Ab-Initio LCAO–MO–SCF Calculations of Morphine and Nalorphine and Measurement of Their Photoelectron Spectra

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Received December 31, 1974

Abstract: Ab-initio LCAO–MO–SCF calculations were carried out for morphine and nalorphine. A Gaussian 4,3G basis set was picked by test calculations on pyrazole and comparison with our previous large basis set calculations for pyrazole which had agreed with measured photoelectron spectra. This comparison indicated that eigenvalues calculated with the smaller 4,3G set would have to be lowered by 1.85 eV to agree with the larger basis set results and with PES spectra. Application of this correction gave results that were consistent with the measured photoelectron spectra of morphine and nalorphine. The ab-initio quantum chemical calculated electron densities on the nitrogen atom were virtually identical in morphine and nalorphine and agreed with our earlier less rigorously calculated electron densities which had been validated by our subsequent measured ESCA spectra results.

Introduction

Ab-initio LCAO–MO–SCF calculations were carried out for morphine, an *N*-methyl narcotic agonist, and nalorphine, an *N*-allyl narcotic antagonist. The morphine atomic coordinates were taken as those from the recent crystal structure determination of Gylbert.[1] (The numbering system is shown in Figure 1.) The nalorphine coordinates were taken as a combination of the skeletal coordinates of morphine and the same position of the allyl group relative to the piperidine ring of morphine as was found by Karle[2] for the position of the allyl group of naloxone relative to the piperidine ring of the oxymorphone skeleton. The reasonableness of this assumption for the position of the side chain was verified by our recent calculation of the conformational profile of nalorphine[3] by the PCILO method[4] which indicated that this was the position of minimum energy and any other low-energy positions were also very close to this conformation.

Computational Details

In order to pick a minimum contracted Gaussian basis set a number of test calculations were performed on the pyrazole molecule and compared with our previous larger C,N $9^s5^p \rightarrow 4^s3^p$; H $4^s1^p \rightarrow 3^s1^p$ Gaussian basis set calculations.[5] Comparison of the energy eigenvalues indicated that if one used the STO 6,3G set[6] (a fit to Slater type orbitals) or a 4,3G set (comprised of the same valence basis functions as the STO 6,3G set with a somewhat smaller set of inner shell orbitals), the valence orbital eigenvalues would have to be lowered by 0.068 au (1.85 eV) to match those resulting from our larger basis set calculation. This larger basis set calculation had reproduced well the experimentally measured photoelectron spectrum for the two highest occupied molecular orbitals (HOMO's) of pyrrole and pyrazole,[7,8] both of which were of the π type.

The 4,3G set was used in this research for the calculations on morphine and nalorphine. (The pyrazole population analyses for these two sets are compared in Table I.)

Results and Discussion

A. Orbital Energies and PES. The calculated orbital energy levels and total energy for morphine are listed in Table II and those for nalorphine in Table III. Analysis of our final wave function for morphine (Table IV) indicated that the two HOMO's of morphine were primarily π type on the aromatic ring (plus a contribution in the HOMO also from the lone pair on the alkyl OH), the third HOMO was primarily from the nitrogen atom and the fourth HOMO was primarily a contribution from the double bond in the alkyl ring.

Chart I. Morphine/Nalorphrine Computational Statistics[a]

	Morphine	Nalorphine
No. of basis functions	124	136
No. of 2-electron integrals	30×10^6	43×10^6
No. of 2-electron integrals kept	7×10^6	5×10^6
Integral cutoff, au	10^{-6}	10^{-5}
Integral time, min	110	70[b]
SCF time, min	70[c]	50[c]
No. of SCF iterations	13	12

[a] 360/195 computer using IBMOL-5A program. [b] Time to compute extra integrals for nalorphine. [c] The longer SCF time for morphine than for nalorphine, which is a bit larger than morphine, reflects the higher integral cutoff for nalorphine which led to fewer total integrals to be processed for its SCF than for the morphine SCF.

For nalorphine (Table V), the HOMO was similar to that of morphine, primarily π type on the aromatic ring plus a contribution from the lone pair on the alkyl OH. The second HOMO (which was very close energywise to the third HOMO) was now primarily from the nitrogen atom, while the third HOMO was again mostly due to the π system of the aromatic ring this time with a small admixture of N. The fourth HOMO, as in morphine, was primarily a contribution from the double bond in the alkyl ring. The fifth HOMO is an extra one, due primarily to the double bond in the allyl group with a small contribution from N.

We measured the photoelectron spectra of the free bases of morphine and nalorphine. The HeI spectra of the free bases of nalorphine and morphine are presented in Figure 2. For molecules as complex as the ones covered by this study it is difficult to make unambiguous assignments to the peaks because of overlapping of peaks, peak width, and the absence of fine structure. Some of these difficulties are illustrated by the following comments. By comparing the MO calculations with the photoelectron spectra some assignments can be made. Counting from left to right in the nalorphine spectrum, peak II at about 9.4 eV is the narrow-

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Morphine

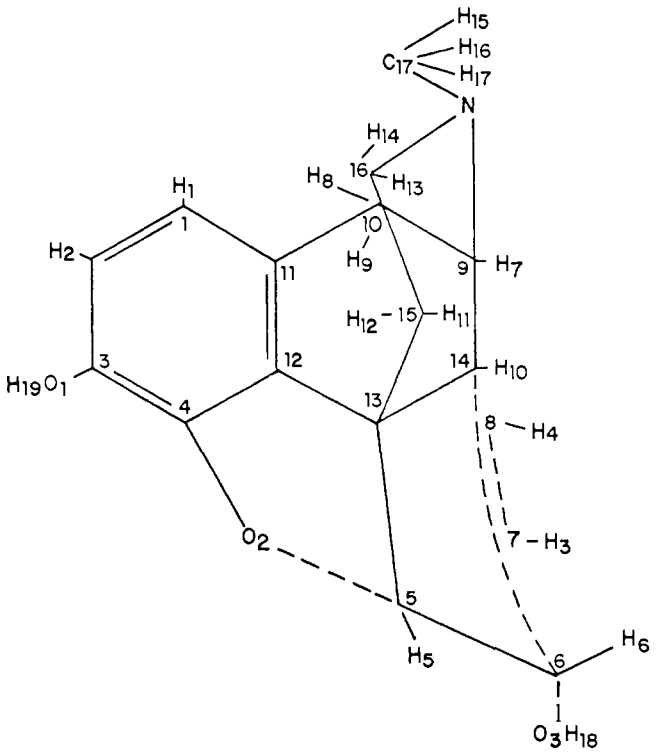

Figure 1.

Table I. Gross Atomic Populations of Pyrazole

Atom	Large Basis[a]	STO 4,3G[b]
N1	7.302	7.231
C1	5.947	5.964
C2	6.189	6.109
C3	6.030	6.001
N2	7.127	7.156
HN	0.731	0.760
H1	0.887	0.919
H2	0.895	0.932
H3	0.892	0.928

[a] Preston–Kaufman[5] ab-initio large-basis calculation using Dunning C,N $9^s5^p \rightarrow 4^s2^p$; H $4^s1^p \rightarrow 3^s1^p$ basis set. [b] Ab-initio minimum basis calculation using Slater exponents from Pople et al.[6]

est of all peaks. In examining the photoelectron spectra of a number of structurally related narcotic molecules it was found that the spectra were characterized by the same narrow peak in the same energy region. It is therefore reasonable to assign this peak to an orbital having a major contribution from the nitrogen orbital and this peak probably corresponds to the ionization of a nitrogen lone pair. If one pegs the spectrum to the nitrogen peak, an examination of the MO calculations suggests that the first peak which is a component of two peaks is due to a contribution from two MO's involving a dominant contribution from the π electrons of the aromatic ring in the molecule. Peak III which is distinct in the nalorphine spectrum and appears as a shoulder in the morphine case is due to an orbital with a strong contribution from the π electron of the double bond between the sixth and seventh carbon atoms. The contribution from the allyl group in nalorphine is expected to fall in the region of peak IV. Here again a clean cut assignment is prevented by the overlapping of orbitals, since the number 2 oxygen atomic orbitals of morphine and nalorphine make a

Table II. Energy Levels and Total Energy (au) of Morphine ($C_{17}H_{19}NO_3$) (STO 4,3G Basis Set)

ϵ_{77}	+0.258	ϵ_{49}	−0.605	ϵ_{21}	−11.141
ϵ_{76}	−0.244	ϵ_{48}	−0.609	ϵ_{20}	−11.142
ϵ_{75}	−0.270	ϵ_{47}	−0.627	ϵ_{19}	−11.142
ϵ_{74}	−0.280	ϵ_{46}	−0.630	ϵ_{18}	−11.143
ϵ_{73}	−0.303	ϵ_{45}	−0.634	ϵ_{17}	−11.152
ϵ_{72}	−0.360	ϵ_{44}	−0.653	ϵ_{16}	−11.163
ϵ_{71}	−0.379	ϵ_{43}	−0.663	ϵ_{15}	−11.172
ϵ_{70}	−0.380	ϵ_{42}	−0.679	ϵ_{14}	−11.172
ϵ_{69}	−0.390	ϵ_{41}	−0.701	ϵ_{13}	−11.173
ϵ_{68}	−0.401	ϵ_{40}	−0.733	ϵ_{12}	−11.186
ϵ_{67}	−0.421	ϵ_{39}	−0.777	ϵ_{11}	−11.187
ϵ_{66}	−0.429	ϵ_{38}	−0.793	ϵ_{10}	−11.188
ϵ_{65}	−0.443	ϵ_{37}	−0.815	ϵ_{9}	−11.192
ϵ_{64}	−0.462	ϵ_{36}	−0.837	ϵ_{8}	−11.200
ϵ_{63}	−0.469	ϵ_{35}	−0.849	ϵ_{7}	−11.201
ϵ_{62}	−0.481	ϵ_{34}	−0.909	ϵ_{6}	−11.212
ϵ_{61}	−0.487	ϵ_{33}	−0.936	ϵ_{5}	−11.226
ϵ_{60}	−0.494	ϵ_{32}	−0.961	ϵ_{4}	−15.458
ϵ_{59}	−0.497	ϵ_{31}	−0.983	ϵ_{3}	−20.455
ϵ_{58}	−0.513	ϵ_{30}	−0.998	ϵ_{2}	−20.496
ϵ_{57}	−0.524	ϵ_{29}	−1.028	ϵ_{1}	−20.516
ϵ_{56}	−0.534	ϵ_{28}	−1.049		
ϵ_{55}	−0.538	ϵ_{27}	−1.098	E_T	−927.984
ϵ_{54}	−0.549	ϵ_{26}	−1.126		
ϵ_{53}	−0.563	ϵ_{25}	−1.185		
ϵ_{52}	−0.566	ϵ_{24}	−1.325		
ϵ_{51}	−0.579	ϵ_{23}	−1.339		
ϵ_{50}	−0.586	ϵ_{22}	−1.378		

Table III. Energy Levels and Total Energy (au) of Nalorphine ($C_{19}H_{21}NO_3$) (STO 4,3G Basis Set)

ϵ_{84}	+0.257	ϵ_{56}	−0.566	ϵ_{28}	−1.122
ϵ_{83}	−0.247	ϵ_{55}	−0.572	ϵ_{27}	−1.179
ϵ_{82}	−0.273	ϵ_{54}	−0.586	ϵ_{26}	−1.326
ϵ_{81}	−0.277	ϵ_{53}	−0.592	ϵ_{25}	−1.338
ϵ_{80}	−0.302	ϵ_{52}	−0.601	ϵ_{24}	−1.378
ϵ_{79}	−0.322	ϵ_{51}	−0.606	ϵ_{23}	−11.140
ϵ_{78}	−0.356	ϵ_{50}	−0.631	ϵ_{22}	−11.141
ϵ_{77}	−0.369	ϵ_{49}	−0.633	ϵ_{21}	−11.142
ϵ_{76}	−0.376	ϵ_{48}	−0.652	ϵ_{20}	−11.142
ϵ_{75}	−0.383	ϵ_{47}	−0.662	ϵ_{19}	−11.145
ϵ_{74}	−0.396	ϵ_{46}	−0.667	ϵ_{18}	−11.149
ϵ_{73}	−0.408	ϵ_{45}	−0.683	ϵ_{17}	−11.153
ϵ_{72}	−0.419	ϵ_{44}	−0.703	ϵ_{16}	−11.163
ϵ_{71}	−0.425	ϵ_{43}	−0.731	ϵ_{15}	−11.171
ϵ_{70}	−0.443	ϵ_{42}	−0.775	ϵ_{14}	−11.171
ϵ_{69}	−0.452	ϵ_{41}	−0.792	ϵ_{13}	−11.174
ϵ_{68}	−0.469	ϵ_{40}	−0.817	ϵ_{12}	−11.187
ϵ_{67}	−0.481	ϵ_{39}	−0.833	ϵ_{11}	−11.190
ϵ_{66}	−0.482	ϵ_{38}	−0.849	ϵ_{10}	−11.190
ϵ_{65}	−0.487	ϵ_{37}	−0.878	ϵ_{9}	−11.192
ϵ_{64}	−0.492	ϵ_{36}	−0.932	ϵ_{8}	−11.201
ϵ_{63}	−0.499	ϵ_{35}	−0.961	ϵ_{7}	−11.202
ϵ_{62}	−0.512	ϵ_{34}	−0.965	ϵ_{6}	−11.214
ϵ_{61}	−0.521	ϵ_{33}	−1.000	ϵ_{5}	−11.228
ϵ_{60}	−0.529	ϵ_{32}	−1.014	ϵ_{4}	−15.456
ϵ_{59}	−0.537	ϵ_{31}	−1.030	ϵ_{3}	−20.454
ϵ_{58}	−0.546	ϵ_{30}	−1.049	ϵ_{2}	−20.495
ϵ_{57}	−0.552	ϵ_{29}	−1.093	ϵ_{1}	−20.515
				E_T	−1004.41

dominant contribution to this region. In the region beyond 12 eV the overlapping is even more severe, preventing any assignments. It may be noted that the first ionization potentials determined from the photoelectron spectra of these compounds are consistent with the mass spectroscopic appearance potentials measured in our laboratory (unpublished results by W. S. Koski).

The PES spectra of the free bases were measured in the 175–190 °C region. We did not measure the spectra of the

Table IV. Orbital Energies (au) and Largest MO Coefficients for Morphine ($C_{17}H_{19}NO_3$) (STO 4,3G Basis Set)

$\epsilon_{76} = -0.244$	$\epsilon_{75} = -0.270$	$\epsilon_{74} = -0.280$
0.411 C1 ($2p_z$)	0.449 C2 ($2p_z$)	0.590 N ($2p_y$)
−0.390 C4 ($2p_z$)	−0.429 C12 ($2p_z$)	0.505 N ($2p_z$)
0.366 O3 ($2p_z$)	−0.334 C11 ($2p_z$)	0.320 N (2s)
−0.344 C3 ($2p_z$)	0.277 C3 ($2p_z$)	0.320 N ($2p_x$)
−0.254 O3 ($2p_y$)	0.222 O1 ($2p_y$)	0.200 H17c (1s)
$\epsilon_{73} = -0.303$	$\epsilon_{72} = -0.360$	$\epsilon_{71} = -0.379$
0.458 C8 ($2p_z$)	0.848 O2 ($2p_y$)	0.483 O1 ($2p_y$)
0.371 C7 ($2p_z$)	0.204 C7 ($2p_y$)	0.289 O1 ($2p_x$)
0.347 C7 ($2p_x$)	−0.191 C6 ($2p_y$)	−0.285 O3 ($2p_x$)
0.300 C7 ($2p_y$)	0.143 H6 (1s)	0.237 C5 ($2p_x$)
0.288 C8 ($2p_x$)	0.137 C7 (2s)	0.229 C13 ($2p_y$)
$\epsilon_{70} = -0.380$	$\epsilon_{69} = -0.390$	
0.382 O2 ($2p_y$)	0.265 O2 ($2p_y$)	
0.247 C13 ($2p_x$)	−0.245 C13 ($2p_z$)	
0.217 C9 ($2p_x$)	0.235 C2 ($2p_z$)	
−0.201 C14 ($2p_x$)	−0.222 H9 (1s)	
0.184 O2 ($2p_x$)	−0.208 C14 ($2p_y$)	

Table V. Orbital Energies (au) and Largest MO Coefficients for Nalorphine ($C_{19}H_{21}NO_3$) (STO 4,3G Basis Set)

$\epsilon_{83} = -0.247$	$\epsilon_{82} = -0.273$	$\epsilon_{81} = -0.277$
0.413 Cl ($2p_z$)	0.520 N ($2p_y$)	0.417 C2 ($2p_z$)
−0.392 C4 ($2p_z$)	0.465 N ($2p_z$)	−0.385 C12 ($2p_x$)
0.373 O3 ($2p_z$)	0.262 N ($2p_x$)	−0.313 C11 ($2p_z$)
−0.329 C3 ($2p_z$)	0.258 N (2s)	0.269 N ($2p_y$)
−0.264 O3 ($2p_y$)	0.210 H17b (1s)	0.266 C3 ($2p_z$)
$\epsilon_{80} = -0.302$	$\epsilon_{79} = -0.322$	$\epsilon_{78} = -0.356$
0.471 C8 ($2p_z$)	0.409 C19 ($2p_y$)	0.797 O2 ($2p_y$)
0.373 C7 ($2p_z$)	0.399 C18 ($2p_z$)	0.184 C7 ($2p_y$)
0.350 C7 ($2p_x$)	0.318 C18 ($2p_y$)	−0.180 C6 ($2p_y$)
0.310 C7 ($2p_y$)	−0.305 C19 ($2p_x$)	−0.138 C8 ($2p_y$)
0.289 C8 ($2p_x$)	−0.271 N ($2p_x$)	0.135 C7 (2s)
$\epsilon_{77} = -0.369$	$\epsilon_{76} = -0.376$	$\epsilon_{75} = -0.383$
0.241 C9 ($2p_x$)	0.561 O1 ($2p_y$)	0.217 C9 ($2p_z$)
−0.228 C14 ($2p_x$)	0.345 O1 ($2p_x$)	0.216 C13 ($2p_z$)
0.227 C13 ($2p_x$)	0.266 C4 ($2p_x$)	−0.200 H18 (1s)
−0.225 H18 (1s)	−0.229 C12 ($2p_x$)	0.198 C18 ($2p_y$)
−0.223 C5 ($2p_x$)	0.184 C13 ($2p_y$)	0.183 N ($2p_y$)

corresponding acid salts because of complications resulting from the decomposition of the salts upon heating.

In Table VI are shown the calculated Koopmans' theorem ionization potentials, the calculated ionization potentials, plus the calibration of 1.85 eV to correct the small basis set results to the larger ones and our measured photo-

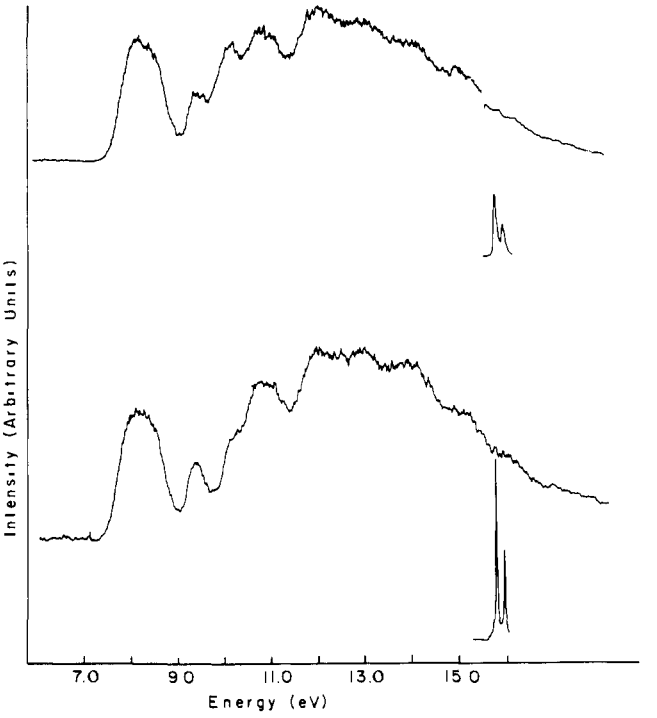

Figure 2. HeI spectra of the free bases of nalorphine (upper curve) and morphine (lower curve). The sharp peaks on the right side of each spectrum are the argon calibration peaks.

Table VII. Gross Atomic Populations for Morphine and Nalorphine (STO 4,3G Basis Set)

Atom	Morphine	Nalorphine	Atom	Morphine	Nalorphine
C1	6.120	6.121	H6	0.921	0.922
C2	6.067	6.067	H7	0.916	0.918
C3	5.904	5.905	H8	0.915	0.915
C4	5.905	5.903	H9	0.939	0.933
C5	5.985	5.985	H10a	0.902	0.902
C6	5.977	5.975	H10b	0.918	0.918
C7	6.082	6.083	H14	0.924	0.924
C8	6.110	6.109	H15a	0.919	0.917
C9	5.952	5.953	H15b	0.923	0.924
C10	6.187	6.188	H16a	0.923	0.924
C11	5.982	5.981	H16b	0.915	0.914
C12	6.033	6.033	HO1	0.806	0.804
C13	5.965	5.961	HO2	0.749	0.751
C14	6.045	6.044	C17	6.208	6.047
C15	6.137	6.138	H17a	0.910	0.932
C16	6.084	6.088	H17b	0.890	0.949
O1	8.271	8.272	H17c	0.919	
O2	8.350	8.351	C18		6.048
O3	8.250	8.251	C19		6.053
N	7.258	7.259	H18		0.978
H1	0.915	0.915	H19a		0.969
H2	0.923	0.923	H19b		0.949
H5	0.904	0.903			

Table VI. Koopmans' Theorem Ionization Potentials and PES (eV) for Morphine and Nalorphine (STO 4,3G Basis Set)

Morphine				Nalorphine			
MO	Eigenvalue	Eigenvalue (corrected by −1.85 eV)	PES (Exptl)	MO	Eigenvalue	Eigenvalue (corrected by −1.85 eV)	PES (Exptl)
76	−6.64	−8.49	8.3	83	−6.72	−8.57	8.15
75	−7.35	−9.20		81	−7.54	−9.39	8.42
74	−7.62	−9.47	9.4	82	−7.43	−9.28	9.42
73	−8.24	−10.09	10.2	80	−8.22	−10.07	10.13
				79	−8.76	−10.61	10.8
72	−9.80	−11.65	10.8	78	−9.69	−11.54	11.0
71	−10.31	−12.16	12.0	77	−10.04	−11.89	11.95
70	−10.34	−12.19		76	−10.23	−12.08	

electron spectra. The agreement is extremely good considering the large size and complexity of these molecules.

B. Population Analysis. The comparisons of the calculated gross atomic populations (GAP's) for morphine and nalorphine are presented in Table VII. Most of the electron densities on comparable atoms are very similar in the two molecules. Most notable is the fact that these ab-initio GAP's on the N atom in morphine, 7.258, and nalorphine, 7.259, verify unambiguously our earlier CNDO/2 results[9-12] that the electron densities were the same on these two atoms. This result was contrary to what the pharmacologists had customarily assumed which was that the difference in the agonist activity of morphine and the antagonist activity of nalorphine was due to a difference in the charges on the N atoms in the two compounds. Subsequent to our CNDO/2 calculations, in collaboration with colleagues, Carlson and Saethre, the ESCA spectra of a number of narcotics and narcotic antagonists were measured.[13] The ESCA results also confirmed unambiguously that to within ±0.2 eV (corresponding to ±0.01 electron charge unit) the electron densities on the N atom in morphine and nalorphine were identical.

The comparison of the calculated total overlap populations in morphine and nalorphine indicated that these are very similar between the comparable atoms in the two molecules.

Conclusion

This research indicates that it is perfectly feasible to perform ab-initio LCAO-MO-SCF calculations on drug molecules of the size of morphine and nalorphine. The SCF calculations for these molecules are well behaved and converge smoothly. These calculations were performed in a reasonable amount of computer time, and with the current version of our new ab-initio program, MOLASYS,[14] it would be possible to perform such calculations faster by a factor of ~2.

The calculated ionization potentials were in good agreement with our measured photoelectron spectra. The ab-initio calculated gross atomic populations verified unambiguously our earlier conclusion, based on our CNDO/2 calculations, that, contrary to the popular misconception, the electron densities on the N atoms in morphine and nalorphine were virtually identical. We had earlier verified this experimentally by measurement of their ESCA spectra, which showed the two charges to be identical to within better than 0.01 unit of electronic charge.

Acknowledgment. This research was supported in part by NIDA, Division of Research, Biomedical Research Branch under Grant DA 00539 to The Johns Hopkins University. We should like to thank Dr. Monique Braude and Dr. Robert Willette of that Branch for their perceptiveness in visualizing the contributions such studies could make. The photoelectron spectra measurements were performed on the Perkin-Elmer PES spectrometer at CCNY. We thank Dr. Paul Winson and Dr. Michael Martin of Perkin-Elmer for arranging for the measurements and Dr. Michael Weiner of CCNY for allowing the use of his instrument.

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