

STERIC EFFECTS IN ORGANIC REACTIONS.

III¹⁾ THEORETICAL CONSIDERATIONS, APPLICATION,
FORTRAN PROGRAM.I. Motoc^{a)}, I. Cotăescu^{b)} and R. Vancea^{a)}a) Chemistry Research Centre
B-dul M. Viteazul 24
1900 Timișoara, Romaniab) University of Timișoara
Department of Physics
B-dul V. Pârvan 4
1900 Timișoara, Romania

(Received: March 5, 1982)

Abstract. The Overlapping Volumes Analysis (OVA) method was developed as an alternative to the Taft-type approaches for describing steric effects in organic reactions. OVA provides the steric parameter OV (i.e. Overlapping Volumes, in Å³) which accounts quantitatively for the steric effects in the framework of the linear free-energy relationships. OVA takes into account explicitly the conformation of the reaction partners and the reaction coordinate. The paper presents the theoretical basis of OVA and an application with good results on the demethylation of N-methylpyridinium salts under the influence of triphenylphosphine. Finally, the algorithm (ALGOL) and the complete listing (FORTRAN IV) of the OVA-VAWAV program, which computes the OV values and van der Waals volumes, are also given.

1. Introduction

The OVA (i.e., Overlapping Volumes Analysis) method¹ was developed in order to account quantitatively for the steric effects in the framework of the linear free-energy relationships (LFER). The aim of the OVA method is to avoid the known deficiencies of the Taft-type approaches (i.e.,

¹⁾For the preceding part see ref. 11.

E_S , E_S^c , E_S^o , E_S^e , E_S^i and ρ - see refs. (2) - (7), respectively). Three such deficiencies are: i) they apply⁸ in cases where conformational changes in the parent structure are not important; ii) the values of the E_S - type steric constants depend on the transition state geometry in the standard reaction series⁹; iii) E_S - type constants have no clear physical meaning¹⁰.

2. The OVA Method

In principle, OVA implies the use of the steric parameter OV (i.e., Overlapping Volumes, $\overset{0}{A}^3$) which signifies the overlapping volume of the van der Waals envelopes of the reaction partners in the transition state.

The reaction partners are characterized by the Cartesian coordinates (X, Y, Z) and van der Waals radii (R) of their atoms. In this way, the computed OV values depend explicitly on the reaction coordinate and the conformation of the chemical species involved in the transition state.

The steric effects are conditioning the property Q measured for a reaction series (i.e., N chemically reactive species which undergo the same chemical reaction via the same mechanism) according to the equation (1):

$$Q_I = a + b \text{OV}_I(d_0) \quad (1)$$

where d_0 is the appropriate position of the transition state on the reaction coordinate. I indexes the compounds of the considered reaction series and the constants a and b are computed by the least squares method.

Because the electronic parameters used in LFER, namely σ -Hammett type (denoted here collectively by σ) do not

depend on the reaction coordinate d , i.e., $\partial\sigma/\partial d = 0$, we developed¹¹ the following strategy to determine the d_0 value : one computes m sets of $OV_I(d)$ values, $I = 1, 2, \dots, N$, corresponding to $d = d_1, d_2, \dots, d_m$. Then, one computes the m equations of type (1), and finally one selects the best equation according to the correlation coefficient. The d value of this equation is designed d_0 .

OVA may take into account explicitly the conformational flexibility as follows : the different conformers are calculated from the OVA point of view and then weighted according to the conformers population.

2.1. Computing Method

The OV values are computed¹¹ by means of the Monte Carlo techniques^{12,13}.

The OV values are given the equation :

$$OV = \mathcal{C} \text{ card } W_2 / \text{card } W_1 \quad (2)$$

where \mathcal{C} stands for the volume of the parallelepiped which circumscribes the van der Waals envelopes of the chemical species involved in the transition state. W_2 is the set of the uniform random Points which lie within the overlapping volume of the van de Waals envelopes, and W_1 is the set of the uniform random points generated within the parallelepiped of volume \mathcal{C} . Card denotes the cardinal (obviously, $\text{card } W_1 > \text{card } W_2$).

The random points (w_x, w_y, w_z) generated within the parallelepiped of volume \mathcal{C} (i.e., the W_1 set) are obtained according to the relations :

$$\begin{aligned} w_X &= a + (d - a)\zeta_1 \\ w_Y &= a + (b - a)\zeta_2 \\ w_Z &= a + (c - a)\zeta_3 \end{aligned} \quad (3)$$

where $(d - a)$, $(b - a)$ and $(c - a)$ are the lengths of the parallelepiped edges (obviously, $(b-a)(c-a)(d-a) = \mathcal{C}$). ζ_1 , ζ_2 and ζ_3 are three consecutive uniform random numbers belonging to the interval $(0,1)$ and are obtained according to Lehmer algorithm¹³.

The set W_2 is obtained by selecting the points (w_X, w_Y, w_Z) belonging to W_1 which satisfy at least one of the systems of inequations :

$$\begin{aligned} (X_{AJ} - w_X)^2 + (Y_{AJ} - w_Y)^2 + (Z_{AJ} - w_Z)^2 &< R_{AJ}^2 \\ (X_{BJ} - w_X)^2 + (Y_{BJ} - w_Y)^2 + (Z_{BJ} - w_Z)^2 &< R_{BJ}^2 \end{aligned} \quad (4)$$

where A and B ($A \neq B$) index the chemical species involved in the transition state, and J and I index the atoms of the species A and B, respectively.

Because the error in Monte Carlo computations is proportional to $(\text{card } W_1)^{-1/2}$, one achieves by trial and error a satisfying accuracy for $\text{card } W_1 = 10^5 - 10^6$.

2.2. Theoretical Basis

Consider the interaction between a molecule and an atom with the quantum number n within the following simple model: (i) the molecule is represented as a rectangular potential barrier, with the potential $\zeta = 0$ outside the van der Waals surface, and $\zeta = \zeta_0 = \text{constant}$ inside the van der Waals surface ; (ii) in the neighbourhood of the considered atom, the van der Waals surface of the molecule is considered a planar

one.

The mean potential, $\mathcal{V}(\vec{r})$, of the molecule is given by :

$$\mathcal{V}(\vec{r}) = \mathcal{V}_0 \Theta(z-a) \quad (5)$$

where a is the distance between the atom and the molecule and z is a reference point. Because \mathcal{V}_0 is small, the potential (5) is viewed as a perturbation. The corrections to the energy E_n , denoted by δE_n , are given by the equation :

$$\delta E_n = -Ze \mathcal{V}_0 \int |\Psi_{n0c}|^2 \Theta(z-a) d^3x \quad (6)$$

where Z stands for the atomic number and Ψ_{n0c} is the wave function of the atom. In polar coordinates, equation (6) becomes :

$$\delta E_n = -\frac{Ze \mathcal{V}_0}{2} \int_a^\infty |R_{n0}|^2 (1-a/r) r^2 dr \quad (7)$$

where R_{n0} is the radial part of the wave function.

Supposing that a is less than Bohr radius, one gets :

$$\begin{aligned} \delta E_n &= -\frac{Ze \mathcal{V}_0}{2} \int_a^\infty |R_{n0}|^2 (1-a/r) r^2 dr = \\ &= -\frac{Ze \mathcal{V}_0}{2} (1 - a \langle n|r^{-1}|n \rangle) \end{aligned} \quad (8)$$

Because

$$\langle n|r^{-1}|n \rangle = \frac{3}{2} (\langle n|r|n \rangle)^{-1} = (3/2)(1/r_w) \quad (9)$$

where $\langle n|r|n \rangle$ is van der Waals radius r_w of the considered atom, equation (8) becomes :

$$\delta E_n = (-Ze \mathcal{V}_0 / 2) (1 - (3/2)(a/r_w)) \quad (10)$$

Observe that the overlapping van der Waals volume, OV , between the atom and molecule is given by the volume of the spherical calotte with the radius r_w and heigh $(r_w - a)$, na-

mely

$$OV = \frac{V}{2} \left[1 - \frac{3}{2} \frac{a}{r_w} + \left(\frac{a}{r_w} \right)^3 \right] \approx \frac{V}{2} \left(1 - \frac{3}{2} \left(1 - \frac{3}{2} \frac{a}{r_w} \right) \right) \quad (11)$$

and equation (10) becomes :

$$\delta E_n = - \frac{Ze \zeta_0}{V} OV \quad (12)$$

where V stands for the van der Waals volume of the atom. Because $\zeta_0 < 0$ (ζ_0 is produced by an electronic cloud), δE_n corresponds to the steric repulsion energy between the considered atom and molecule.

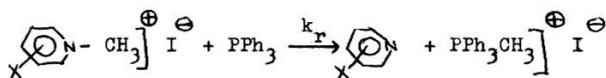
For a reaction series equation (12) may be extrapolated as :

$$\delta E = \text{constant } OV' \quad (13)$$

where OV' is the overlapping volume of the van der Waals envelopes of the reactant and substrate.

2.3. Applications

For the demethylation reaction of pyridinium salts (150°C, in DMF),



The relative rate constants, k_r , and the studied substituent parameters are collected in Table 1.

The geometry of the transition state considered in OVA computations is depicted in Figure 1

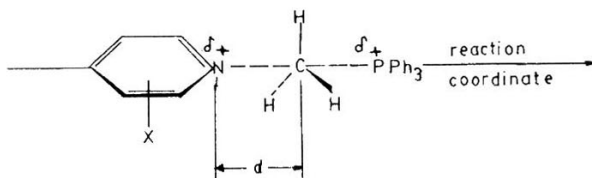


Figure 1. The geometry of the transition state.

The following equations were determined by the procedure described in section 2.1. :

$$\log k_r = 2.378 - 0.352 pK_a - 0.542 E_S \quad (14)$$

$$(r = 0.97, s = 0.20, F = 47.76)$$

$$\log k_r = 1.721 - 0.355 pK_a - 0.574 E_S^e \quad (15)$$

$$(r = 0.96, s = 0.22, F = 38.26)$$

$$\log k_r = 1.622 - 0.336 pK_a + 1.271 \nu \quad (16)$$

$$(r = 0.96, s = 0.23, F = 35.42)$$

$$\log k_r = 1.896 - 0.369 pK_a + 0.540 \text{OV} (2.8) \quad (17)$$

$$(r = 0.96, s = 0.22, F = 38.87)$$

where r , s and F have the usual statistical connotation ; pK_a takes into account the electronic effects of the substituents ; $d_o = 2.8 \text{ \AA}$ leads to the best OVA-type equation.

The statistics corresponding to the equations (14)-(17) argue that these equations compare very well. They show that the bulkier the substituent, the larger will be the increase of k_r . It is interesting to note that the value $d_o = 2.8$ agrees well with ab initio calculations¹⁶ which show that in SN_2 transition state the bond being formed varies between 1.10 to 1.50 times the length of the bond in the stable compound.

Conclusions

i) A method has been presented to treat quantitatively the steric effects in organic reactions. The results from the reactions series studied here suggest that OVA method represents an interesting alternative to the Taft-type approaches of the steric effects. Use of the OVA method yields the

transition state distance (d_0), a valuable, physically meaningful parameter which cannot be obtained in a Taft approach.

- ii) We note that OVA method and the steric congestion function developed¹⁷ by Wipke and Gund belong to the same class of methods. Since the OVA method takes into account any and all reaction partners and any postulated transition-state structure it is to a certain extent superior to the method to the method of Wipke and Gund.

REFERENCES

1. I.Motoc, *Math.Chem.*, 4, 113(1978).
2. R.W.Taft, in "Steric Effects in Organic Reactions", M.S.Newman ed., Wiley, New York, 1956, p. 597.
3. K.Hancock, E.A.Meyers and B.J.Yager, *J.Am.Chem.Soc.*, 83, 4211 (1961).
4. V.A.Palm, "Fundamentals of the Quantitative Theory of Organic Chemistry", Khimiya, Leningrad, 1967, chap. 10(Russian).
5. S.H.Unger and C.Hansch, *Progr.Phys.Org.Chem.*, 12, 91(1976).
6. J.A.MacPhee, A.Panaye and J.E.Dubois, *Tetrahedron*, 3553(1978).
7. M.Charton, *J.Am.Chem.Soc.*, 91, 615 (1969).
8. A.Babadjanian, M.Chanon, R.Gallo and J.Metzger, *J.Am.Chem.Soc.*, 95, 3807 (1973).
9. M.Charton and B.I.Charton, *J.Org.Chem.*, 43, 2383 (1978).
10. I.Motoc, *Arzneim.-Forsch.*, 31, 290 (1981).
11. I.Motoc, R.Vancea and I.Muscutariu, *Math.Chem.*, 5, 263(1979).
12. Yu.A.Schreider, ed., "The Monte Carlo Method", Pergamon, New York 1966, chap. 6.
13. I.M.Sobol, "The Monte Carlo Method", Mir, Moscow, 1975.

TABLE 1. The demethylation reaction of pyridinium salts:
experimental data and parametrization^a.

No.	X	k_r	pK_a	E_S	E_S^e	ν	OV(2.8)	OV(3.0)	OV(3.2)	OV(3.4)
1.	H	1.000	5.19	1.24	0.00	0.00	0.126	0.000	0.000	0.000
2.	3,4-Me	0.255	6.48	1.24	0.00	0.00	0.126	0.000	0.000	0.000
3.	3-NH ₂	0.263	6.04	1.24	0.00	0.00	0.126	0.000	0.000	0.000
4.	3,5-Me ₂	0.279	6.15	1.24	0.00	0.00	0.126	0.000	0.000	0.000
5.	4-Me	0.566	6.00	1.24	0.00	0.00	0.126	0.000	0.000	0.000
6.	3-Me	0.619	5.70	1.24	0.00	0.00	0.126	0.000	0.000	0.000
7.	2-Me	1.000	5.96	0.00	-1.24	0.52	0.337	0.059	0.000	0.000
8.	2-Et	1.490	5.89	-0.07	-1.31	0.56	0.337	0.059	0.000	0.000
9.	2-1-Pr	2.880	5.83	-0.47	-1.71	0.76	0.337	0.059	0.000	0.000
10.	3-Br	9.760	2.85	1.24	0.00	0.00	0.126	0.000	0.000	0.000
11.	3-Cl	6.680	2.81	1.24	0.00	0.00	0.126	0.000	0.000	0.000
12.	2-t-Bu	50.200	5.76	-1.86	-2.78	1.24	3.677	2.447	1.671	1.056
13.	2-Cl	70.400	0.49	0.18	-0.97	0.55	0.282	0.034	0.000	0.000

a) E_S , E_S^e and ν values correspond to the substituents which interact sterically with CH_3 , i.e., the substituents in the position 2 of the ring; pK_a values are taken from ref.(14); k_r values are taken from ref. (15).

14. D.D.Perrin, "Dissociation Constants of Organic Basis in Aqueous Solution", Butterworths, London, 1965.
15. U.Berg, R.Gallo and Z.Metzger, J.Org.Chem., 41, 2621 (1976).
16. N.D.Epiotis et al., "Structural Theory of Organic Chemistry" Springer, Berlin, 1977.
17. W.T.Wipke and P.Gund, J.Am.Chem.Soc., 96, 299 (1974) ; 98, 8107 (1976)

Appendix

The OVA-VAWAV program computes the OV values for M=2 or 4 reaction partners in the transition state (M = 3 may be handled using the routine for M = 4 considering that one partner consists of one atom with atomic van der Waals radius zero) and the van der Waals volumes for molecules, radicals, substituents etc., respectively. The program complete listing is given below.


```
C      IF(M.EQ.4) GO TO 5544
C
      WRITE(100,606)
666  FORMAT(' ERROR FOR INPUT DATA (M=?,N1=?,N2=?)')
      GU TO 2222
C
      *** SECTION OVA n=2 ***
C
4455 READ(105,143) NAME
      READ(105,777) (X1(I),Y1(I),Z1(I),R1(I),I=1,N1),
      *(X2(J),Y2(I),Z2(I),R2(J),J=1,N2)
777  FORMAT(4F8,3)
      WRITE(100,143) NAME
      WRITE(100,888) (X1(I),Y1(I),Z1(I),R1(I),I=1,N1)
888  FORMAT('1',///,10X,'ATOMIC CARTEZIAN COORDINATES',///,
      *' X1 ', ' Y1 ', ' Z1 ', ' R1 ',///,
      X(4F8,3,2X))//
      WRITE(100,889) (X2(I),Y2(I),Z2(I),R2(I),I=1,N2)
889  FORMAT(///, ' X2 ', ' Y2 ', ' Z2 ', ' R2 ',///,
      *(4F8,3,2X))//
C
      XMAX1=MAMI(N1,X1,R1,1)
      XMIN1=MAMI(N1,X1,R1,2)
C
      YMAX1=MAMI(N1,Y1,R1,1)
      YMIN1=MAMI(N1,Y1,R1,2)
C
      ZMIN1=MAMI(N1,Z1,R1,2)
      ZMAX1=MAMI(N1,Z1,R1,1)
C
      XMAX2=MAMI(N2,X2,R2,1)
      XMIN2=MAMI(N2,X2,R2,2)
C
      YMAX2=MAMI(N2,Y2,R2,1)
      YMIN2=MAMI(N2,Y2,R2,2)
C
      ZMAX2=MAMI(N2,Z2,R2,1)
      ZMIN2=MAMI(N2,Z2,R2,2)
C
      XMAX=AMAX1(XMAX1,XMAX2)
      XMIN=AMIN1(XMIN1,XMIN2)
C
      YMAX=AMAX1(YMAX1,YMAX2)
      YMIN=AMIN1(YMIN1,YMIN2)
      ZMAX=AMAX1(ZMAX1,ZMAX2)
      ZMIN=AMIN1(ZMIN1,ZMIN2)
C
      VOL=ABS(XMAX-XMIN)*ABS(YMAX-YMIN)*ABS(ZMAX-ZMIN)
C
      NI=0
      I1=05539
      N=MAX0(N1,N2)
      OVA=0
      DO 40 J=1,NI
C
      CALL MAS
      CALL UNIREL(XMAX,XMIN,S,I1,XX)
      CALL UNIREL(YMAX,YMIN,P,I1,XX)
      CALL UNIREL(ZMAX,ZMIN,Q,I1,XX)
```



```
YMIN1=MAMI (N1,Y1,R1,2)
YMAX2=MAMI (N2,Y2,R2,1)
YMIN2=MAMI (N2,Y2,R2,2)
YMAX3=MAMI (N3,Y3,R3,1)
YMIN3=MAMI (N3,Y3,R3,2)
YMAX4=MAMI (N4,Y4,R4,1)
YMIN4=MAMI (N4,Y4,R4,2)

C
ZMAX1=MAMI (N1,Z1,R1,1)
ZMIN1=MAMI (N1,Z1,R1,2)
ZMAX2=MAMI (N2,Z2,R2,1)
ZMIN2=MAMI (N2,Z2,R2,2)
ZMAX3=MAMI (N3,Z3,R3,1)
ZMIN3=MAMI (N3,Z3,R3,2)
ZMAX4=MAMI (N4,Z4,R4,1)
ZMIN4=MAMI (N4,Z4,R4,2)

C
XMAX=AMAX1 (XMAX1,XMAX2,XMAX3,XMAX4)
YMAX=AMAX1 (YMAX1,YMAX2,YMAX3,YMAX4)
ZMAX=AMAX1 (ZMAX1,ZMAX2,ZMAX3,ZMAX4)

C
XMIN=AMIN1 (XMIN1,XMIN2,XMIN3,XMIN4)
YMIN=AMIN1 (YMIN1,YMIN2,YMIN3,YMIN4)
ZMIN=AMIN1 (ZMIN1,ZMIN2,ZMIN3,ZMIN4)

C
VOL=ABS (XMAX-XMIN)*ABS (YMAX-YMIN)*ABS (ZMAX-ZMIN)

C
NI=0
I1=65539
N=MAX0 (N1,N2,N3,N4)
OV=0
DU 400 J=1,NT

C
CALL MAS
CALL UNIREL (XMAX,XMIN,S,I1,XX)
CALL UNIREL (YMAX,YMIN,P,I1,XX)
CALL UNIREL (ZMAX,ZMIN,Q,I1,XX)
CALL NMAS

C
DU 201 I5=1,N1
IF (((S=X1(I5))**2+(P=Y1(I5))**2+(Q=Z1(I5))**2).GT.
*(R1(I5)**2)) GO TO 201
DU 202 I2=1,N2
IF (((S=X2(I2))**2+(P=Y2(I2))**2+(Q=Z2(I2))**2).GT.
*(R2(I2)**2)) GO TO 202
DU 203 I3=1,N3
IF (((S=X3(I3))**2+(P=Y3(I3))**2+(Q=Z3(I3))**2).GT.
*(R3(I3)**2)) GO TO 203
DU 204 I4=1,N4
IF (((S=X4(I4))**2+(P=Y4(I4))**2+(Q=Z4(I4))**2).GT.
*(R4(I4)**2)) GO TO 204
NI=NI+1
GO TO 400
204 CONTINUE
GO TO 400
203 CONTINUE
GO TO 400
202 CONTINUE
GO TO 400
201 CONTINUE
```

```
400 CONTINUE
C
OV=(DFLOAT(NI)/DFLOAT(NT))*VOL
C
WRITE(108,50) OV
GO TO 1122
C
C
C ***** SECTION VAWAV *****
C
3344 READ(105,143) NAME
READ(105,1) N1
1 FORMAT(I3)
READ(105,2) (X1(I),Y1(I),Z1(I),R1(I),I=1,N1)
2 FORMAT(4F6,2)
WRITE(108,143) NAME
WRITE(108,3) (X1(I),Y1(I),Z1(I),R1(I),I=1,N1)
3 FORMAT('1',////,'ATOMIC CARTEZIAN COORDINATES',////,
*' X1 ', ' Y1 ', ' Z1 ', ' R1 ',//,(4F6,2)/)
C
XMAX=MAMT(N1,X1,R1,1)
XMIN=MAMT(N1,X1,R1,2)
C
YMAX=MAMI(N1,Y1,R1,1)
YMIN=MAMT(N1,Y1,R1,2)
C
ZMAX=MAMI(N1,Z1,R1,1)
ZMIN=MAMT(N1,Z1,R1,2)
C
VOL=ABS(XMAX-XMIN)*ABS(YMAX-YMIN)*ABS(ZMAX-ZMIN)
C
NI=0
I1=65539
N=N1
NV=0
DO 4 J=1,NT
C
CALL MAS
CALL UNIREL(XMAX,XMIN,S,T1,XX)
CALL UNIREL(YMAX,YMIN,P,I1,XX)
CALL UNIREL(ZMAX,ZMIN,Q,I1,XX)
CALL NMAS
C
DO 6 I=1,N
IF(((S=X1(I))**2+(P=Y1(I))**2+(Q=Z1(I))**2).GT.
*(N1(I)**2)) GO TO 6
NI=NI+1
GO TO 4
6 CONTINUE
GO TO 4
4 CONTINUE
C
VW=(DFLOAT(NI)/DFLOAT(NT))*VOL
C
WRITE(108,8) VW
8 FORMAT(//,' VW VALUE = ',F9,3)
GO TO 1122
2222 STOP
END
```



```

REAL FUNCTION MAMI(N,X,R,KOD)
DIMENSION X(50),R(50)

C
IF(KOD,EO,1) MAMI=X(1)+R(1)
IF(KOD,EO,2) MAMI=X(1)-R(1)
DO I=1,2,N
IF(KOD,EO,1,AND,MAMI,LT,X(I)+R(I)) MAMI=X(I)+R(I)
1 IF(KOD,EO,2,AND,MAMI,GT,X(I)-R(I)) MAMI=X(I)-R(I)
RETURN
END
SUBROUTINE UNIREL(A,B,Z,IU,X)
CALL MAS
CALL ALEAT(IU,IU,X)
CALL NMAS
IU=IB
ENTRY UNIRELI(A,B,Z,X)
Z=A+(B-A)*X
RETURN
END
SUBROUTINE ALEAT(IA,IU,Z)
IB=IA*65539
IF(IB,GE,0) GO TO 1
IB=IB+2147483647+1
1 Z=IB
Z=Z*0,4656613E-9
IA=IB
RETURN
END

```

```

. ENTSC MAS,NMAS
. COMPILE ASSIRIS
MASKEP CSECT P
MASQUE OFF MAS,NMAS
MAS DATA,4,4 X'50400000'
MAS LDTM,13 MASQUE
NMAS BRU *32
NMAS LDTM,13 MASQUE+1
NMAS BRU *32
END
LINK
.
. FETCH LN:*4
. RUN TIME:999,NL:500000

```

```

OVA
2,3,3,
TEST
0,,0,,0,,3,,
0,,0,,0,,4,,
0,,0,,0,,5,,
0,,0,,0,,4,,
0,,0,,0,,5,,
0,,0,,0,,6,,
VAVAV
TEST
3,
0,,0,,0,,3,,
0,,0,,0,,4,,
0,,0,,0,,5,,
EOF

```



INPUT EXAMPLE