, at least, for conjugated lactones and lactams.

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In the MM2 force field, the type number of this carbon atom is three C(3), and the conjugation with the adjacent O or N atoms is not normally taken into account i.e. these atoms are not engaged in the π calculations. In our study, they now are and the new atom type is 44 (Fig. 1).

As a consequence, the C(44)=O(7), C(44)-N(40) and C(44)-O(41) bond parameters had to be reevaluated because most of them are now π-bond-order-dependent. These reparameterisations have been the topic of two previous papers [1,2]. In a first step, the assumption was made that for the other adjacent bond, i.e. C(44)-C(2), the parameters of the "classical" C(3)-C(2) were transferable because they were already π-bond-order-dependent.

The results already obtained show large deviations concerning the C(44)-C(2) bond length and an effective parameterisation of that bond proved to be necessary. This is the object of the present paper.

Parameterisation of the C(44)-C(2) bond adjacent to a cross-conjugated carbonyl

For the C(44)-O(41) and C(44)-N(40) adjacent bonds, the splitting of the dipolar bond moment into a σ- plus a π-part and the correction we have introduced [3] on the π bond moment, led to the reevaluation of the σ bond moments of these two bonds. In this process, and in accor-
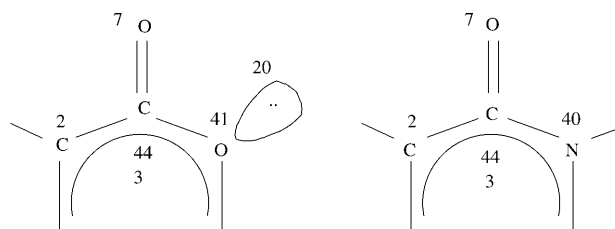
Fig. 1 Type numbers of the atoms involved in the π system of the conjugated lactones and "lactams" used in the present study

Table 1 List of the molecules involved in this study

Molecule number	Name	Refcode
Cyclic lactones (five-membered ring)		
1	*N*-Acetyl-5,6-dihydrofuro(2,3-b)pyrid-2-one	**AFURPO10**
2	3-Acetyl-5-(α-methylbenzylidene)-2,4-oxolanedione	**CIJHOS**
3	5-Benzylidene-3-acetyl-oxolan-2,4-dione	**COCVIZ**
4	(*Z*)-3-Bromo-5-(bromonitromethylene)-furan-2-(5H)-one	**COLJUI**
5	5*Z*-Carboxymethylene-3-chloro-4-methyl-2-(5H)-furanone	**COMFRN**
6	*cis*-Octa-2,4,6-triene-1,4,5,8-diolide	**COTROL 10**
7	5-(*trans*-(Z)-β,γ-Epoxy-α-methoxy-cinnamylidene)-4-methoxy-furan-(5H)-one	**EPMCMF 10**
8	3,9-Dimethyl-2,5,6,7-tetrahydrofuro-(2,3-*b*)-indolizin-2-one	**GAKGOO**
9	4-Chloro-5-dichloromethylene-2-furanone	**GEXWUB**
10	4,5,6,7-Tetrafluoro-8-methoxy-2*H*-cyclohepta-(*b*) furan-2-one	**JIYJAC**
11	8-Benzyl-3-phenyl-2*H*-indeno-(2,1-*b*)furan-2-one	**JOPDIB**
12	3,4-Dichloro-2-(methoxycarbonyl(chloro)methylenefuran-4-one	**JUNFUT**
13	Acetylmelodorinol	**KETDOC**
14	2-Cyclohexenyl-4-cyclohexylidene-2-butenolide	**KUPXIC**
15	*trans*-2,7-Dimethyl-2,4,6-octatriene-1,4–5,8-diolide	**MOTROL**
16	5-(*p*-Methoxyphenyl)-3-methoxy-penta-2,4-dien-4-olide	**MXPENO**
17	1-Oxa-azulen-2-one	**OXAZUL**
18	DL-4-Hydroxy-4*H*-furo-(3,2-*c*)pyran-2-(6H)-one	**PATULO**
19	*N*-(2-Phenyl-4Z,6E-2,4,6-heptatriene-4-olide-7-yl)-morpholine	**SAMGOC**
20	*trans*-Octa-2,4,6-triene-1,4,5,8-diolide	**TOTROL 10**
21	3-Diphenylmethylene-7-phenyl-9-oxabicyclo(4.3.0)non-1,4,6-trien-8-one	**VOBRUZ**
22	7-Methyl-7-methoxy-5-phenyl-oxatricyclo(6.3.0.0)undeca-1,5-dien-4-one	**VOCREK**
23	(4Z,6Z)-6-Acetyl-7-hydroxy-2,4,6-octatriene-4-olide	**VOXGOE**
Cyclic lactones (six-membered ring)		
24	4-Methoxy-6-(2,4-dihydroxy-6-methylphenyl)-2-pyrone	**ALOAGL 10**
25	5-Crotonoyl-4-methoxy-6-methyl-pyrone	**BABNIB**
26	7,8-Dihydro-4,7,7-trimethyl-2H,5*H*-pyrano-(4,3-*b*)pyran-2,5-dione	**BINTUN**
27	6-Ethoxycarbonylamino-4-chloro-5-methyl thio carbonyl-2-oxo-3*H*-pyran	**CATMOZ**
28	Coarctatin dibromide	**COARDB**
29	3-Acetyl-4-hydroxy-6-phenyl-2-pyrone	**CUZXUQ**
30	3,3'-Diacetyl-5,5'-bis-(ethoxycarbonyl)-glaucyrone	**ETGLAU 01**
31	(–)-Dimethyl 1-acetyl-1,2,3,7-tetrahydro-7-oxopyrano-(3,4-*b*)pyrrol-2,5-dicarboxylate	**FAFYEQ**
32	(*E,E*)-7-(2-Butenylideno)-1,7-dihydro-1-oxo-cyclopenta(*c*)pyran-4-carboxylic acid methyl ester	**FIJHIP**
33	3-(Diphenylmethylene)-6-di-isopropylamino-5-di-isopropylaminocarbonyl-2,4-dioxo-3,4-dihydro-2*H*-pyran	**FINZUX**
34	3-Chloro-5,6-dihydro-4-methylphenylaminoangelicin	**FIVRIL**
35	7-(Dimethylamino)-3,4-dihydro-*N,N*-dimethyl-5-oxo-2H,5*H*-pyrano-(4,3-*b*)pyran-8-carboxamide	**GEWBOZ**
36	3-(1-(Ethylamino)ethylidene)-6-methyl-3*H*-pyran-2,4-dione	**HABNED**
37	2-(beta-Hydroxyisopropyl)-2,3-dihydro-6,7-furano-coumarin	**JECPUC**
38	α-3(1-Phenyl-*N*-(dimethylcarboxamide)methylimine)-4,5-trimethylene-pyran-2-one	**JEDYAS**
39	4-Hydroxy-6-methyl-3-(3-dimethylaminoacryloyl)-2*H*-pyran-2-one	**JIHJOZ**
40	3-Benzoylamino-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydrocoumarin	**JUKZUK**
41	3,7-Dimethyl-1*H*,9*H*,10*H*-dipyrano(4,3-*b*:3',4'-e)pyran-1,9-dione	**KEMZUX**
42	trans-7,8-Dihydro-7-hydroxy-4-methoxy-7,8-dimethyl-2*H*,5*H*-pyrano-(4,3-*b*) pyran-2-one (benzene solvate)	**KITRIO**
Cyclic lactones (five-membered ring)		
43	6-*t*-Butyl-2-(dipivaloymethylene)-5-pivaloyl-1,3-dioxin-4(2*H*)-one	**LACVAM**
44	3-(1-(Phenylamino)ethylidene)-6-methyl-2,4-dioxo-2,3-dihydro-4*H*-pyran	**PAEXPY**
45	5-(4-Acetoxy-6-methyl-2-pyron-3-yl)-3-ethoxycarbonyl-1-phenylpyrazole	**PANDEN**
46	4-Methoxy-6((5E,9E,2R,3S,4R,7S,8S)-2,4,8-trihydroxy-3,7,9-trimethyl-undeca-5,9-dienyl)-pyran-2-one	**PEXYIA**
47	3-Acetoacetyl-7-methyl-2H,5*H*-pyrano(4,3-b)pyran-2,5-dione	**POCRAA**
48	Reductiomycin	**RDCTMC**
49	4-Methoxy-6-(2-(2-furyl)ethenyl)pyran-2-one	**SOWBOV**
50	2,6-Dimethyl-5*H*-furo-(3,2-*b*)pyran-5-one	**VASDOI**
51	2,7-Dimethyl-5*H*-furo-(3,2-*b*)pyran-5-one	**VASDUO**
52	9-Hydroxy-3-methyl-2*H*-naphtho-(2,3-*b*)pyran-2,5,10-trione	**VUTDAP**
53	3-(5-Chloro-2-benzoxazolyl)-7-diethylamino-2*H*-1-benzopyran-2-one	**VUWZUI**
54	3-Acetyl-6-methyl-2*H*-pyrano-(2,3-*b*)indolizin-2-one	**WANPAC**
55	α-Pyrone	**WIKCAU**
56	Methyl-4,5-dichloro-3-methyl-2-oxo-2*H*-pyran-6-carboxylate	**YABYIJ**
Cyclic "lactams" (five-membered ring)		
57	Methyl-3-(((dimethylamino)methylene)amino)-2,5-dimethyl-1,4,6-trioxo-1,2,5,6-tetrahydro-4*H*-pyrrolo (3,4-*C*)pyridine-7-carboxylate	**VAKZAI**

Table 1 (continued)

Molecule number	Name	Refcode
	Cyclic "lactams" (six-membered ring)	
58	11-Hydroxy-6*H*-indolo-(3,2,1-de)(1,5)naphthyridin-6-one monohydrate	**AMARRN**
59	5,5-Diethylbarbituric acid-*N*-methyl-2-pyridone complex	**BARMPN**
60	7-Chloro-8-methyl-2(1*H*)-quinolinone	**BAWVAW**
61	1-Benzyl-5-ethyl-1,2,5,6-tetrahydro-2-oxo-4-pyridine-acetic acid	**BEPYAC**
62	8-Acetoxy-2-quinolone	**BIMSIZ**
63	4-Bromo-1-methyl-3,5-diphenyl-2-pyridone	**CANRAK**
64	4-Hydroxy-2-pyridone	**CAXKOB**
65	1-Phenyl-1,2-dihydro-2-quinolidone	**CIPGIR**
66	5-Chloro-2-pyridone	**CLPYRO**
67	*N*-Carbomethoxyamino-3,6-dimethyl-4,5-diphenyl-2-pyridone	**CMXPYO**
68	*N*,*N*-Dimethyl-1-hydroxy-2(1H)-pyridinone-6-carboxamide	**DAHBAP**
69	2-(Methoxycarbonyl)canthin-6-one	**DUTTOB 10**
70	11-*o*-Bromobenzoyl-canthin-6-one	**FAWLAQ**
71	(–)-1,2,3,4,5,6-Hexahydro-3-methyl-1,5-methano-8*H*-pyrido-(1,2-*a*)(1,5)diazocin-8-one	**FITPON**
72	2,5,6,7,8,9-Hexahydro-3,4-dimethyl-2-phenyl-1*H*-cyclohepta(*c*)pyridin-1-one	**GIPCAJ**
73	2-Quinolone	**HXQUIO 01**
74	1-Formyl-8-methoxy-3-methyl-5,6-dihydrobenz(*f*)-isoquinolin-2(3H)-one	**JAMNOA**
75	Cerpegin	**JEGVOG**
76	1-Hydroxypyridine-2-one	**JEMJUG**
77	6-(3,3-Dimethyl-2-oxo-2,3-dihydro-5-furanyl)-2-pyridone	**JUKZIY**
78	6-(2,4-Dimethylimidazol-1-yl)-8-methyl-2(1*H*)-quinoline	**KAGYUM**
79	2-Methyl-6,7-bis(dimethylthio)isoquinoline-3,5,8(2*H*)-trione	**KUNKUZ**
80	Mimosamycin	**MIMOSA 10**
81	3-Benzoyl-2-phenyl-6(1*H*)-pyridone	**PEXLAF**
82	7,8-Dihydro-7-methyl-2,5(1*H*,6*H*)-quinoline-1,5-dione	**PEXLEJ**
83	2-Pyridone (neutron study)	**PYRIDO 04**
84	2-Pyridone	**PYRIDO 11**
85	*N*-*n*-Butyl-3-hydroxy-2(1*H*)-pyridone	**SABKEL**
86	Methyl 3-methoxycarbonyl-1,2,3,5-tetrahydro-8-hydroxy-5-oxoindolizin-6-yl propanoate	**SAFRUM**
	Cyclic "lactams" (six-membered ring)	
87	3-Ethyl-4-methoxycarbonyl-6-phenyl-1*H*-2-pyridone	**SEKMOK**
88	Methyl-1,6-dihydro-1-(dimethylcarbamoyl)-4-methyl-6-oxo-2-phenyl-3-pyridinecarboxylate	**SIFJAS**
89	2-Methyl-3,4'-bipyridine-6(1H)-one (1st conformation)	**SIVCAB**
90	2-Methyl-3,4'-bipyridine-6(1H)-one (2nd conformation)	**SIVCAB01**
91	8-Benzoyl-1-methyl-7-methoxycarbonylimidazo-(1,2-*a*)pyridin-5-one	**SOWJIX**
92	Ethyl-1,2-dihydro-2-oxo-3,6-diphenyl-4-pyridinecarboxylate	**VAFJOB**
93	3-(1,2,5,6-Tetrahydropyrid-4-yl)-pyrrolo-(3,2-*b*)pyridin-5-one	**VEWZEC**
94	1,2,3,3,8-Pentamethyl-5-trifluoromethyl-2,3-dihydro-1*H*-pyrrolo(2,3-*g*)quinolin-7(8H)-one	**VIGXAK**
95	1-Amino-4-(2-hydroxy-4-methoxyphenyl)-2,6-(1*H*,3*H*)-pyridinedione	**VIVTAV**
96	Anagyrine	**VOFDEZ**
97	3,6-Diphenyl-1-methylquinoline	**VORXAB**
98	2-(α-Isopropylbenzylideneamino)-1-methyl-2*H*-indeno-(2,3-*c*)pyridine-3,9-dione	**WEPNUA**
99	1-Methyl-2-(-*p*-tolylethylideneamino)-2*H*-indeno(2,3-e)pyridine-3,9-dione	**WEPPAI**
100	5-Fluoro-8,8-dimethyl-7-oxa-3,9-diazabicyclo(4.3.0)nona-1(9),5-diene-2,4-dione	**WINXIA**
101	5,7-Dimethyl-1,8-naphthyridin-2-one	**YAXFIM**
102	Picrasidine	**YECYUA**
	Cyclic "ones" (six-membered ring)	
103	5,8-Dihydroxy-1,4-naphthoquinone	**DHNAPH05**
104	3-Hydroxy-1,2-dimethylpyridin-4(1*H*)-one	**GALDEC01**
105	1-Ethyl-2-methyl-3-hydroxy-4-pyridinone	**JASMAR01**
106	3,5-Dichloro-2,6-dimethyl-4-pyridinol	**MCHYPY10**
107	Tropolone	**TROPOL10**
	Extra test-molecules	
108	Coumarin	**COUMAR02**
109	Furo-(2,3-*h*)coumarin	**FUCOUM**
110	Gnidicoumarin	**GNIDOC 20**
111	3,5,8-Trimethyl-7-oxo-azuleno-(6,5-*b*)furanone	**CALLIK**
112	2,5,6-Trimethyl-9-methoxy-4*H*-pyrrolo-3,2,1-*ij*)quinolin-4-one	**VIFCUI**
113	3-Ethyl-4-oxa-1,5,6-trihydrophthalimide	**VOBDEV**

Table 1 (continued)

Molecule number	Name	Refcode
Phthalimides		
114	(2,4,6-Trimethylphenyl)-phthalimide	**COMGOA**
115	Phthalimide	**PHALIM 01**
116	2-Methylpyrrolo-(3,4-*c*)pyrrole-1,3(2*H*,5*H*)-dione (1st conformation)	**SIWDAD**
117	2-Methylpyrrolo-(3,4-*c*)pyrrole-1,3(2*H*,5*H*)-dione (2nd conformation)	**SIWDAD**
118	*N*-Phenyl-phthalimide	**ZZZAWJ 10**
Caffeine derivatives. Isocaffeine		
119	Bis(caffeine) Hexa-aqua-magnesium (II) dibromide	**BIKPUG**
120	Bis(caffeine) Hexa-aqua-manganese (II) tri-iodide iodide (1st conformation)	**BIKRAO**
121	Bis(caffeine) Hexa-aqua-manganese (II) tri-iodide iodide (2nd conformation)	**BIKRAO**
122	Bis (barbital-caffeine) complex	**CAFBAR 20**
123	Caffeine monohydrate	**CAFINE**
124	Caffeine-5-chlorosalicylic acid complex	**CAFSAL**
125	Caffeine methyl gallate	**DIJVOH**
126	Caffeine *m*-nitrobenzoic acid	**DIJVUN**
127	Caffeine potassium chlorogenate dihydrate	**DIJWAU 10**
128	*N*-acetylsulfanilamide-caffeine	**SACCAF**
129	1,3,9-Trimethyl-2,6-dioxopurine (isocaffeine)	**ISCOFF**

Table 2 Results of the statistical study of the correlation of the experimental C(44)-C(2) bond length with the π bond order.

	δ-Lactones[a]	α-Pyrones[b]	Conjugated lactams[c]	Cyclic conjugated ketones	Full set of molecules
Number of observations	26	38	49	12	126
Mean of P_{exp}	0.27285	0.31372	0.32960	0.35590	0.31472
Standard deviation of P_{exp}	0.03111	0.03025	0.04148	0.03451	0.04380
Mean of l_{exp}	1.45189	1.43920	1.43781	1.43100	1.44079
Standard deviation of l_{exp}	0.01876	0.01687	0.01764	0.01252	0.01836
Correlation coefficient	−0.79546	−0.67090	−0.84407	−0.46153	−0.78168
Slope	−0.47965	−0.37424	−0.35890	−0.16744	−0.32772
Standard error on slope	0.07459	0.06894	0.03326	0.10177	0.02348
Intercept	1.58276	1.55660	1.55610	1.49059	1.54393
Standard error on intercept	0.02048	0.02173	0.01105	0.03638	0.00746

[a] Five-membered rings
[b] Six-membered rings
[c] Six-membered rings

dance with the MM2 philosophy, a zero σ-moment was attributed to the C-C and C-H bonds. So, for the C(44)-C(2) bond, no modification of the dipole moment was necessary.

Stretching parameters

*First estimation of* l_2, k_2, *TSLOPE and SSLOPE*

The first estimation of the stretching parameters was performed in the way we described previously [1, 2, 3]. The reference molecules were the α-pyrones, δ-lactones and conjugated lactams which were used in the previous studies to which were added a few cyclic ones, i.e. molecules containing a carbonyl group cross-conjugated with two adjacent C(44)-C(2) bonds. Quinones were excluded for the reason already mentioned [1]. The reference molecules are listed in Table 1.

The calculation of the π-bond orders P_{exp}, based on the X-ray geometries provided by the Cambridge Structural Database System (C.S.D.S.) [4,5], has led to corre-

lations described by the statistical parameters recorded in Table 2 and illustrated by Fig. 2, Fig. 3, Fig. 4, and Fig. 5.

The five membered ring conjugated lactams that we found in the C.S.D.S. were in fact phthalimides, i.e. molecules in which the nitrogen atom is located between two carbonyls. So, it is not certain that type 40 is suitable and we did not retain these molecules. Only one ring remained as part of a larger moiety (**57**) and was not included in the statistical study. As the experimental bond length is also the result of steric effects, one cannot expect good correlation coefficients with the bond-order. Most of them are therefore acceptable. For the cyclic conjugated ketones, the correlation is very low for at least two reasons: the small number of bonds (12) and the short domain of variation for P_{exp} (0.30–0.40). For the α-pyrones the number of bonds is rather large (38) and the range of P_{exp} is also larger (0.225-0.375). As shown in Fig. 3, the dispersion is large.
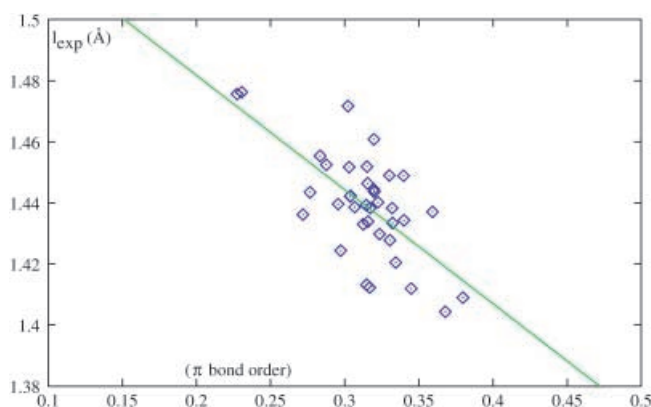
In accordance with MM2 philosophy for the stretching parameters, there was no reason to make a distinction between five- and six-membered rings, so for the 126
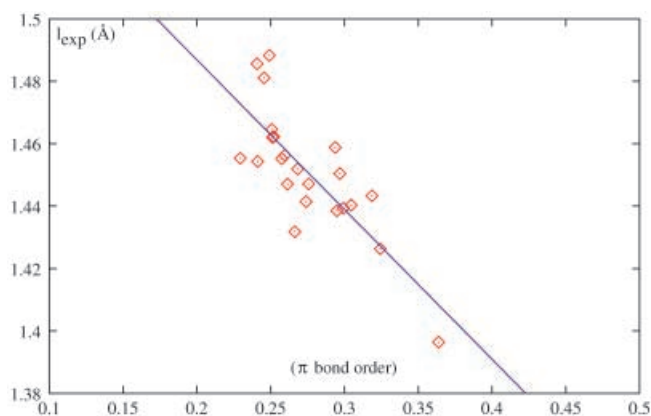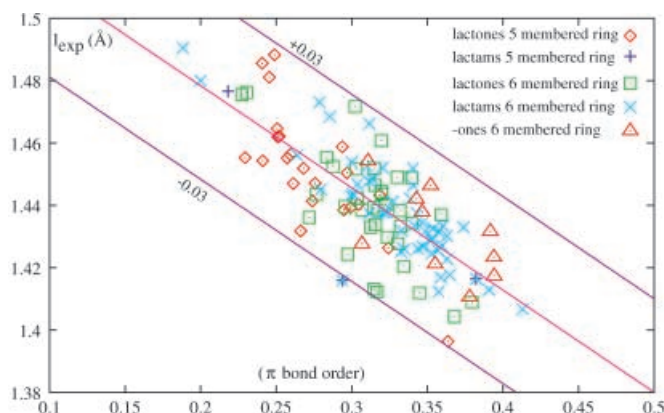
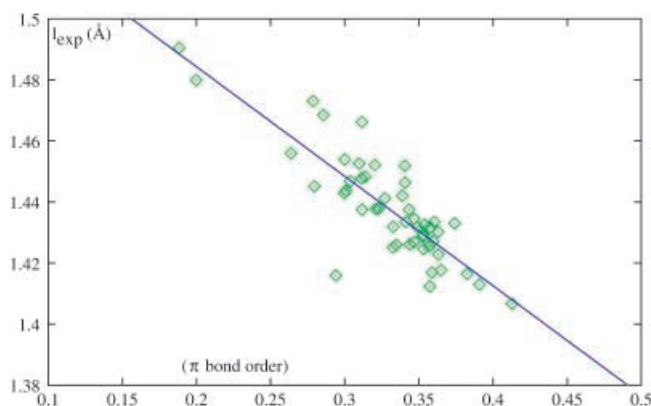**Fig. 2** Plot of l_{exp} versus P_{exp} for the adjacent C(44)-C(2) bond. Conjugated δ-lactones (five-membered ring)
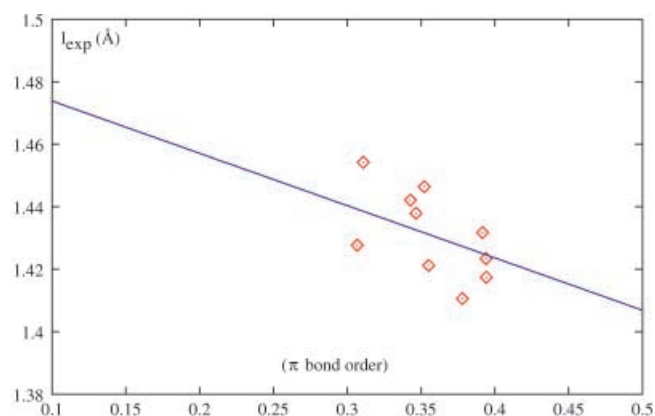
Fig. 5 Plot of l_{exp} versus P_{exp} for the adjacent C(44)-C(2) bond. Cyclic conjugated "ones" (six-membered ring)

Fig. 3 Plot of l_{exp} versus P_{exp} for the adjacent C(44)-C(2) bond. Conjugated α-pyrones (six-membered ring)

Fig. 6 Plot of l_{exp} versus P_{exp} for the adjacent C(44)-C(2) bond. Whole set of conjugated lactones, "lactams" and "ones" (126 bonds)

Fig. 4 Plot of l_{exp} versus P_{exp} for the adjacent C(44)-C(2) bond. Conjugated "lactams" (six-membered ring)

bond lengths together, the statistical study (Table 2, Fig. 6) led to the best fit straight-line:

$$l_{exp}=1.544-0.329\times P_{exp} \tag{1}$$

Fig. 6 shows that the dispersion can reach ±0.03Å, which is somewhat larger than that observed for the C-O and C-N adjacent bonds [2].

An estimation of the bond force constant k_s can be obtained by Badger's rule [6, 7], which can be written:

$$k_s\times[A_{ij}\times(l_0-B_{ij})]^3=10 \tag{2}$$

In Badger's work, the parameters A_{ij} and B_{ij}, which depend on the rows of the periodical classification where atoms i and j are located, were derived from experimental interatomic distances and force constants. The B_{ij} constant can be interpreted in molecular mechanics as a correction term for the interatomic distance between atoms of relative types i and j and modified for a better fit, provided that at least one force constant is known for the corresponding bond length. For the C(3)-(C2) bond, the evolution of k_s with P_{exp} is given by the linear approximation:

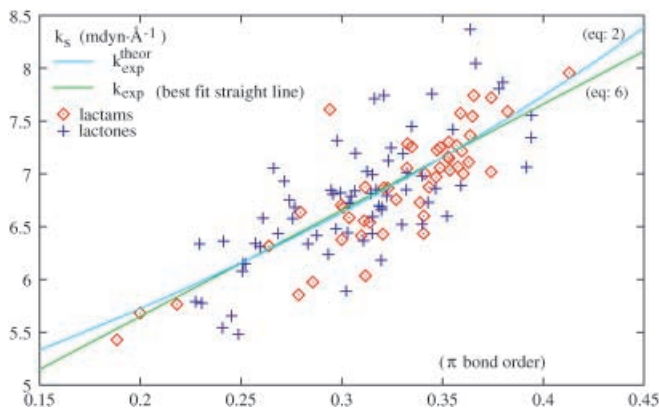$$k_s=5.00+4.60\times P_{exp} \tag{3}$$

with:

$$l_{exp}=1.517-0.166\times P_{exp} \tag{4}$$

In the domain of P_{exp} we are concerned with (0–0.4), the two straight lines (1) (C(44)-C(2)) and (4) (C(3)-C(2)) diverge but have a common point P_{exp}=0.16, l=1.49 Å for which Eq. (3) gives:

$$k_s=5.736 \text{ mdyn·Å}-1$$

Fig. 7 Plot of k_{exp} versus P_{exp} for the adjacent C(44)-C(2) bond. Whole set of molecules. The *blue line* corresponds to Eq. (2) with A_{ij}=1.75 and B_{ij}=0.79. The *green line* corresponds to the best-fit straight-line [Eq. (6)]

Fig. 8 Plot of the sum, for the whole set of reference molecules (89), of $|l_{calc} - l_{exp}|$ deviations for the C(44)-C(2) bonds (97), versus k_2 with l_2=1.082 Å and TSLOPE=0.520 Å (see text)

Table 3 First estimation of the stretching parameters for the C(44)-C(2) bond

Atom types	k_2 (mdyn·Å^{-1})	l_2 (Å)	SSLOPE (mdyn·Å^{-1})	TSLOPE (Å)
44–2	13.7	1.216	10.05	0.328

One way to obtain an estimate of B_{ij} for the C(44)-C(2) bond is to consider that at that point, for the same bond length, the stretching force constant is also the same as that of the C(3)-C(2) bond. Thus, Eq. (2) with A_{ij}=1.75 [6] gives B_{ij}=0.79. Substitution of Eq. (1) in Eq. (2) finally gives the theoretical relation:

$$k_s \times (1.544 - 0.329\, P_{exp} - 0.79)^3 = 1.866 \qquad (5)$$

Figure 7 shows the representative curve of Eq. (5) and also plots the values of k_s found for the experimental bond lengths using Eq. (2) with B_{ij}=0.79 for the reference molecules. The dispersion is well balanced around the curve and the graph shows that a linear approximation is justified. The equation of the best fit straight line was found to be:

$$k_s = 3.64 + 10.05 \times P_{exp} \qquad (6)$$

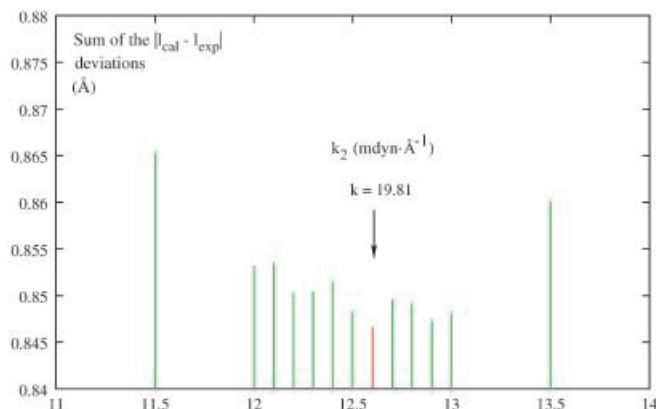with r=0.8155.

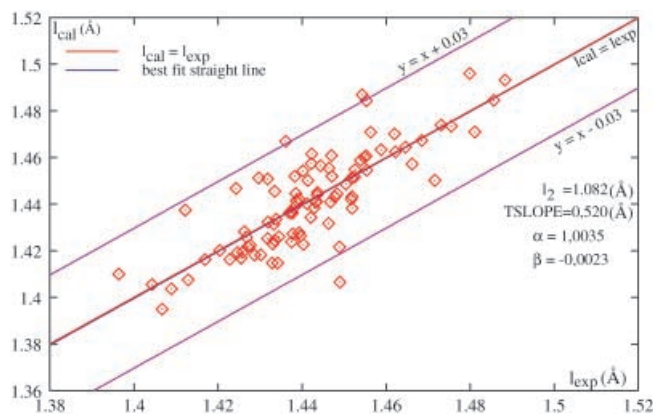Finally, the first estimation of the stretching parameters for the C(44)-C(2) bond is given by Table 3.

Refinement of the stretching parameters for the C(44)-C(2) bond

Refinement of l_2, TSLOPE, k_2 and SSLOPE was performed in the same way as for the adjacent C(44)-O(41) and C(44)-N(40) bonds, using the programs previously constructed [2].

First estimations, besides geometry of the molecules, required only quantum parameters. For the refinement, mechanical calculations are required. So, all bond parame-

Fig. 9 Comparison of the calculated and experimental C(44)-C(2) bond lengths using the proposed parameters (whole set of reference molecules)

ters as well as MM2 types of all atoms need to be known without ambiguity. Some conjugated "lactams" exhibiting an *N*-X *exo*-bond (X=N or O) were eliminated for that reason (**67, 68, 95, 98, 99**). The same is true for molecules containing unknown types of atoms or unknown parameters (**27, 28, 39, 57, 93**). For **48**, the exact nature of the molecule does not appear to be known (formula isomers).

Finally for 97 C(44)-C(2) bonds included in 89 molecules, successive grid searches based on the above values of k_2 and SSLOPE led to l_2=1.069 Å and TSLOPE=0.540 Å, values that satisfy the criteria $\alpha \cong 1$ and $\beta \cong 0$ in the expression:

$$l_{cal} = \alpha \times l_{exp} + \beta \qquad (7)$$

i.e. α=1.00065 and β=–0.00098 with r=0.82

Then, with these values added to the value of SSLOPE, k_2 was optimised by letting it range from 9.7 to 18.7 md.Å^{-1} by steps of 1.0 and subsequently from 11.7 to 13.7 by steps of 0.1 with simultaneous examination of:

$$\delta = \sum_{C(44)-C(2)}^{all} |l_{cal} - l_{exp}| \qquad (8)$$

The minimum of δ gave k_2= 12.6 md.Å^{-1}. A further refinement of l_2 and TSLOPE with k_2 = 12.6 md.Å^{-1} gave l_2=1.082 Å and TSLOPE = 0.520 Å with α=1.00135 and β=–0.0023 with r=0.82

A further attempt to improve k_2 did not change its value (Fig. 8). The fit of l_{calc} with l_{exp} is illustrated in Fig. 9.

Table 4 Stretching parameters proposed for the C(44)-C(2) bond

Atom types	k_2 (mdyn·Å^{-1})	l_2 (Å)	SSLOPE (mdyn·Å^{-1})	TSLOPE (Å)
44–2	12.6	1.082	10.05	0.520

Table 5 Comparison of the global results obtained with the former parameters (C(3)-C(2) bond) and the proposed parameters (C(44)-C(2) bond) on a set of test molecules

Lactones	Unsigned mean deviations (Å) on bond lengths		
Bond	Former results[a]	This work	Maximum
C(44)=O(7)	0.0093 (26)[b]	0.0077 (37)[c]	0.0323
C(44)-O(41)	0.0246 (26)	0.0291 (37)[c]	0.0688
C(44)-C(2)	0.0276 (26)	0.0168 (37)[c]	0.0453
Lactams			
C(44)=O(7)	0.0167 (29)	0.0186 (21)	0.0458
C(44)-N(40)	0.0222 (28)	0.0221 (21)	0.0583
C(44)-C(2)	0.0339 (29)	0.0117 (21)	0.0466
Lactones+Lactams			
C(44)=O(7)	0.0132 (55)	0.0117 (58)	
C(44)-X[d]	0.0234 (54)	0.0265 (58)	
C(44)-C(2)	0.0309 (55)	0.0149 (58)	

[a] Former results were obtained using the C(3)-C(2) parameters for the C(44)-C(2) bond (see [2], Tables 7 and 12)
[b] Numbers in parentheses indicate the number of values used to get the unsigned mean deviation
[c] Value obtained omitting compound 43 (LACVAM). (See text)
[d] X=O or N

The dispersion remains large and three molecules (**5**, **33**, and **43**) show a deviation $|l_{calc}–l_{exp}|>0.03$ Å.

Most of the bending parameters for the intra- and *exo*-cyclic angles involving the C(44), O(41) and N(40) atoms were already optimised [2]. An attempt to improve the results by adjusting the parameters of the angle type C(44)-C(2)-X (X type: 1, 2, 3 or 5 – X exocyclic) failed. Thus, the stretching parameters finally proposed are presented in Table 4.

First evaluation tests

The evaluation was made after full relaxation of 58 selected cyclic molecules (test molecules). Some of them were chosen among the reference molecules, to which were added compounds **108**–**113**. In order to limit as far as possible the experimental errors on the bond lengths, only the X-ray structures for which the reliability factor R was equal to or below 0.06 were taken into account. Some lateral chains were conjugated with the ring, at least theoretically; their orientation was kept – using the "driver" – for a valid comparison. Indeed the full relaxation of an isolated molecule, modifying the dihedral angle determined by packing effects would modify the conjugation.

Table 5 compares the global results for the bond lengths of interest obtained in the present study with those obtained in the two previous papers [1, 2] when the C(44)-C(2) bond was not optimised. As can be seen, the new parameters substantially improve the results for that bond. The improvement on the C(44)=O(7) bond is possibly not significant but at least there is no deterioration. If one looks at the intracyclic C-O or C-N bond, the C-N bond does not seem to be affected but the C-O bond is weakened. This is also apparent from looking at the maximum unsigned deviation.

Table 6 shows that better results are obtained statistically with these parameters for six-membered rings rather than for five-membered rings [C(44)-C(2), C(44)-X

Table 6 Mean and maximum unsigned deviations on bond lengths for five- and six-membered lactones and lactams

Mean and maximum unsigned deviations (Å) on:					
Lactones		C(44)=O(7)	C(44)-C(2)	C(44)-X [a]	Moiety [b]
5-Membered rings (15) [c]	Mean	0.0082	0.0215	0.0350	0.0194
	Maximum	0.0202	0.0453	0.0688	
6-Membered rings (22)	Mean	0.0074	0.0136	0.0251	0.0152
	Maximum	0.0323	0.0418	0.0655	
Lactams					
5-Membered rings (1)	Mean	0.0089	0.0065	0.0561	
	Maximum				
6-Membered rings (20)	Mean	0.0191	0.0119	0.0204	0.0165
	Maximum	0.0458	0.0466	0.0583	
Lactones+Lactams					
5-Membered rings (16)	Mean	0.0083	0.0206	0.0363	0.0194
	Maximum	0.0202	0.0453	0.0688	
6-Membered rings (42)	Mean	0.0130	0.0128	0.0228	0.0158
	Maximum	0.0458	0.0466	0.0655	

[a] X=O or N (intracyclic bond)
[b] The moiety considered here is constituted by the set of ring bonds+the carbonyl bond
[c] Number in parentheses designates the number of bonds considered

and the set of ring's bonds plus C=O bonds], but this could be due to the smaller number of observations for the five-membered rings. In the MM3 force field, it should be possible to try to improve the results in searching for two distinct sets of parameters, one for each type of ring. There is no justification for this in the MM2 force field.

As shown above, the improvement of the simulation of the C(44)-C(2) bond statistically results in the spoiling of the opposite adjacent bond C(44)-X, the C-O bond being more damaged than the C-N bond. In a few instances (**43**), the discrepancy can even reach 0.120 Å! This raises the question of the origin of these discrepancies.

Broadly speaking, one must consider that for the present problem, difficulties accumulate. At the quantum level, the numbers of heteroatoms and π-atoms are often high and numerous rings are chained or fused. At the mechanical level, reference structures are found in the solid state, implying surrounding effects, the effective dielectric constant varying from one crystal to another. Some bonds are polar. The cyclic or polycyclic structures, through the closure requirement and the cross-conjugation, cause the bonds lengths to be strongly correlated. Errors on the π bond orders generate errors on the "natural" (standard) bond lengths which, in turn, lead to errors on the π-bond orders... This latter consideration explains the concentration of errors on the C(44)-O(41) bond. It is indeed the bond which exhibits the largest slope for the $l_{exp}=f(P_{exp})$ curve. Examination of the results facing the number of π-atoms or the number of heteroatoms, though, has shown no correlation.

If one turns to the curves $l_{exp}=f(P_{exp})$, they do not depend, strictly speaking, on the molecular mechanics parameters but they exhibit a large dispersion in the observations. This can partly be attributed to steric effects and partly to the experimental uncertainty in the geometry on which the calculation of P_{exp} is based. These two factors seem insufficient to explain the dispersion fully, because the subsequent mechanical calculations (if the parameters were correct) should reduce it, which is generally not the case. For this problem we thus feel that we have reached the limits of the SCF π-method's possibilities. It
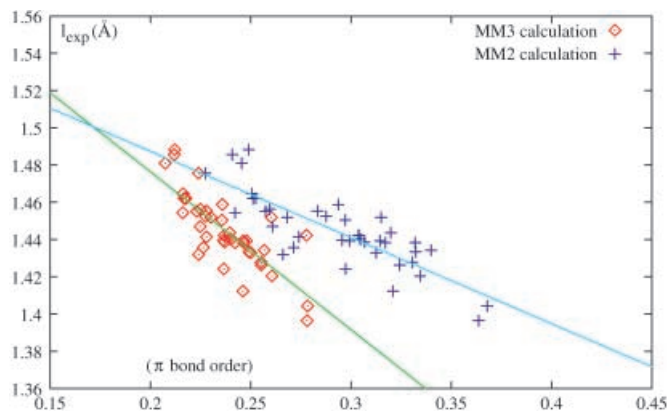
Fig. 10 Plot of l_{exp} versus P_{exp} for the adjacent C(44)-C(2) bond. P_{exp} calculated by both MM3 (VESCF method) and MM2 (SCF method). Set of 41 bonds included in δ-lactones and α-pyrones

may be that switching to the VESCF method as it is implemented in MM3 could improve the results.

Further Tests

The test was performed on a set of α-pyrones and δ-lactones only, for the MM3 program does not allow changing the atom types of the amide function without modification of the source-code.

Figure 10 shows, as expected, that the slope of the best-fit straight line $l_{exp}=f(P_{exp})$ for MM3 is different to that for MM2. The statistical study based on 41 C(44)-C(2) bonds shows that the dispersion is similar (Table 7) and that, consequently, for the present problem, the VESCF method does not bring a better correlation l_{exp}/P_{exp}.

An attempt to reevaluate the C(44)-O(41) bond mechanical parameters, using, that time, the new parameters obtained for the C(44)-C(2) bond, did not bring any changes.

Although conceptually more satisfying, the way we have taken into account the cross-conjugation may underestimate, the ionic character of the C=O, C-O and C-N bonds and consequently their length variations with the effective dielectric constant of the surroundings. As

Table 7 Comparison of the results of the statistical studies of the correlations of the C(44)-C(2) bond lengths with the π bond order calculated by MM3 and MM2 for a set of 41 bonds included in δ-lactones and α-pyrones

	Five-membered rings		Six-membered rings		All rings	
	MM3	MM2	MM3	MM2	MM3	MM2
Number of observations	20	20	21	21	41	41
Mean of P_{exp}	0.22801	0.27256	0.24586	0.31018	0.23715	0.29182
Standard deviation of P_{exp}	0.01702	0.03197	0.01525	0.02877	0.01831	0.03552
Mean of l_{exp}	1.45289	1.45289	1.43631	1.43631	1.44440	1.44440
Standard dev of l_{exp}	0.02111	0.02111	0.01322	0.01322	0.01922	0.01922
Correlation coefficient	−0.88006	−0.83375	−0.51531	−0.65904	−0.78943	−0.80893
Slope	−1.09186	−0.55058	−0.44672	−0.30278	−0.82854	−0.43768
Standard error on slope	0.13887	0.08594	0.17044	0.07927	0.10316	0.05094
Intercept	1.70184	1.60295	1.54615	1.53023	1.64089	1.57212
Standard error on intercept	0.03175	0.02358	0.04198	0.02469	0.02454	0.01497

the dispersion of the observed experimental bond lengths with the π-bond order (SCF and VESCF methods) is high, one is led to ask whether these π-methods are appropriate for this type of problem. We then come up against the difficulty of proposing a quantum method, without σ/π-separation, compatible with the molecular mechanics philosophy. On the other hand, if cross-conjugation is ignored, then the difficulty arises of attribution, a priori, of a "natural" (standard) bond length to the polar bond in a medium whose effective dielectric constant must be known. The debate remains open and further investigations are necessary.
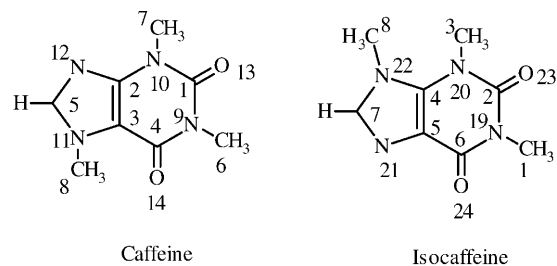

Fig. 11 Labelled schemes of the caffeine and isocaffeine molecules. The atom numbers correspond to the X-ray structures (**123** and **129** respectively)

Comparison with other methods

Although taking into account the cross-conjugation in heterocyclic rings is not as satisfying as expected, and shows, here and there, some failings, statistically the results are somewhat improved and it is logical to compare the results obtained by molecular mechanics using the parameters proposed here with those obtained either by semiempirical methods (AM1, PM3) or by DFT and ab initio calculations.

It was not possible, for technical reasons, to perform the calculations by all these methods for the complete set of molecules. A single test was made on a two-fused-ring molecule containing a reasonable number of hetero and π-atoms. This widely used laboratory molecule –caffeine (Fig. 11) – affords an instructive example

In the C.S.D.S. there are at least ten X-ray structures of crystals containing the caffeine moiety in weak interaction with other entities (Table 1). They are of various qualities. If those for which the R factor is not satisfactory and/or the hydrogen atoms are not located are rejected (**120, 121, 123, 127**), six acceptable geometries remain (**119, 122, 124, 125, 126,** and **128**).

For these six geometries, Table 8 reports the observed bond lengths and, for each of them, the minimum and maximum observed values. For the same bond, differ-

ences are observed which range from 0.017 Å (2–10 bond) to 0.035 Å (5–12 bond). For the bonds which are particularly relevant in this paper (3–4, 4–9, and 4–14) the difference is in the range 0.0235–0.0336 Å! So, depending on the surroundings, a fused-ring heterocyclic molecule, which seems relatively rigid, can exhibit large variations in the experimental bond lengths.

Table 9 gives the results of the calculations by different theoretical methods: semi-empirical (AM1, PM3), molecular mechanics (MM2), DFT (B3LYP2) and ab initio (HF), the last two with the extended basis 6–31G**. The comparison to "experimental" data uses an X-ray hypothetical structure whose bond lengths are the mean values given in Table 8. This is due to the fact that we do not have here a real reference structure; that of hydrated caffeine is of poor quality (**123**). As can be seen, the best results are obtained for ab initio and DFT methods. But the MM2 calculations with our parameters come just after and remain better than those performed with AM1 and PM3. This conclusion remains valid if one considers as reference the ab initio structure (column 6 of Table 9) instead of the "mean X-ray structure" which has no physical reality and could be inconsistent.

The reference structure ambiguity disappears if one turns to isocaffeine (Fig. 11) for which there is an X-ray

Table 8 Comparison of experimental bond lengths of the caffeine moiety within six solid-state structures. Each bond is designated by the atom numbers of Fig. 11

Compound	**119**	**122**	**124**	**125**	**126**	**128**	Mean value	Minimum	Maximum
R factor	0.046	0.053	0.077	0.055	0.063	0.050			
H located?	Yes	Yes	Yes[a]	Yes	Yes	Yes			
Bond length									
1–9	1.4100	1.3935	1.3898	1.3765	1.4025	1.3803	1.3921	1.3765	1.4100
1–10	1.3687	1.3781	1.3857	1.3588	1.3767	1.3730	1.3735	1.3588	1.3857
1–13	1.2301	1.2142	1.2079	1.2272	1.2338	1.2280	1.2235	1.2079	1.2338
2–3	1.3805	1.3644	1.3528	1.3462	1.3547	1.3702	1.3615	1.3462	1.3805
2–10	1.3669	1.3698	1.3677	1.3720	1.3837	1.3791	1.3734	1.3669	1.3837
2–12	1.3552	1.3615	1.3577	1.3474	1.3577	1.3388	1.3531	1.3388	1.3615
3–4	1.4102	1.4211	1.4333	1.4058	1.4266	1.3984	1.4159	1.4058	1.4333
3–11	1.3851	1.3811	1.3831	1.3628	1.3921	1.3794	1.3806	1.3628	1.3921
4–9	1.3897	1.4032	1.4072	1.3917	1.4132	1.4095	1.4024	1.3897	1.4132
4–14	1.2276	1.2237	1.2027	1.2363	1.2170	1.2350	1.2237	1.2027	1.2363
5–11	1.3547	1.3388	1.3354	1.3355	1.3307	1.3645	1.3433	1.3307	1.3645
5–12	1.3486	1.3391	1.3375	1.3277	1.3452	1.3629	1.3435	1.3277	1.3629
6–9	1.4884	1.4728	1.4760	1.4692	1.4935	1.4758	1.4793	1.4692	1.4935
7–10	1.4868	1.4594	1.4731	1.4661	1.4694	1.4650	1.4700	1.4594	1.4868
8–11	1.4859	1.4647	1.4644	1.4513	1.4669	1.4516	1.4641	1.4513	1.4859

[a] Two hydrogens poorly located

Table 9 Comparison of the calculated bond lengths of the caffeine molecule with the "experimental" ones (see text). Each bond is designated by the atom numbers of Fig. 11

Bond	Calculated bond lengths (Å)					Difference from X-ray ("mean structure") (Å)				
	AM1	PM3	MM2	B3LYP2[a]	HF [a]	Δ AM1	Δ PM3	Δ MM2	Δ B3LYP2[a]	Δ HF [a]
1–9	1.4200	1.4460	1.4051	1.4070	1.3910	0.0279	0.0539	0.0130	0.0149	−0.0011
1–10	1.4160	1.4420	1.3942	1.3910	1.3720	0.0425	0.0685	0.0207	0.0175	−0.0015
1–13	1.2510	1.2240	1.2423	1.2230	1.1990	0.0275	0.0005	0.0188	−0.0005	−0.0245
2–3	1.4340	1.4000	1.3910	1.3820	1.3570	0.0725	0.0385	0.0295	0.0205	−0.0045
2–10	1.3860	1.4140	1.3966	1.3760	1.3690	0.0126	0.0406	0.0232	0.0026	−0.0044
2–12	1.4040	1.3910	1.3639	1.3600	1.3460	0.0509	0.0379	0.0108	0.0069	−0.0071
3–4	1.4510	1.4520	1.4325	1.4330	1.4330	0.0351	0.0361	0.0166	0.0171	0.0017
3–11	1.3990	1.4120	1.3861	1.3870	1.3830	0.0184	0.0314	0.0055	0.0064	−0.0024
4–9	1.4110	1.4420	1.4390	1.4190	1.3950	0.0086	0.0396	0.0366	0.0166	−0.0 74
4–14	1.2450	1.2220	1.2290	1.2280	1.2020	0.0213	−0.0017	0.0053	0.0043	−0.0217
5–11	1.3940	1.3870	1.3422	1.3560	1.3290	0.0507	0.0437	−0.0011	0.0127	−0.0143
5–12	1.3610	1.3590	1.3383	1.3300	1.3090	0.0175	0.0155	−0.0052	−0.0125	−0.0335
6–9	1.4450	1.4830	1.4663	1.4660	1.4640	−0.0343	0.0037	−0.0130	−0.0133	−0.0153
7–10	1.4390	1.4770	1.4593	1.4620	1.4580	−0.0310	0.0070	−0.0107	−0.0080	−0.0120
8–11	1.4270	1.4620	1.4482	1.4570	1.4520	−0.0371	−0.0021	−0.0159	−0.0071	−0.0121
Sum of unsigned deviations (Å)						0.4879	0.4207	0.2259	0.1609	0.1789
Mean deviation						0.0325	0.0280	0.0151	0.0107	0.0119
Minimum deviation						0.0086	0.0005	0.0011	0.0005	0.0011
Maximum deviation						0.0725	0.0685	0.0366	0.0205	0.0335

[a] 6–31G**

Table 10 Comparison of the calculated bond lengths of the isocaffeine molecule with the "experimental" ones (see text). Each bond is designated by the atom numbers of Fig. 11

Bond	Bond lengths (Å)					Difference from X-ray (Å)			
	X-ray	AM1	PM3	MM2	HF 6–31G**	AM1	PM3	MM2	HF 6–31G**
1–19	1.4710	1.4450	1.4830	1.4666	1.4650	−0.0260	0.0120	−0.0044	−0.0060
2–19	1.3880	1.4090	1.4350	1.4031	1.3770	0.0210	0.0470	0.0151	−0.0110
2–20	1.3820	1.4270	1.4560	1.3980	1.3870	0.0450	0.0740	0.0160	0.0050
2–23	1.2150	1.2510	1.2230	1.2440	1.2000	0.0360	0.0080	0.0290	−0.0150
3–20	1.4640	1.4360	1.4800	1.4613	1.4570	−0.0280	0.0160	−0.0027	−0.0070
4–5	1.3660	1.4350	1.3970	1.3817	1.3560	0.0690	0.0310	0.0157	−0.0100
4–20	1.3740	1.3850	1.4260	1.4356	1.3750	0.0110	0.0520	0.0616	0.0010
4–22	1.3650	1.4000	1.4060	1.3972	1.3600	0.0350	0.0410	0.0322	−0.0050
5–6	1.4170	1.4560	1.4600	1.4738	1.4450	0.0390	0.0430	0.0568	0.0280
5–21	1.3840	1.3970	1.3960	1.3598	1.3730	0.0130	0.0120	−0.0242	−0.0110
6–19	1.4080	1.4210	1.4550	1.4614	1.4070	0.0130	0.0470	0.0534	−0.0010
6–24	1.2240	1.2390	1.2150	1.1953	1.1930	0.0150	−0.0090	−0.0287	−0.0310
7–21	1.2990	1.3420	1.3380	1.3155	1.2740	0.0430	0.0390	0.0165	−0.0250
7–22	1.3760	1.4220	1.4140	1.3634	1.3800	0.0460	0.0380	−0.0126	0.0040
8–22	1.4600	1.4240	1.4630	1.4502	1.4530	−0.0360	0.0030	−0.0098	−0.0070
Sum of unsigned deviations (Å)						0.4760	0.4720	0.3787	0.1670
Mean deviation						0.0317	0.0315	0.0252	0.0111
Minimum deviation						0.0110	0.0030	0.0027	0.0010
Maximum deviation						0.0690	0.0740	0.0616	0.0310

structure of the free molecule (**129**). Examination of Table 10 leads to the same conclusion.

Conclusion

Finally, even if the parameters we propose here for the C(44)=O(7), C(44)-O(41), C(44)-N(40) and C(44)-C(2) bonds, when the cross-conjugation is taken into account in heterocyclic molecules, do not lead to simulations as good as expected, they do provide an improvement statistically. Part of the discrepancy is due to the solid-state origin of the experimental data (but how could one proceed otherwise?) and part is also probably due to the π-quantum method. Nevertheless, there is no reason to reject the MM2 method. One must just be aware that, in some cases, for heterocyclic rings, the "errors" can concentrate on one bond.

Technical considerations

As mentioned earlier, handling a large number of molecules required the use of several utility programs in C-shell or Fortran for Unix systems. They will be published elsewhere. The MM2 source-code was modified as previously described [1]. Quantum calculations were performed on an SGI Origin 2000 by use of GAUSSIAN-94 [7].

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