OFFICE OF NAVAL RESEARCH

CONTRACT N00014-99-1-0393

R&T Code 33e 1806

Dr. Judah Goldwasser

Technical Report No. 111

Conformational Dependence of Molecular Surface Electrostatic Potentials

by

Jane S. Murray, Zenaida Peralta-Inga and Peter Politzer

Prepared for Publication

in

International Journal of Quantum Chemistry

Department of Chemistry
University of New Orleans
New Orleans, LA 70148

June 8, 1999

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. AGENCY USE ONLY (*Leave blank*)

2. REPORT DATE
6/9/99

3. REPORT TYPE AND DATES COVERED
preprint

4. TITLE AND SUBTITLE
Conformational Dependence Of Molecular Surface
Electrostatic Potentials

5. FUNDING NUMBERS
N00014-99-1-0393
Dr. Judah Goldwasser
R&T Code 33e 1806

6. AUTHOR(S)
Jane S. Murray, Zenaida Peralta-Inga and Peter Politzer

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
University of New Orleans
Department of Chemistry
New Orleans, Louisiana 70148

8. PERFORMING ORGANIZATION REPORT NUMBER
111

9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)
Office of Naval Research
Code 333
800 N. Quincy Street
Arlington, VA 22217

10. SPONSORING/MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION/AVAILABILITY STATEMENT
Approved for public release.
Unlimited distribution.

12b. DISTRIBUTION CODE

13. ABSTRACT (*Maximum 200 words*)

In a series of earlier studies, we have shown that a variety of solution, liquid and solid phase properties can be represented analytically in terms of quantities related to the electrostatic potentials on molecular surfaces. These quantities include the positive and negative extrema, the positive and negative average values and variances, and the average deviation. We have now investigated how sensitive these quantities are to the molecular conformation. Surface potentials were computed at the HF/6-31G* level for a total of 35 conformations of ten different molecules. Our overall conclusion is that conformational effects upon applications of molecular surface electrostatic potentials are most likely to be of concern if (a) formation of the conformer considerably diminishes internal polarity, and/or (b) the application in question is strongly dependent upon the positive variance.

14. SUBJECT TERMS
molecular surfaces, electrostatic potentials, conformational dependence, statistical quantities

15. NUMBER OF PAGES
13

16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT
Unclassified

18. SECURITY CLASSIFICATION OF THIS PAGE
Unclassified

19. SECURITY CLASSIFICATION OF ABSTRACT
Unclassified

20. LIMITATION OF ABSTRACT
Unlimited

CONFORMATIONAL DEPENDENCE OF MOLECULAR SURFACE ELECTROSTATIC POTENTIALS

Jane S. Murray, Zenaida Peralta-Inga and Peter Politzer*
Department of Chemistry
University of New Orleans
New Orleans, LA 70148

Abstract

In a series of earlier studies, we have shown that a variety of solution, liquid and solid phase properties can be represented analytically in terms of quantities related to the electrostatic potentials on molecular surfaces. These quantities include the positive and negative extrema, the positive and negative average values and variances, and the average deviation. We have now investigated how sensitive these quantities are to the molecular conformation. Surface potentials were computed at the HF/6-31G* level for a total of 35 conformations of ten different molecules. Our overall conclusion is that conformational effects upon applications of molecular surface electrostatic potentials are most likely to be of concern if (a) formation of the conformer considerably diminishes internal polarity, and/or (b) the application in question is strongly dependent upon the positive variance.

*Author to whom correspondence should be addressed.

KEYWORDS: molecular surfaces, electrostatic potentials, conformational dependence, statistical quantities

Introduction

The electrostatic potential V(**r**) created in the space around a molecule by its nuclei and electrons is well established as a guide to molecular reactive behaviour. (For reviews, see refs. [1-6].) It is defined by eq. (1), in which the molecule is treated as a collection of stationary point charges, the nuclei, surrounded by a continuous but static distribution of electrons:

$$V(\mathbf{r}) = \sum_{A} \frac{Z_A}{|\mathbf{R}_A - \mathbf{r}|} - \int \frac{\rho(\mathbf{r}')\,d\mathbf{r}'}{|\mathbf{r}' - \mathbf{r}|} \qquad (1)$$

Z_A is the charge on nucleus A, located at $\mathbf{R}_A$, and ρ(**r**) is the electronic density function of the molecule. The first term on the right side of eq. (1) is the nuclear contribution to V(**r**), and is positive; the second term is due to the electrons and is accordingly negative.

Over a period of many years, the electrostatic potential was used extensively as a tool for identifying and ranking the molecular regions most susceptible to electrophilic and/or nucleophilic attack and for determining general patterns of positive and negative potential that promote or inhibit molecular interactions, such as those between drugs and receptors. Bernard and Alberte Pullman and their collaborators were pioneers in applying the electrostatic potential to the analysis of particularly biochemical systems; some of their numerous contributions are discussed in refs. [2-4]. The quantitative analysis of V(**r**) initially emphasized locating and evaluating the most negative potentials, V_{min}. These are usually associated with (a) the more electronegative atoms, such as N, O, F, Cl, S and Br, and (b) unsaturated, aromatic and strained carbon-carbon bonds. The magnitudes of the V_{min} can often be related to reactive properties, for instance the pK_a values of azine nitrogens [5], and epoxide carcinogenicity [4]. More recently, attention has focused upon the electrostatic potential $V_S(\mathbf{r})$ on the molecular surface. It was shown that both the positive and negative surface extrema, $V_{S,max}$ and $V_{S,min}$, can be related to reactive behavior. For example, $V_{S,max}$ and $V_{S,min}$ for a large variety of molecules correlate with hydrogen bond acidity and basicity, respectively [7]. (We take the molecular surface to be the 0.001 au contour of the electronic density, as suggested by Bader *et al* [8]. We have earlier discussed the use of ρ(**r**) contours to define molecular surfaces [9,10].) This approach was still limited in scope however; V_{min}, $V_{S,min}$ and $V_{S,max}$ are certainly key features of the molecular electrostatic potential, but these site-specific quantities do not convey all the information that is contained in V(**r**).

Accordingly, in recent years we have sought to develop mechanisms for more adequately describing and quantitatively characterizing the electrostatic potential over an entire molecular surface. We have found that this can be achieved through the introduction of several statistically-defined global quantities that explicitly reflect the magnitude of $V_S(\mathbf{r})$ at each point on the molecular surface [11-14]:

(a) $\overline{V}_S^+$, $\overline{V}_S^-$ and $\overline{V}_S$ are the positive, negative and overall average potentials on the surface.

$$\overline{V}_S^+ = \frac{1}{n}\sum_{i=1}^{n} V_S^+(\mathbf{r}_i) \qquad (2)$$

$$\overline{V}_S^- = \frac{1}{m}\sum_{i=1}^{m} V_S^-(\mathbf{r}_i) \qquad (3)$$

$$\overline{V}_S = \frac{1}{m+n}\left[\sum_{i=1}^{n} V_S^+(\mathbf{r}_i) + \sum_{i=1}^{m} V_S^-(\mathbf{r}_i)\right] \qquad (4)$$

(b) Π is the average deviation of $V_S(\mathbf{r})$,

$$\Pi = \frac{1}{m+n}\sum_{i=1}^{m+n}\left|V_S(\mathbf{r}_i) - \overline{V}_S\right| \qquad (5)$$

which we interpret as a measure of the local polarity, or internal charge separation, that is present even in molecules with zero dipole moment.

(c) σ_+^2, σ_-^2 and σ_{tot}^2 are the positive, negative and total variances of $V_S(\mathbf{r})$, which reflect the range or variability of $V_S(\mathbf{r})$, emphasizing its extrema,

$$\sigma_+^2 = \frac{1}{n}\sum_{i=1}^{n}\left[V_S^+(\mathbf{r}_i) - \overline{V}_S^+\right]^2 \qquad (6)$$

$$\sigma_-^2 = \frac{1}{m}\sum_{i=1}^{m}\left[V_S^-(\mathbf{r}_i) - \overline{V}_S^-\right]^2 \qquad (7)$$

$$\sigma_{tot}^2 = \sigma_+^2 + \sigma_-^2 \qquad (8)$$

(d) ν indicates the degree of balance between the positive and negative surface potentials,

$$\nu = \frac{\sigma_+^2 \sigma_-^2}{(\sigma_{tot}^2)^2} \tag{9}$$

When $\sigma_+^2 = \sigma_-^2$, then ν achieves its maximum possible value of 0.25.

In a series of studies, we have demonstrated that it is possible to develop quantitative analytical relationships of good accuracy for a variety of solution, liquid and solid phase properties in terms of some subset of these quantities (plus V_{min}, $V_{S,max}$ and $V_{S,min}$), which are computed for the individual, isolated molecules. These properties include heats of fusion [15], vaporization [11] and sublimation [16], solubilities [17-19], solvation free energies [20,21], boiling points and critical constants [22], partition coefficients [23,24], diffusion coefficients [25], surface tensions [15], lattice energies [26], liquid and solid densities [15], and impact sensitivities [27].

In calculating the quantities defined by eqs. (1)–(9), our first step is to optimize the molecular geometry, so that we are presumably dealing with the most stable conformation. An important and frequently-posed question concerns the sensitivity of the computed quantities (and subsequent relationships) to the conformation of the molecule. How much is the surface electrostatic potential affected if the molecule is induced to adopt another conformation, perhaps due to thermal or environmental factors? Our objective in the present work has been to address this question.

Procedure and Results

For the molecules **1–10**, we have investigated the conformations shown in Figures 1 and 2. Each molecular geometry was first fully optimized in the ground state, and then re-optimized in one or more different conformations (local minima). All calculations were carried out with Gaussian 92 [28] at the HF/6-31G* level. For each conformation, we computed the surface area, $V_{S,max}$ and $V_{S,min}$, and the properties defined by eqs. (2)–(9). The results are listed in Table 1, along with the HF/6-31G* relative energies within each conformer group.

$CH_3{-}CH_3$	$CH_3{-}CH_2F$	$CH_3{-}CH_2NO_2$	$CH_3{-}CH_2OH$	$CH_2Cl{-}CH_2F$
1	**2**	**3**	**4**	**5**
$CH_2NH_2{-}CH_2NO_2$	$CH_2OH{-}CH_2OH$	$CH_3{-}CH_2{-}CH_2OH$	$CH_2{=}CH{-}COOH$	$NH{=}CH{-}CH_2NO$
6	**7**	**8**	**9**	**10**

Discussion

Ethane and Its Monosubstituted Dervatives

Both the staggered and the eclipsed conformer have been examined for molecules **1–4.** The latter is invariably the less stable, by approximately 3 - 4 kcal/mole. (The experimental value for ethane is 3.0 kcal/mole [29].) The computed properties tend to be quite similar for each pair of conformers. In the case of **4,** we also considered the structure (**4c**) resulting from a 64° rotation around the C–O bond of the staggered form. This requires an energy of only 0.1 kcal/mole, but produces a rather large change in the global property $\overline{V}_S^-$, indicating its sensitivity to the precise juxtaposition of the hydroxyl and neighboring hydrogens.

1,2–Disubstituted Ethanes

Four conformers were investigated for each disubstituted ethane. The least stable structure is usually that in which the two substituents are eclipsed; **8c** is an exception, presumably due to the short distance (1.95 A) between one of the methyl hydrogens and one on the substituted carbon. In terms of our present objective, it is **5d** that is of particular interest, in that it differs significantly from its conformers in terms of nearly *all* of its computed surface properties. This is not observed for any other of the disubstituted ethanes. In **5a**, **5b** and **5c**, the negative halogen potentials evidently overlap and reinforce each other, creating a relatively strong negative region and a corresponding positive one. In **5d**, on the other hand, the negative region are separate and therefore weaker. The magnitudes of Π confirm that **5d** has much less internal polarity than do its conformers. For **6** - **8**, the surface properties generally tend to be fairly similar among the conformers. The most striking exceptions to this are σ_+^2, σ_-^2 for **8a** and $\overline{V}_S^-$ for **8b**.

Molecules 9 and 10

The four conformers of **9** fall neatly into two groups; **9a** and **9c** are significantly less stable than **9b** and **9d**, presumably because of the proximity of the hydrogens in the former, which creates considerable internal polarity. The surface properities are fairly uniform within the two groups. Six different conformers of **10** have been investigated. Overall, they do not vary markedly in their surface properties.

Summary

From the data in Table 1, certain generalizations can be made concerning the effects of conformational changes upon the molecular surface properties of present interest:

(a) The surface areas are only slightly affected.

(b) The two site-specific properties, $V_{S,max}$ and $V_{S,min}$, and the global properties $\overline{V}_S^+$ and Π usually change relatively little. The only exceptions to this are **5d** and the pair **9a/9c**, which were formed by rotations that either eliminated or produced regions of markedly reinforced negative or positive potential. This is then reflected in all of the properties of $V_S(\mathbf{r})$. However increasing the internal polarity can normally be expected to significantly decrease molecular stability, so that conformers such as **9a** and **9c** are less apt to play important roles.

(c) σ_+^2 is the most sensitive to conformational variations. It is probable that σ_{tot}^2 and ν will consequently be affected, although perhaps not to the same extent because they also include σ_-^2.

On the basis of the results in Table 1, therefore, it appears that conformational effects upon applications of molecular surface electrostatic potentials are most likely to be of concern if (a) formation of the conformer considerably diminishes internal polarity, and/or (b) the application in question is strongly dependent upon σ_+^2.

Acknowledgement

We greatly appreciate the financial support of the Office of Naval Research, through contract N00014–97–1–0066 and Program Officer Dr. Judah Goldwasser.

References

[1] E. Scrocco and J. Tomasi, in *Topics in Current Chemistry*, Vol. 42, Springer-Verlag, Berlin, 1973, p.95.

[2] P. Politzer and K. C. Daiker, in *The Force Concept in Chemistry*, B.M. Deb, Ed., Van Nostrand Reinhold, New York, 1981, ch. 6.

[3] P. Politzer and D. G. Truhlar, Eds., *Chemical Applications of Atomic and Molecular Electrostatic Potentials*, Plenum Press, New York, 1981.

[4] P. Politzer, P. R. Laurence and K. Jayasuriya, Env. Health Persp. **61**, 191 (1985).

[5] P. Politzer and J. S. Murray, in *Reviews in Computational Chemistry*, Vol. 2, K. B. Lipkowitz and D. B. Boyd, Eds., VCH Publishers, New York, 1991, ch. 7.

[6] G. Naray–Szabo and G. G. Ferenczy, Chem. Rev. **95**, 829 (1995).

[7] H. Hagelin, T. Brinck, M. Berthelot, J. S. Murray and P. Politzer, Can. J. Chem. **73**, 483 (1995).

[8] R. F. W. Bader, M. T. Carroll, J. R. Cheeseman and C. Chang, J. Amer. Chem. Soc. **109**, 7968 (1987).

[9] P. Sjoberg and P. Politzer, J. Phys. Chem. **94**, 3959 (1990).

[10] J. S. Murray, T. Brinck, M. E. Grice and P. Politzer, J. Mol. Struct. (Theochem) **256**, 29 (1992).

[11] J. S. Murray and P. Politzer, in *Quantitative Treatments of Solute/Solvent Interactions*, J. S. Murray and P. Politzer, Eds., Elsevier, Amsterdam, 1994, ch. 8.

[12] J. S. Murray, T. Brinck, P. Lane, K. Paulsen and P. Politzer, J. Mol. Struct. (Theochem) **307**, 55 (1994).

[13] P. Politzer, J. S. Murray, T. Brinck, and P. Lane, in *Immunoanalysis of Agrochemicals: Emerging Technologies*, J. O. Nelson, A. E. Karn and R. B. Wong, Eds. ACS Symp. Ser. 586, American Chemical Society, Washington, 1995, ch. 8.

[14] J. S. Murray and P. Politzer, J. Mol. Struct. (Theochem) **425**, 107 (1998).

[15] J. S. Murray, T. Brinck and P. Politzer, Chem. Phys. **204**, 289 (1996).

[16] P. Politzer, J. S. Murray, M. E. Grice, M. DeSalvo and E. Miller, Mol. Phys. **91**, 923 (1997).

[17] P. Politzer, P. Lane, J. S. Murray and T. Brinck, J. Phys. Chem. **96**, 7938 (1992).

[18] P. Politzer, J. S. Murray, P. Lane and T. Brinck, J. Phys. Chem. **97**, 729 (1993).

[19] J. S. Murray, S. Gagarin and P. Politzer, J Phys. Chem. **99**, 12081 (1995).

[20] J. S. Murray, F. Abu-Awwad and P. Politzer, J. Phys. Chem., submitted.

[21] P. Politzer, F. Abu-Awwad and J. S. Murray, Inter. J. Quant. Chem., submitted.

[22] J. Murray, P. Lane, T. Brinck, K. Paulsen, M. E.Grice and P. Politzer, J. Phys. Chem. **97**, 9369 (1993).

[23] T. Brinck, J. S. Murray and P. Politzer, J. Org. Chem. . **58**, 7070 (1993).

[24] J. S. Murray, T. Brinck and P. Politzer, J. Phys. Chem. **97**, 13807 (1993).

[25] P. Politzer, J. S. Murray and P. Flodmark, J. Phys. Chem. **100**, 5538 (1996).

[26] P. Politzer and J. S. Murray, J. Phys. Chem. A **102**, 1018 (1998).

[27] P. Politzer and J. S. Murray, Mol. Phys, **93**, 187 (1998).

[28] M. J. Frisch, G. W. Trucks, H. B. Schlegel, P. M. W. Gill, B. G. Johnson, M. W. Wong, J. B. Foresman, M. A. Robb, M. Head-Gordon, E. S. Replogle, R. Gomperts, J. L. Andres, K. Raghavachari, J. S. Binkley, C. Gonzalez, R. L. Martin, D. J. Fox, D. J. Defrees, J. Baker, J. J. P. Stewart and J. A. Pople, GAUSSIAN 92/DFT, Revision G.2, Gaussian, Pittsburgh, PA, 1993.

[29] D. R. Lide, J. Chem. Phys. **29**, 1426 (1958).

Table 1. Computed surface electrostatic potential quantities for conformers of **1 - 10**.

Molecule	Relative Energy (kcal/mole)	Surface Area ($Å^2$)	$\overline{V}_S^+$ (kcal/mole)	$\overline{V}_S^-$ (kcal/mole)	Π (kcal/mole)	σ_+^2 $(kcal/mole)^2$	σ_-^2 $(kcal/mole)^2$	σ_{tot}^2 $(kcal/mole)^2$	ν	$V_{S,max}$ (kcal/mole)	$V_{S,min}$ (kcal/mole)
1a	0.0	81.5	2.77	–1.45	2.15	3.28	0.62	3.88	0.135	6.2	–2.7
1b	3.6	81.0	3.19	–1.49	2.41	3.42	0.59	4.01	0.125	6.5	–2.7
2a	0.0	85.5	9.26	–17.93	11.08	19.6	90.2	109.8	0.147	20.0	–28.0
2b	3.6	85.3	9.08	–18.49	10.96	22.7	88.0	110.7	0.163	20.4	–28.3
3a	0.0	108.4	18.12	–22.37	19.32	42.4	83.6	126.0	0.223	30.9	–36.3
3b	3.5	108.8	18.27	–22.52	19.47	43.6	82.7	126.2	0.226	30.7	–36.3
4a	0.0	90.4	9.59	–14.32	11.28	100.6	169.5	270.1	0.234	47.4	–39.6
4b	3.1	92.7	11.05	–14.14	12.05	98.0	161.9	259.9	0.235	48.7	–38.4
4c	0.1	90.4	9.54	–19.37	11.55	86.6	172.0	258.7	0.223	47.1	–40.2
5a	0.8	105.1	18.32	–14.12	16.24	57.4	42.5	99.9	0.244	32.6	–27.3
5b	7.8	104.5	18.93	–15.85	17.41	59.0	56.0	115.0	0.250	35.8	–32.8
5c	0.8	105.1	18.31	–14.12	16.23	57.3	42.5	99.8	0.245	32.6	–27.3
5d	0.0	105.2	14.00	–10.20	12.15	30.6	26.3	56.9	0.249	21.8	–20.1
6a	0.0	122.4	21.00	–19.29	19.90	87.0	79.1	166.1	0.249	38.7	–33.8
6b	4.2	121.4	20.27	–18.95	19.32	68.4	78.2	146.6	0.249	35.4	–33.1
6c	0.1	122.1	21.09	–19.17	19.87	91.8	80.3	172.1	0.249	39.5	–33.4
6d	1.0	124.7	22.17	–20.04	20.81	115.6	84.6	200.0	0.244	43.2	–35.1
7a	0.0	101.2	14.86	–18.61	16.06	135.5	131.4	266.9	0.250	55.0	–39.7
7b	2.9	101.0	17.29	–21.58	18.28	114.5	114.2	228.7	0.250	48.6	–36.4
7c	1.0	101.0	16.33	–19.56	16.97	138.4	123.0	261.4	0.249	55.3	–38.1
7d	2.1	101.6	17.00	–18.14	17.33	188.5	134.6	323.1	0.243	54.0	–37.7
8a	0.1	110.8	9.16	–11.27	9.95	96.9	123.1	219.0	0.249	49.0	–37.6
8b	0.6	110.7	8.88	–19.81	10.15	64.2	168.5	232.7	0.200	47.1	–40.1

(continued)

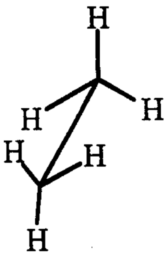
Table 1. Computed surface electrostatic potential quantities for conformers of **1–10** (continued).

Molecule	Relative Energy	Surface Area	$\overline{V}_S^+$	$\overline{V}_S^-$	Π	σ_+^2	σ_-^2	σ_{tot}^2	ν	$V_{S,max}$	$V_{S,min}$
	(kcal/mole)	(Å^2)	(kcal/mole)			(kcal/mole)^2				(kcal/mole)	
8c	13.7	113.1	9.42	–12.91	10.40	84.9	166.1	251.0	0.224	48.3	–39.0
8d	0.0	111.7	8.23	–15.29	9.90	83.5	173.1	256.6	0.220	48.6	–39.6
9a	7.5	105.2	19.54	–24.29	21.28	212.0	211.0	423.0	0.250	70.3	–46.7
9b	0.0	105.5	13.25	–15.94	14.35	121.1	143.7	264.8	0.248	56.1	–38.1
9c	9.0	105.3	19.40	–27.08	21.56	191.1	162.1	353.2	0.248	69.3	–45.8
9d	0.5	105.5	13.39	–16.06	14.39	125.3	167.9	293.2	0.245	56.8	–39.5
10a	0.6	110.7	17.51	–15.11	16.23	83.3	66.5	149.8	0.247	38.8	–33.8
10b	2.8	110.5	19.34	–15.27	17.28	98.3	82.8	181.1	0.248	42.3	–37.7
10c	0.0	110.5	17.53	–15.56	16.43	84.1	70.7	154.8	0.248	38.4	–35.0
10d	2.0	110.3	19.46	–15.44	17.39	97.4	86.8	184.2	0.249	40.6	–38.4
10e	0.3	108.8	17.87	–15.31	16.56	73.8	71.8	145.6	0.250	36.4	–35.0
10f	2.9	108.9	20.88	–16.26	18.61	104.0	93.8	197.8	0.249	41.4	–40.1

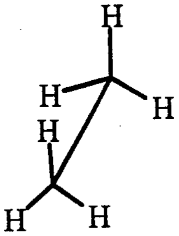
Figure Captions

Figure 1. Conformers investigated for molecules **1 - 6**.

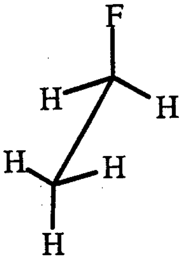
Figure 2. Conformers investigated for molecules **7 - 10**.



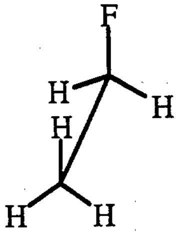
1a



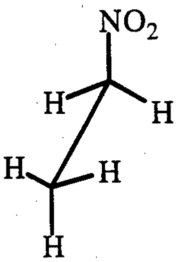
1b



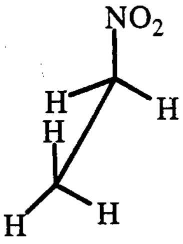
2a



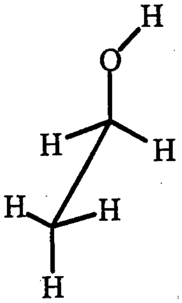
2b



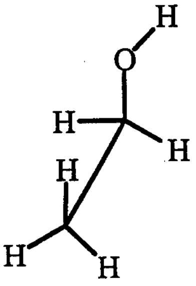
3a



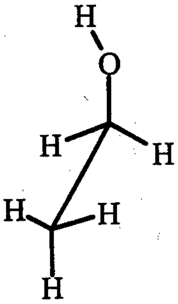
3b



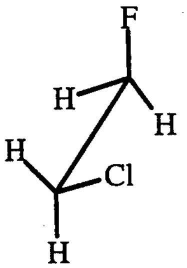
4a



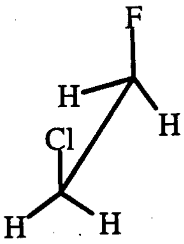
4b



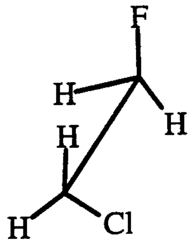
4c



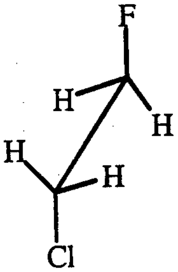
5a



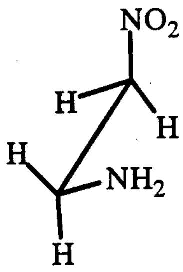
5b



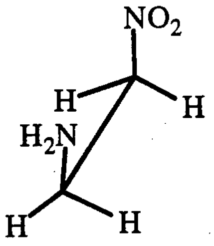
5c



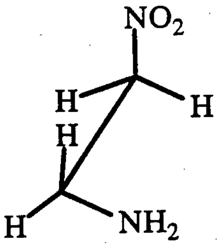
5d



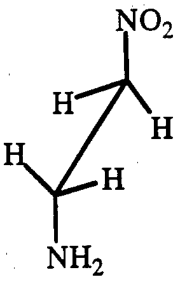
6a



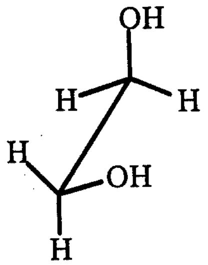
6b



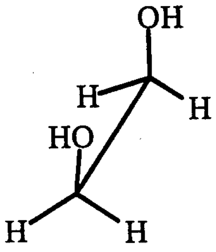
6c



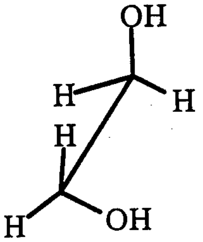
6d



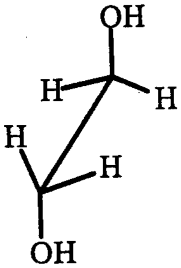
7a



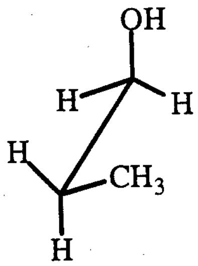
7b



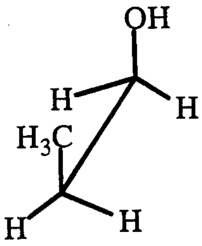
7c



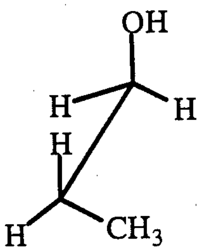
7d



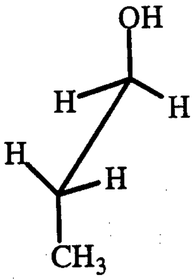
8a



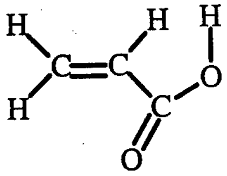
8b



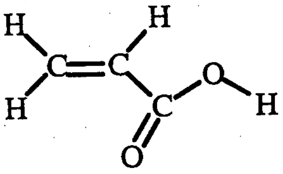
8c



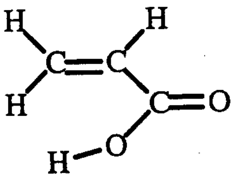
8d



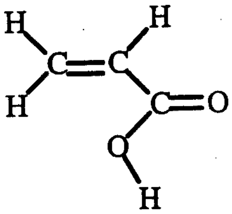
9a



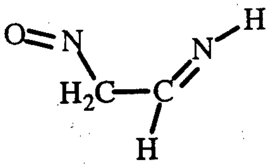
9b



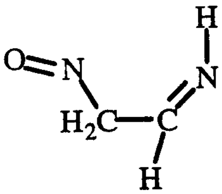
9c



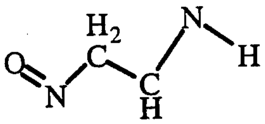
9d



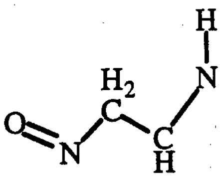
10a



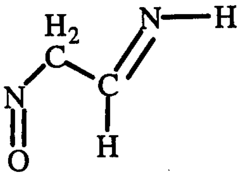
10b



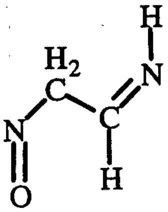
10c



10d



10e



10f