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84. The Optical Activity of the Amide Chromophore, I.
MO-Theoretical Calculation of the Long-Wavelength
Optical Activity of γ-Lactams and of Related Isoelectronic Molecules

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(28. I. 75)

Summary. The rotational strength of the longest-wavelength electronic transition in some simple γ-lactams and some related isoelectronic molecules is calculated using the CNDO-CI method. Qualitative agreement with experimental values is obtained. In all investigated systems the long-wavelength transition corresponds to the $n\pi^*$ transition. A quadrant rule seems to hold for this transition.

I. Introduction. – The amide chromophore is of particular interest, as it is the smallest subunit from which the chiroptic properties of polypeptides and proteins may be interpreted. For some general reviews see ref [1–3]. *Litman & Schellman* [4] appear to have been the first to measure the $n \to \pi^*$ *Cotton* effect in a simple amide.

The optical activity due to the corresponding n → π* band in polypeptides and proteins had already been observed and described [5] [6].

Substituted pyrrolidones are the simplest easily accessible model compounds which are both experimentally and theoretically well suited for an investigation of the optical activity of the amide chromophore. The five-membered ring gives these molecules a certain rigidity, so that it seems justified to consider merely a single predominant conformation for a given molecule.

If, in order to interpret the n → π* *Cotton* effect, one considers the molecule as being composed of a symmetric chromophore perturbed by an unpolarizable asymmetric environment, the 'one-electron theory' of optical activity should be applicable [7]. As the isolated amide chromophore itself has symmetry C_s, one would expect a planar sector rule to hold [8]. However, as pointed out previously [4] [6], it is rather a quadrant rule which is valid, leading to the idea of an effective C_{2v}-symmetry of the chromophore with regard to the n → π* transition.

With modern computer facilities all-valence MO calculations of relatively large molecules can be effected, at least within the frame of semi-empirical approximations. The molecule in question is then no longer considered as a symmetric chromophore with perturbing substituent(s), but rather as inherently dissymmetric. This approach, differing from that mentioned above, may conceivably give added insight into the mechanisms determining the sign and absolute value of *Cotton* effects. Besides considering γ-lactams we have, for the sake of comparison, also performed calculations on homoserine-γ-lactone and on 3-methyl-cyclopentanone. All compounds chosen for investigation were isoelectronic.

The aim of our investigation was twofold: Firstly we sought to further test the applicability of different MO procedures to medium-sized molecules [9] [10], in the hope of deriving some practical rules from them [11]. Secondly, the present study was envisaged as a point of departure for the calculation of chiroptic properties of polypeptides within the frame of MO theory, as outlined by us previously [12]. For this reason we chose the CNDO-SCF-CI procedure, which is the simplest computational method taking into account all valence electrons and explicitly electron interaction.

Some computed results on the n → π* *Cotton* effects of γ-lactams have been already published by us, but with little detailed comment [3]. Since completing the present study we have become aware of a recent publication by *Richardson et al.* [13] who have used the INDO method for computing the optical activity of some of the compounds considered here; consequently we shall also compare our results with theirs.

In the experimental part we report the measured CD. spectrum of (−)-4-hydroxy-2-pyrrolidone, recently isolated and put at our disposal by *Eugster et al.* [14].

2. Calculations. – The semi-empirical all-valence electron SCF-CI wave functions are calculated by the CNDO method [15] (for CI calculations see *e.g.* [16]). The CNDO-CI program was written by *Kuhn* [17]. The CI calculation includes the 120 energetically lowest-lying singly excited configurations. Our parametrization is described in the appendix.

The rotational strength of the transition from the ground state to the j-th excited state, R_{oj}, is calculated according to the procedure developed by *Hug & Wagnière* [9] [18]. Using real wave functions and expressing the matrix elements of the electric and magnetic dipole operator in atomic units and the energy ΔE_j in eV, R_{oj} in cgs units can be written as

$$R_{oj} = -6.41 \times 10^{-37} \langle o | \vec{\nabla} | j \rangle \cdot \langle j | \vec{r} \times \vec{\nabla} | o \rangle / \Delta E_j \qquad (1)$$

$$\Delta E_j = E_j - E_o$$

where the electric dipole operator is used in the gradient form. The evaluation of the integrals in (1) is described in former papers [9] [18]. All interatomic terms are included. The CNDO-MO coefficients are transferred to the computation of the optical activity without any transformation. Our test calculations have shown that the so-called 'deorthogonalization' or '*Löwdin* transformation' of the CNDO-MO's [18] [19] does not essentially affect the computed rotational strengths. Concerning the rotational strengths including mixing of singly excited configurations, the computed results show clearly that the highly excited configurations with small CI coefficients have little physical significance for the longest-wavelength transitions. Therefore only all the singly excited configurations with CI coefficients greater than 0.1 are taken into account explicitly for a given excited state. The wavefunctions are renormalized accordingly.
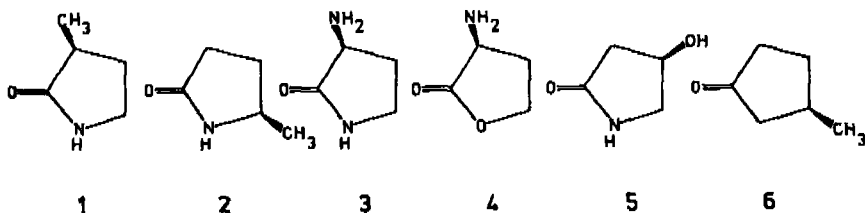
The geometrical parameters of the molecules to be treated [*S*-3-methyl-2-pyrrolidone (**1**), L-5-methyl-2-pyrrolidone (**2**), L-3-amino-2-pyrrolidone (**3**), L-homoserine-γ-lactone (**4**), (−)-4-hydroxy-2-pyrrolidone (**5**), (+)-3-methyl-cyclopentanone (**6**)] were determined according to known experimental data [20] [21] and generally accepted facts (*e.g.* a staggered conformation is more stable than an eclipsed one). The five-membered rings of the pyrrolidones and of L-homoserine-γ-lactone are assumed to be planar for two reasons:

i) There are two sp^2-centers in the ring with tendency to valence angles much greater than 108° (the average value in a planar pentagon). It follows from geometrical considerations that increasing one or two ring angle(s) favors a flattening of the ring.

ii) From X-ray analysis and CD. spectra of two 5-substituted pyrrolidones (L-5-iodomethyl-2-pyrrolidone and L-2-pyrrolidone-5-carboxamide, [21]) it may be deduced that the sign of the rotational strength of the amide $n \rightarrow \pi^*$ transition in these asymmetrically substituted γ-lactams depends on the peripheral molecular asymmetry and not on the skeletal geometry, since both lactams have the same ring chirality in the solid state but have large and oppositely signed rotational strengths

in solution. Probably, the ring chirality in the solid state (due to a slight non-planarity of the ring) disappears in solution owing to a certain flexibility of the molecule.

It is known that cyclopentanone has a puckered ring [22]. This is quite plausible because there is only one sp^2-center within the ring. Consequently, the present calculations have been performed on both the planar and the non-planar form of (+)-3-methyl-cyclopentanone.
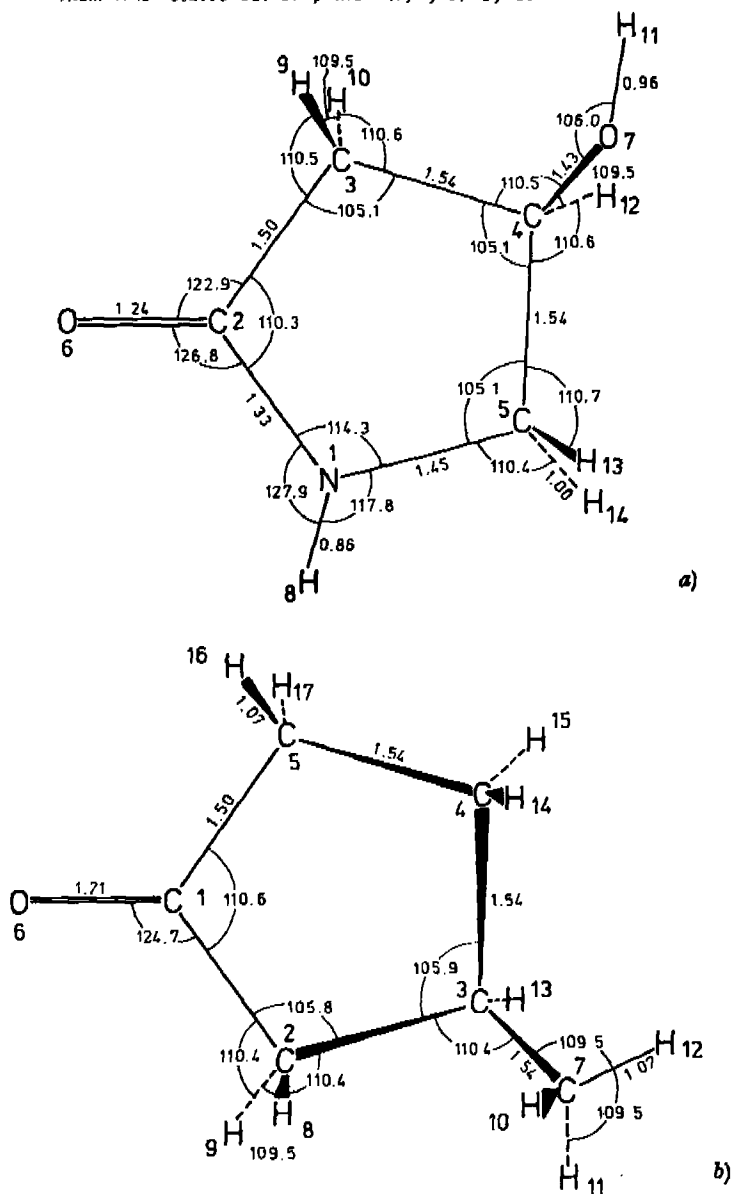

Fig. 1. *Geometrical parameters of a)* (−)-*4-hydroxy-2-pyrrolidone* (*planar*) *and b*) (+)-*3-methyl cyclopentanone* (*puckered*). Bond lengths are in Å, valence angles in degrees

Table 1. *Cartesian atomic coordinates (in Å) of (−)-4-hydroxy-2-pyrrolidone and (+)-3-methyl-cyclopentanone corresponding to the geometrical parameters in Fig. 1*

(−)-4-Hydroxy-2-pyrrolidone (planar ring)					(+)-3-Methyl-cyclopentanone (puckered ring)			
Atom	x	y	z		Atom	x	y	z
1	0.794	−1.061	0.0		1	0.0	0.0	0.0
2	0.0	0.0	0.0		2	0.853	−1.234	0.0
3	0.812	1.260	0.0		3	2.300	−0.744	−0.198
4	2.279	0.791	0.0		4	2.300	0.744	0.198
5	2.209	−0.747	0.0		5	0.853	1.234	0.0
6	−1.240	0.0	0.0		6	−1.210	0.0	0.0
7	2.957	1.263	1.168		7	3.263	−1.539	0.703
8	0.567	−1.890	0.0		8	0.760	−1.751	0.932
9	0.618	1.803	0.816		9	0.568	−1.884	−0.800
10	0.618	1.803	−0.816		10	2.969	−1.426	1.726
11	3.076	2.207	1.041		11	3.230	−2.574	0.435
12	2.753	1.121	−0.816		12	4.259	−1.168	0.576
13	2.651	−1.119	0.816		13	2.549	−0.857	−1.221
14	2.651	−1.119	−0.816		14	2.594	0.857	1.221
					15	2.969	1.296	−0.428
					16	0.568	1.884	0.800
					17	0.760	1.751	−0.932
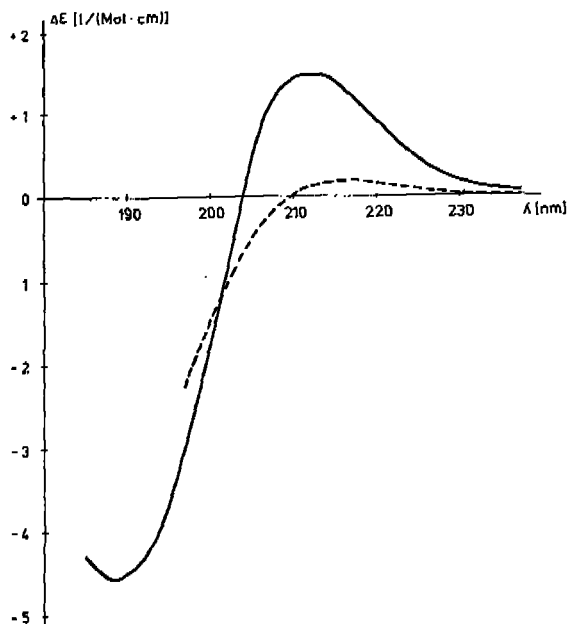
Fig. 2. *CD. spectra of* 5. 1.00×10^{-3} mol/l in water (————); 0.99×10^{-3} mol/l in ethanol (— — — —)

The computation of cartesian atomic coordinates from bond lengths, valence angles and dihedral angles was performed with one of the customary coordinate programs[1]). The redundant internal coordinates of the puckered cyclopentanone

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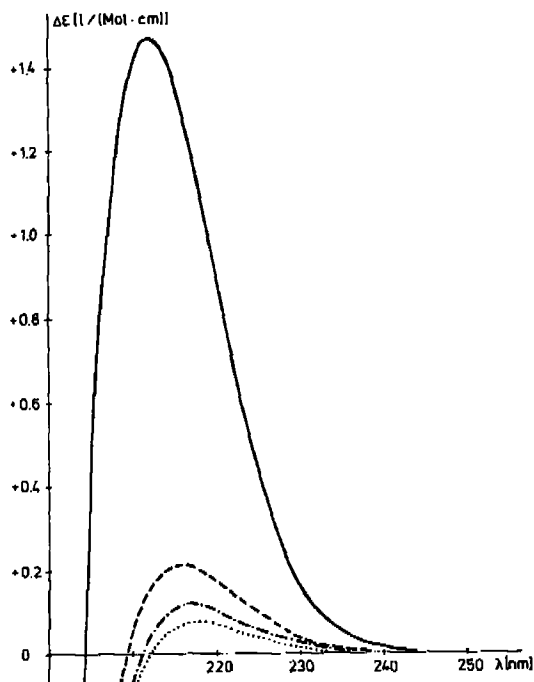[1]) Program COORD, *M. J. S. Dewar*, Quantum Chemistry Program Exchange, No. 136.

Fig. 3. *CD. spectra of the longest wavelength band of* **5.** 1.00×10^{-3} mol/l in water (————); 0.99×10^{-3} mol/l in ethanol (– ·····–); 0.56×10^{-3} mol/l in hexane/ethanol $(v/v\ 1:1)$ (–·–·–); 0.69×10^{-3} mol/l in hexane/ethanol $(v/v\ 5:1)$ (·····)
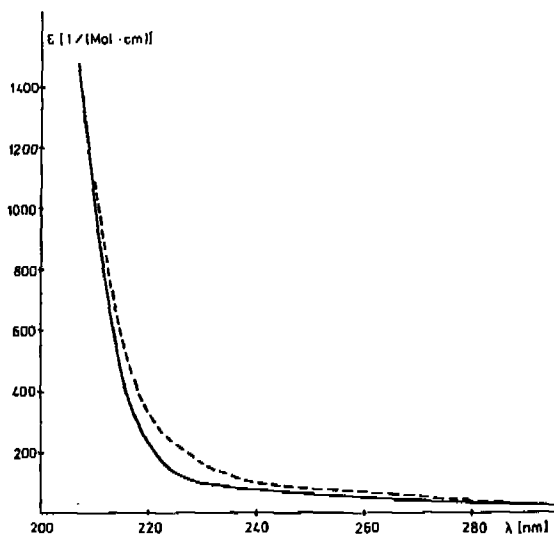
Fig. 4. *UV. spectra of* **5.** 1.00×10^{-3} mol/l in water (————); 0.99×10^{-3} mol/l in ethanol (–––––)

ring have been determined by means of an iterative program written according to an algorithm by *Vitek* [23].

As an example the geometrical parameters and pertinent atomic coordinates of (–)-4-hydroxy-2-pyrrolidone (planar) and (+)-3-methyl-cyclopentanone (puckered)

are given in Fig. 1 and Table 1 respectively (see pp. 741–742). The coordinates of the other molecules have been determined analogously [24].

3. (–)-4-Hydroxy-2-pyrrolidone (5). – *Experimental data.* Compound **5** furnished by Prof. *Eugster* had been isolated from the fungus *Amanita muscaria* [14]. Fig. 2–4 (see pp. 742–743) show the CD. and UV. spectra of **5** in different solvents[a]).
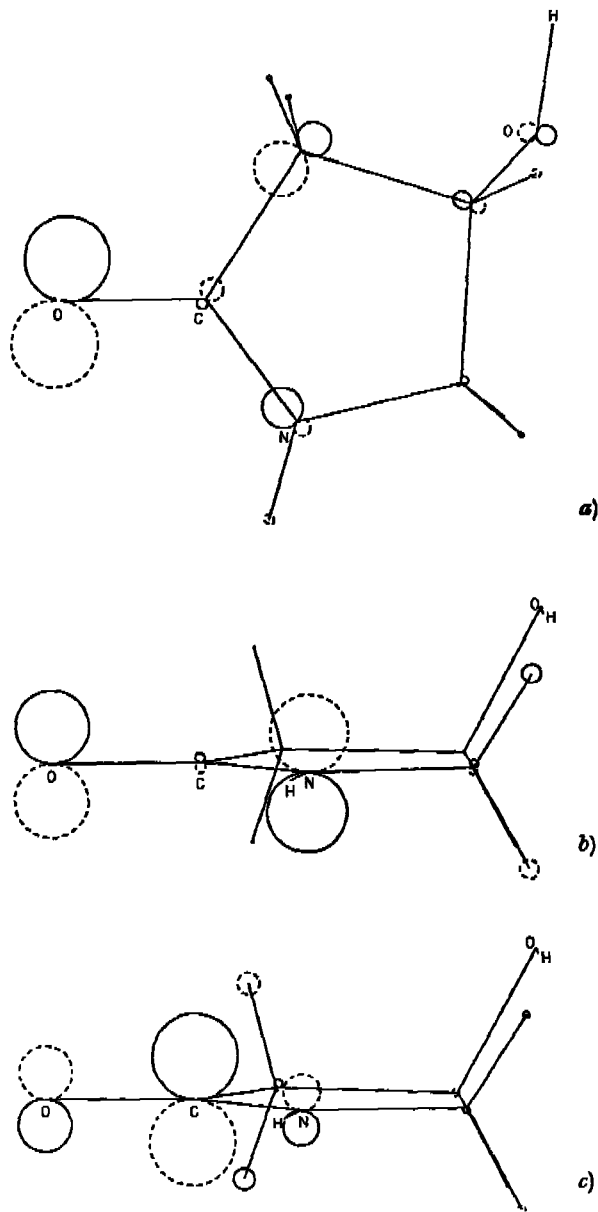

Fig. 5. n, π, and π* MO's of (–)-4-hydroxy-2-pyrrolidone obtained by CNDO calculation[a])

The remarkable enhancement of the long-wavelength *Cotton* effect (nπ*) in water might originate from a hindered rotation of the hydroxyl group due to a 'hydrogen bond skeleton' of solvent molecules.

Computed results together with experimental data are summarized in Table 2.

Fig. 5 is a pictorial representation of the typical amide MO's resulting from the CNDO calculation.

Table 2. *Summary of calculated and experimental transition energies and rotational strengths of the nπ* transition of some substituted 2-pyrrolidones and related isoelectronic systems*

Molecule	Calculated				Experimental		
	transition energy [eV]		rotational strengths [cgs × 10^{-40}]		transition energy [eV]	rotational strengths [cgs × 10^{-40}]	reference
	CI not included	CI included	CI not included	CI included			
1	6.0	4.7	+24	+42	5.4–5.9	+6.1	[25]
2	6.4	4.8	+26	− 6	5.6–6.0	−6.5	[2]
3	5.7	4.6	+22	+34	5.4–5.7	+4	[26]
4	5.5	4.3	+ 9.0	+ 6.4	5.5	+7	[2]
5	5.1	4.8	+18	+18	5.6–5.9	+3	
6 (planar)	4.2	3.8	+ 4	+ 2 }	4.4	+5	[2]
6 (puckered)	4.5	3.8	+56	+14 }			

The absolute configuration of **1**. *Greenfield & Fasman* [25], based on [27], assign the *R* configuration to (+)-**1**. This is not supported by our calculation (see also [13]). By a private communication *Fleš* has subsequently informed us that the *R* configuration mentioned in [27a] and [25] is in error, and that the correct absolute configuration is indeed *S* [27b].

4. Discussion. – All calculated longest-wavelength transitions in compounds **1** to **6** are of nπ* type; with our parametrization, however, the nπ* energies are rather low.

All rotational strengths that have been calculated, including configuration interaction, agree with experimental values with regard to sign. In all compounds except L-5-methyl-2-pyrrolidone agreement is achieved already without CI. The INDO results of *Richardson et al.* [13] are similar to ours.

L-Homoserine-γ-lactone and L-3-amino-2-pyrrolidone (which have the same absolute configuration) both have a positive nπ* *Cotton* effect. Therefore lactones do not generally have a longest-wavelength *Cotton* effect opposite to that of lactams with the same configuration, as *Urry* [2] supposed. On the other hand our results are not contradictory to the statement by *Klyne & Scopes* [29] that the CD. maxima of the 220 nm bands in lactams and lactones have opposite signs in rigid ring compounds (*e.g.* in steroids), but have the same sign in flexible ring compounds.

In agreement with experiment the calculated nπ* rotational strength of the (*R*)-enantiomer of methyl-cyclopentanone (**6**) is positive. Therefore our theoretical

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results also confirm the 'anti-octant' (or 'anti-quadrant') behaviour of this molecule [4] [30].

It follows from Table 2 that all our compounds except 3-methyl-cyclopentanone obey *Schellman*'s quadrant rule on the sign of the $n\pi^*$ *Cotton* effect of amides [4]. This indeed confirms that the optical activity of this transition primarily results from the perturbation of the chromophore by the substituent and not by a deformation of the ring (methyl-cyclopentanone probably behaves differently in this respect).

In interpreting computed values of rotational strengths it is important to take into account the angle between the electric and the magnetic transition moment. If it is near 90° the results must be used with particular caution as a very small variation of the wave function may immediately reverse the sign of the transition.

To sum up, the agreement between calculation and experiment is qualitatively satisfactory. Whether the results can be quantitatively improved, by variation of the empirical parameter, remains questionable. In any case it is essential that a certain set of parameters should be applicable to as many molecules as possible, for the method to become a useful tool in structural chemistry.

Appendix. – The parametrization of the CNDO calculation [17].

The matrix elements of the *Hartree-Fock* matrix in the basis of s and p atomic orbitals (AO's) are calculated as follows:

$$F_{\mu\mu} = U_{\mu\mu} + \left(P_{AA} - \frac{1}{2} P_{\mu\mu}\right) \gamma_{AA} + \sum_{B \neq A} (P_{BB} - Z_B) \gamma_{AB}$$

(AO μ on atom A) Z_B: core charge of atom B

$$F_{\mu\nu} = -\frac{1}{2} P_{\mu\nu} \cdot \gamma_{AA}$$

(AO's μ and ν on Atom A, $\mu \neq \nu$)

$$F_{\mu\nu} = \beta_{AB} \cdot S_{\mu\nu} - \frac{1}{2} P_{\mu\nu} \cdot \gamma_{AB}$$

(AO μ on atom A, AO ν on atom B)

$$P_{AA} = \sum_{\mu} P_{\mu\mu}; \quad P_{\mu\nu} = 2 \sum_{j=1}^{occ} c_{j\mu} c_{j\nu}^*$$
(on atom A)

($c_{j\mu}$ is the coefficient of AO μ in MO j)

$$\beta_{AB} = \frac{\beta'_A + \beta'_B}{2 R_{AB}} \quad ; \quad R_{AB}: \text{distance between A and B}$$

$$\gamma_{AB} = \gamma_{AB}^{th} - \alpha \cdot \exp(-\eta R_{AB}^n); \quad n = 1.80$$

$$\eta = 0.71 \text{ Å}^{-n} = 0.226 \text{ au}^{-n}$$

γ_{AB}^{th} is the coulomb integral evaluated directly from the basis functions (*i.e. Slater* type atomic orbitals), α is the difference between the theoretical and the empirical one-center coulomb integral (if A and B are atoms of different kind, the arithmetic mean of the empirical integrals is taken).

Table 3. *Empirical CNDO parameters* [17]

Atom	*Slater* exponent	U_{ss} [eV]	U_{pp} [eV]	γ_{AA} [eV]	β'_A [eV-Å]
H	1.200	− 13.595	--	12.848	− 12.959
C	1.625	− 50.586	− 41.530	10.333	− 17.551
N	1.950	− 70.093	− 57.848	11.308	− 21.060
O	2.275	− 101.306	− 84.284	13.907	− 24.568
F	2.600	− 129.544	− 108.933	15.233	− 28.081

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