MOLECULAR PHARMACOLOGY, 11, 492-500

Nitrogen Electron Densities in Narcotics and Narcotic Antagonists by X-ray Photoelectron Spectroscopy and Comparison with Quantum Chemical Calculations

LEIF J. SAETHRE[1] AND THOMAS A. CARLSON

Oak Ridge National Laboratory,[2] Oak Ridge, Tennessee 37830

JOYCE J. KAUFMAN[3] AND WALTER S. KOSKI

Department of Anesthesiology, The Johns Hopkins University School of Medicine, Baltimore, Maryland 21205, and Department of Chemistry, The Johns Hopkins University, Baltimore, Maryland 21218

(Received January 23, 1975)

SUMMARY

SAETHRE, LEIF J., CARLSON, THOMAS A., KAUFMAN, JOYCE J. & KOSKI, WALTER S. (1975) Nitrogen electron densities in narcotics and narcotic antagonists by X-ray photoelectron spectroscopy and comparison with quantum chemical calculations. *Mol. Pharmacol.*, 11, 492-500.

Nitrogen 1*s* electron binding energies of narcotics and, where possible, of their congener narcotic antagonists have been measured by X-ray photoelectron spectroscopy (ESCA) (binding energies of the inner 1*s* shell electrons on an atom are known to be directly related to the valence shell electron densities on these atoms). The compounds investigated include the narcotic-(*N*-methyl)-narcotic antagonist (the *N*-allyl derivative of the narcotic) pairs morphine-nalorphine, oxymorphone-naloxone, and levorphanol-levallorphan, as well as methadone and cyclazocine. The ESCA spectra show that to within 0.2 eV (or 0.01 electron charge unit) the electron densities (either total or valence) on the nitrogen atoms in congener agonist-antagonist pairs are identical. These results confirm most convincingly our earlier quantum chemical CNDO/2 (complete neglect of differential overlap) results, which showed most surprisingly, contrary to customary pharmacological assumptions, that these electron densities are the same. These results also indicate that measured solution pK_a values cannot be directly correlated with nitrogen electron densities. For several of these compounds the ESCA spectra were determined for both the free bases and the acid salts. These results also confirm the predictions from the earlier CNDO/2 calculations that for the protonated species the entire positive charge is not localized on the nitrogen atom. Only about 0.2 positive charge (or a little less) resides on the nitrogen, the remainder being delocalized over the neighboring atoms. This has significant implications for the requisites that the complementary "analgesic" or "opiate" receptor must possess, which are somewhat different from those heretofore postulated by pharmacologists.

This work was supported in part by National Institute on Drug Abuse, Division of Research, Biomedical Research Branch, under Grant DA00539 to The Johns Hopkins University.

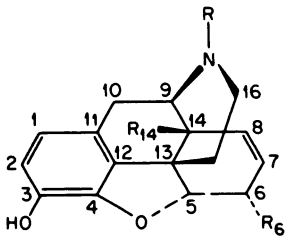
[1] Guest assignee from the University of Bergen, Bergen, Norway; supported by a fellowship from the Royal Norwegian Council for Scientific and Industrial Research.

[2] Operated by Union Carbide Corporation for the United States Atomic Energy Commission.

[3] Enquiries should be addressed to this author.

INTRODUCTION

Morphine is the most important alkaloid of opium and is responsible for its analgesic actions and pharmacological characteristics. The structure of morphine (I) is shown in Fig. 1. Nalorphine (II) differs from morphine only in the substitution of an allyl group for the *N*-methyl group. Nevertheless, nalorphine, while still an analgesic, is a strong narcotic antagonist and is sometimes used as an antidote for overdose of narcotics. Similar replacement of the *N*-methyl group in oxymorphone (III) and levorphanol (V) changes their agonist (morphine-like) properties, and naloxone (IV) and levallorphan (VI) are both power-



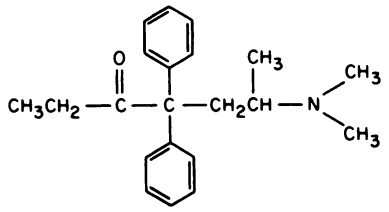
I-VI

FIG. 1. *Structures of narcotics and narcotic antagonists*

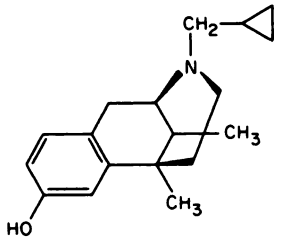
Name	R	R_6	R_{14}	Other changes
I. Morphine	$-CH_3$	—OH	—H	
II. Nalorphine	$-CH_2CH{=}CH_2$	—OH	—H	
III. Oxymorphone	$-CH_3$	=O	—OH	—[a]
IV. Naloxone	$-CH_2CH{=}CH_2$	=O	—OH	—[a]
V. Levorphanol	$-CH_3$	—H	—H	—[a, b]
VI. Levallorphan	$-CH_2CH{=}CH_2$	—H	—H	—[a, b]

[a] Single instead of double bond between C_7 and C_8.

[b] No oxygen between C_4 and C_5.



VII Methadone



VIII Cyclazocine

ful antagonists. Methadone (VIII) is used as a substitute for morphine, and cyclazocine (VIII) is a strong antagonist with analgesic properties (1).

The pharmacological potencies of these compounds appear to be governed partly by their lipophilicities, which determine how much of the compound will penetrate the blood-brain barrier, and partly by their intrinsic geometrical structures (2). Only the free bases partition into lipids, and thus it is in the free base form that these compounds pass the blood-brain barrier. However, because the nitrogen atom is mainly cationic at physiological pH values, it had been proposed that one important element of the analgesic-receptor interaction may be an ionic or electrostatic bond to an anionic site on the receptor surface (3–6). The hypothetical receptor was depicted with a small, highly localized "anionic site" which would give an "ionic bond between cation and anionic receptor" (5). The postulated bond would depend on nitrogen charge, and the observed differences in analgesic activity might thus be related to differences in charge distribution on the nitrogen atoms in the various narcotics and narcotic antagonists. Our earlier quantum chemical CNDO/2[4] calculations, however, had revealed that the charge on nitrogen remains almost invariant for the protonated compounds in Fig. 1, not merely for the different narcotics but also for their congener antagonists (7–9). In particular, the calculated valence electron densities on the nitrogen atom in the congener agonist-antagonist pairs (morphine-nalorphine, oxymorphone-naloxone, and levorphanol-levallorphan) are virtually identical. The calculated valence electron densities on the nitrogen atoms in all of the free bases, while differing somewhat from those in the protonated compounds, are also fairly invariant among themselves (7–9). It should be noted also that the entire positive charge in the protonated compounds does not remain localized on the nitrogen atom. It is delocalized over the surrounding atoms. The calculations indicated that only about 0.2 of the positive charge remains localized on the nitrogen. (Despite charge localization, it is still possible for an ionic bond to be formed between a cation and an anionic receptor.) This charge delocalization of a protonated nitrogen in an organic heterocyclic compound was first observed by us in our all-valence electron calculations on the pyridine aldoxime antagonists to the organophosphorus nerve gases (10, 11). [While the absolute magnitudes of CNDO/2 calculated charges on nitrogen are different from those obtained from *ab initio* calculations on nitrogen-containing heterocyclic molecules using good large Gaussian basis sets (12), the relative magnitudes of these CNDO/2 charges in a series of related molecules are more reliable.]

One way of investigating charge densities experimentally is to measure core electron binding energies by means of X-ray photoelectron spectroscopy (13). Although the core electrons do not take an active part in chemical bonding, they are strongly affected by the valence electron distribution. [The ESCA binding energies of the 1*s* electrons on an atom have been shown previously to be directly proportional to the valence electron densities on that atom in various molecular environments (13).] Therefore, in order to obtain an independent experimental measurement of the relative charge densities in congener agonist-antagonist pairs and of the relative charge densities between the free bases and their protonated species, as well as to evaluate the reliability of the CNDO/2 results, the nitrogen 1*s* binding energies were studied for the narcotics and narcotic antagonists in Fig. 1. Some of the compounds were measured both as free bases and as salts. The observed chemical shifts in binding energies were compared with shifts calculated by the charge model and the electrostatic potential model (13, 14). Molecular and crystal potentials were calculated, treating the atoms as point charges obtained from the CNDO/2 calculations (9).

[4] The abbreviations used are: CNDO/2, complete neglect of differential overlap; ESCA, electron spectroscopy for chemical analysis.

PROCEDURE

Experimental details. The photoelectron spectra were obtained with a 180° electrostatic spectrometer, which has double-focusing spherical plates. The spectrometer is located in the Physics Division of Oak Ridge National Laboratory. Details of the instrument have been described elsewhere (15). The slits and baffles were adjusted to give a spectrometer resolution of 0.1% at full-width-half-maximum. The samples were irradiated with characteristic X-rays of $MgK\alpha_{1,2}$ (1253.6 eV) and $AlK\alpha_{1,2}$ (1486.6 eV).

The samples, which were provided, converted where necessary, and purified by The Johns Hopkins University, were finely ground and mounted with double-stick adhesive tape on aluminum planchettes. The carbon 1*s* peak originating from the pump oil was used as calibration standard and was given the binding energy 285.0 eV (16). Binding energies were measured for nitrogen 1*s* and carbon 1*s*. The oxygen 1*s* peak was also observed, but could not be resolved because of the number of chemically different types of oxygen.

Binding energies and chemical shifts. In X-ray photoelectron spectroscopy (XPS), or, as it sometimes is called ESCA, electron spectroscopy for chemical analysis (13), the binding energies of core electrons E_B are determined by the relationship

$$E_B = h\nu - E_e \qquad (1)$$

where $h\nu$ is the energy of the incident X-ray and E_e is the photoelectron energy. Binding energies for solid samples are normally given relative to a reference level of a material in intimate contact with the sample.

Theoretically the electron binding energy may be defined (17) as

$$E_B = -\epsilon^{HF} + E^{reorg} + \Delta E^{corr} + \Delta E^{rel} \qquad (2)$$

where ϵ^{HF} is the Hartree-Fock orbital energy of the ground state and E^{reorg} is the reorganization or relaxation energy, which the ion gains when the remaining occupied orbitals relax to minimum energy. ΔE^{corr} and ΔE^{rel} are the differences in correlation and relativistic energy of the initial and final states. These last two terms are usually found to be small and may be neglected here. The chemical shift of a core orbital i relative to a reference level then becomes

$$\Delta E_i = -\Delta\epsilon_i^{HF} + \Delta E_i^{reorg} \qquad (3)$$

The last term in Eq. 3 may not be small, but can be disregarded if the reorganization energy is considered to be the same in all molecules under study.

For large molecules a simplification of the theoretical calculation of binding energy shifts can be made by using an electrostatic potential model. It has been shown through a series of approximations (14, 17) that the shifts may be written

$$\Delta E_i = -\Delta\epsilon_i^{HF} \approx \Delta \left(k_i q_i + \sum_{j \neq i} q_j r_{ij}^{-1} \right)$$

or

$$\Delta E_i = k_i \Delta q_i + \Delta V_i \qquad (4)$$

In Eq. 4 the first term represents the change in potential from the difference in charge at the considered atom, and V_i accounts for the potential from the surrounding atoms in the system. The constant k_i depends somewhat on the definition of atomic charge, but is approximately equal to the electrostatic interaction integral between the considered core orbital and a valence atomic orbital in the same atom. Through this model the binding energy shifts are related to charges in the valence electron distribution.

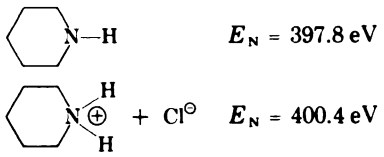
The potential V_i in Eq. 4 is easily calculated provided that the molecular structure is known and the summation is restricted to atomic charges within one molecule. For crystalline solids, and especially for ionic compounds, the potential should preferably be summed over all the atoms in the crystal lattice. This summation is only slowly convergent, but rapid convergence can be achieved by a method pioneered by Ewald (18), in which the potential is obtained by making summation in both direct and reciprocal space. A computer program to calculate crystal potentials has been written by Busing (19). For molecular

crystals with large unit cells this program is more efficient and convenient to use than one available previously (20).

RESULTS AND DISCUSSION

Nitrogen 1*s* binding energies for the various compounds are given in Table 1. The free bases are listed first, and then the protonated compounds. Shifts in binding energies are given relative to the morphine base, which was found to have the lowest binding energy. The results show that we can easily distinguish between the free bases and the salts, whereas only small chemical shifts are observed within each of the groups. Cyclazocine (VIII) seems to have a slightly higher binding energy than the other bases, while the differences in binding energy among the salts are small and probably not significant.

The shifts between the free bases and corresponding salts are 2.7 eV for morphine (I) and nalorphine (VI), and 2.6 eV for oxymorphone (III) and (IV). This corresponds well with the shift of 2.6 eV reported for piperidine and piperidinum chloride (21).



E_N = 397.8 eV

E_N = 400.4 eV

It is seen that, except for methadone, the piperidine ring is common for all the compounds in Fig. 1.

Most important, however, is the observation that shifts due to changes in substituent on the nitrogen are very small. It is seen from Eq. 4 that to a first approximation the chemical shift is proportional to the change in charge density on the considered atom. The results are therefore in excellent agreement with the earlier CNDO/2 calculations (7–9), which indicated virtually no differences in nitrogen charge due to substituent changes in congener agonist (*N*-methyl) - antagonist (*N*-allyl) pairs, as can be seen from the third column in Table I. This holds both for the free bases and for the protonated species. Thus the differences in analgesic activity are most probably not due to differences in charge density on the nitrogen. Moreover, the significant differences in the measured nitrogen pK_a values of congener agonist-antagonist pairs (22, 23) are not directly correlatable with the nitrogen electron densities in the free base, as has often been previously implied.

In Table 2 the observed and calculated shifts are compared. The values are given relative to the morphine base in each case. Among the bases the differences between observed and calculated values are small, and all three models seem to give satisfactory agreement with experiment. The shifts between neutral and protonated species are predicted a little too high in all three models. (See APPENDIX for explanation.) The largest discrepancies are noted for the ΔE_N(mol) values, where the anion contribution is neglected. However, among the protonated compounds the values seem to be fairly constant. This result is encouraging because it indicates that the shifts are qualitatively correct, and that the charge on nitrogen remains fairly constant within each group of compounds.

The ESCA results provide striking confirmation of the CNDO/2 calculations that in the protonated species the entire positive charge is not located on the nitrogen. The CNDO/2 calculations indicated that only approximately 0.2 positive charge remained localized on the nitrogen (7–9). The ESCA results indicate that even a little less of the positive charge, perhaps of the order of 0.1, remains localized on the nitrogen atom.

This has significant implications for the requisites that the complementary "analgesic" or "opiate" receptor must possess, which are somewhat different from those heretofore postulated by pharmacologists. In particular, the "analgesic" receptor site proposed by Beckett, Casy, and co-workers (3–6) has a small, highly localized "anionic" site to accommodate the positively charged nitrogen (and its associated hydrogen atom). However, only between 0.1 (ESCA) and 0.2 (CNDO/2) of the positive charge remains localized on the nitrogen. The remainder of the positive charge is

TABLE 1

Nitrogen 1s binding energies (E_N) and shifts in binding energies (ΔE_N) relative to morphine

Calculated charge and molecular and crystal potential for the nitrogen sites are also listed.

Compound	E_N	ΔE_N	q_N[a]	V_N(mol)[b]	V_N(cryst)[c]
	eV	*eV*		*eV*	*eV*
I. Morphine	398.7	0.0 ± 0.2	−0.175	2.1	1.6
II. Nalorphine	398.8	0.1 ± 0.2	−0.177	2.2	1.8
IV. Naloxone	398.8	0.1 ± 0.2	−0.166	2.3	1.9
VII. Methadone			−0.165	1.8	1.7
VIII. Cyclazocine	399.2	0.5 ± 0.2	−0.176	2.2	2.1
I. Morphine H_2SO_4	401.4	2.7 ± 0.2	0.012	8.1	3.6
II. Nalorphine HCl	401.5	2.8 ± 0.2	0.007	8.1	3.6
III. Oxymorphone HCl	401.5	2.8 ± 0.2	0.037		
IV. Naloxone HCl	401.4	2.7 ± 0.2	0.020	7.3	2.2
V. Levorphanol tartrate	401.7	3.0 ± 0.2			
VI. Levallorphan tartrate	401.7	3.0 ± 0.2			
VII. Methadone HCl	401.6	2.9 ± 0.2	0.045	7.4	2.1
VIII. Cyclazocine HCl			0.017	7.4	2.4

[a] Calculated charge on nitrogen from CNDO/2 calculations.
[b] Molecular potential due to surrounding atoms in the isolated molecule.
[c] Crystal potential due to surrounding atoms in the crystal.

TABLE 2

Observed and calculated shifts in nitrogen 1s binding energies relative to morphine

Compound	ΔE_N(obs)	ΔE_N(charge)[a]	ΔE_N(mol)[b]	ΔE_N(cryst)[c]
	eV	*eV*	*eV*	*eV*
I. Morphine	0.0 ± 0.2	0.0	0.0	0.0
II. Nalorphine	0.1 ± 0.2	0.0	0.1	0.2
IV. Naloxone	0.1 ± 0.2	0.2	0.4	0.5
VII. Methadone		0.2	−0.1	0.3
VIII. Cyclazocine	0.5 ± 0.2	0.0	0.1	0.5
I. Morphine H_2SO_4	2.7 ± 0.2	4.0	10.0	6.1
II. Nalorphine HCl	2.8 ± 0.2	3.9	9.9	5.9
III. Oxymorphone HCl	2.8 ± 0.2			
IV. Naloxone HCl	2.7 ± 0.2	4.2	9.4	4.8
V. Levorphanol tartrate	3.0 ± 0.2			
VI. Levallorphan tartrate	3.0 ± 0.2			
VII. Methadone HCl	2.9 ± 0.2	4.7	10.0	5.2
VIII. Cyclazocine HCl		4.1	9.4	4.9

[a] Calculated shift based on the nitrogen charge alone.
[b] Calculated shift including the molecular potential.
[c] Calculated shift including the crystal potential.

delocalized over the neighboring atoms. Thus the "anionic" site of the complementary "analgesic" (or "opiate") receptor cannot be a small, highly localized area as previously depicted, but rather must be a wider basin in shape.

Our ESCA and quantum chemical results indicate that the genesis of the difference between a narcotic agonist and a narcotic antagonist does not lie in the difference in the electron densities of the nitrogen atoms in these two types of compounds, either in their free bases or in their protonated forms.

CONCLUSION

This ESCA study apparently provides the first experimental confirmations of calculated quantum chemical charge densities of pharmacological molecules. The ESCA study has validated the reliability of the calculated quantum chemical CNDO/2 relative charge densities for narcotics and narcotic antagonists, which indicated that (a) there was virtually no difference in nitrogen change due to substituent changes in the series of either the free bases or the acid salts and (b) in the *N*-protonated acid salts only slightly more than 0.1 charge unit of the positive charge remained localized on the nitrogen atom, remainder being delocalized over the neighboring atoms.

The importance of such studies is not limited to opiates. We have been able to show a very specific calculated electron density on the alkyl nitrogen in various neuroleptics (phenothiazines, butyrophenones, etc.) (8, 24). A CNDO/2 calculated nitrogen electron density of 5.15–5.16 appears to be necessary for neuroleptic effectiveness. This should be mirrored in measured ESCA spectra. We are sufficiently confident of this index that if a potential neuroleptic does not meet this criterion, we do not believe it will be an effective major tranquilizer. This approach obviously can be extended to many other types of drugs.

APPENDIX

The conclusion that the shift due to changes in substituent were very small might have been considered somewhat fortuitous, since a direct shift-charge correlation in some instances may break down (14, 25). It was therefore necessary to calculate the molecular and crystal potentials for the actual molecules. The computer program written by Busing (19), together with the atomic charges from the CNDO/2 calculations, was used. The crystal structures are not known for all the investigated compounds, but those of morphine (26, 27), naloxone (28), methadone (29), and cyclazocine (30) have been determined. For nalorphine the structure of morphine was used, but with the position of the allyl group as in naloxone. The validity of that conformation of nalorphine was subsequently confirmed by our calculation of the conformational profile of nalorphine by the PCILO method of perturbative configuration interaction using localized orbitals (31). The structural data are those reported for the corresponding salts; therefore, in order to calculate the potentials for the bases, the crystal structures were assumed to be the same.

The calculated molecular and crystal potentials for the various compounds are given in the last two columns of Table 1. The molecular potential, V_N(mol), in all cases is higher than the corresponding crystal potential, V_N(cryst). The difference is small among the bases, but becomes quite substantial for the protonated compounds. This might have been expected, since the contribution from negative anions is neglected in V_N(mol). The crystal potentials, taking the anions into account, are still somewhat higher for the salts than for the bases. Normally it is expected that the potential decreases as the considered site becomes more positive (14, 32). Here it seems that the inclusion of a proton increases the positive contribution more than the decrease due to the anion.

The chemical shift in binding energy were then calculated in three different ways. (a) The charge model, $\Delta E_N(\text{charge}) = k_N \Delta q_N$, was used, and the shifts were predicted by the nitrogen charges alone. (b) The potential model, including the molecular potential, was applied: $\Delta E_N(\text{mol}) = k_N \Delta q_N + \Delta V_N(\text{mol})$. (c) The potential model, including the crystal potential, was used: $\Delta E_N = k_N \Delta q_N + \Delta V_N(\text{cryst})$. The value of 21.5 eV/unit charge was given to the parameter k_N. This value had previously been determined for nitrogen from a least-squares fit to experimental data, using charges from CNDO/2 calculations (13).

The small discrepancy between observed and calculated shifts of the acid salts may be due to several reasons. First, it is to be remembered that the CNDO/2 calculations are carried out for free molecules. Measurements on nonionic compounds in

both the solid and the gaseous state indicate that solid-state effects may be small (12), but for ionic compounds one cannot expect the calculated charge distribution to be accurate. One may therefore expect better agreement with experiment for the neutral molecules. On the other hand, one may assume the influence of solid-state effects to be fairly constant, since the structures of the compounds are so similar. The fact that the simple charge model works so well supports this assumption.

The discrepancy may also be due to limitations of the potential model itself. It is seen from Eqs. 3 and 4 that the model does not explicitly take reorganization effects into account. However, since we are comparing molecules with similar environments, the changes in reorganization energy are expected to be almost constant (33). The calculated chemical shifts are therefore in reasonable agreement with the observed values.

ACKNOWLEDGMENTS

We thank the following for their gracious gifts of some of the compounds used in this research: naloxone and oxymorphone, Dr. H. Blumberg, Endo Laboratories, Inc.; nalorphine, Dr. F. Robinson, Merck Sharp & Dohme; levorphanol and levallorphan, Dr. W. E. Scott, Hoffmann-La Roche, Inc.; cyclazocine, Dr. F. Nachod, Sterling-Winthrop Research Institute; and methadone, Dr. E. May, National Institutes of Health.

REFERENCES

1. Eddy, N. B. & May, E. L. (1973) *Science*, **181**, 407-414.
2. Kutter, E., Herz, A., Teschemacher, H.-J. & Hess, R. (1970) *J. Med. Chem.*, **13**, 801-805.
3. Beckett, A. H. & Casy, A. F. (1954) *J. Pharm. Pharmacol.*, **6**, 986-1001.
4. Beckett, A. H. (1956) *J. Pharm. Pharmacol.*, **8**, 848-859. (Part I).
5. Beckett, A. H., Casy, A. F., Harper, N. J. & Phelps, P. M. (1956) *J. Pharm. Pharmacol.*, **8**, 860-873.
6. Beckett, A. H. (1962) *Proc. Int. Union Physiol. Sci.*, **1**, Pt II 805-818.
7. Kaufman, Joyce J. & Kerman, Ellen (1973) *Abstr. 166th Natl. Meet. Am. Chem. Soc. (Chicago)*, MEDI23.
8. Kaufman, Joyce J. & Koski, W. S. (1975) in *Drug Design* (Ariëns, E. J., ed.), Vol. 5, pp. 251-340, Academic Press, New York.
9. Kaufman, Joyce J., Kerman, Ellen & Koski, W. S. (1974) *Int. J. Quantum Chem. Symp.*, **1**, 289-313.
10. Giordano, W., Hamann, J. R., Harkins, J. J. & Kaufman, Joyce J. (1966) Presented at *3rd Int. Congr. Pharmacol. (São Paulo)*.
11. Giordano, W., Hamann, J. R., Harkins, J. J. & Kaufman, Joyce J. (1968) in *Physico-chemical Aspects of Drug Action* (Ariëns, E. J., ed.), Vol. 7, pp. 327-354, Pergamon Press, New York.
12. Kaufman, Joyce J., Preston, H. J. T., Kerman, Ellen & Cusachs, L. C. (1973) *Int. J. Quantum Chem. Symp.*, **7**, 249-260.
13. Siegbahn, K., Nordling, C., Johansson, G., Hedman, J., Heden, P. F., Hamrin, K., Gelius, U., Bergmark, T., Werme, L. O., Manne, R. & Baer, Y. (1969) *ESCA Applied to Free Molecules*, North Holland Publishing Co., Amsterdam.
14. Geilus, U., Heden, P. F., Hedman, J., Lindborg, B. J., Marine, R., Nordberg, R., Nordling, C. & Siegbahn, K. (1970) *Phys. Scr.*, **2**, 70-80.
15. Pullen, B. P., Carlson, T. A., Moddeman, W. E., Schweitzer, G. K., Bull, W. E. & Grimm, F. A. (1970) *J. Chem. Phys.*, **53**, 768-782.
16. Johansson, G., Hedman, J., Berndtsson, A., Klasson, M. & Nilsson, R. (1973) *J. Electron Spectrosc. Relat. Phenom.*, **2**, 295-317.
17. Gelius, U. (1974) *Phys. Scr.*, **9**, 133-147.
18. Ewald, P. P. (1921) *Ann. Phys.*, **64**, 253-287.
19. Busing, W. R. (1974) *Chem. Div. Annu. Prog. Rep. Period Ending May 20, 1974*, ORNL-4976 pp. 154-155, Oak Ridge National Laboratory, Oak Ridge, Tenn.
20. Van Gool, W. & Piken, A. G. (1969) *J. Materials Sci.*, **4**, 95-104.
21. Nordberg, R., Albridge, R. G., Bergmark, T., Ericson, U., Hedman, J., Nordling, C., Siegbahn, K. & Lindberg, B. J. (1967) *Ark. Kemi*, **28**, 257-278.
22. Kaufman, Joyce J., Semo, Nora M. & Koski, W. S. (1975) *J. Med. Chem.*, in press.
23. Kaufman, Joyce J., Semo, Nora M. and Koski, W. S. (1975) Abstr. 169th Natl. Meet. *Am. Chem. Soc.* (Phila.) MEDI 058.
24. Kaufman, Joyce J. & Kerman, Ellen (1974) *Int. J. Quantum Chem. Symp.*, **1**, 259-287.
25. Van der Aviord, A. (1970) *Chem. Commun.*, **12**, 727-730.
26. Mackay, M. & Hodgkin, Dorothy C. (1955) *J. Chem. Soc.* 3261-3267.
27. Gylbert, L. (1973) *Acta Crystallogr. Sect. B*, **29**, 1630-1635.
28. Karle, I. L. (1974) *Acta Crystallogr. Sect. B*, **30**, 1682-1686.
29. Hanson, A. W. & Ahmed, F. R. (1958) *Acta*

Crystallogr., **11**, 724–728.
30. Karle, I. L., Gilard, R. D., Fratini, A. V. & Karle, J. (1969) *Acta Crystallogr. Sect. B*, **25**, 1469–1479.
31. Kaufman, Joyce J. & Kerman, Ellen (1975) *Int. J. Quantum Chem. Symp.*, in press.
32. Gelius, U., Ross, B. & Siegbahn, P. (1970) *Chem. Phys. Lett.*, **4**, 471–475.
33. Davis, D. W. & Shirley, D. A. (1974) *J. Electron Spectrosc. Relat. Phenom.*, **3**, 137–163.